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The Microenvironment of the Cardiomyopathic Process in Response to Pressure Overload

Dissertation

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Für Hannah, Lotte und Antonie,
denen mein Herz gehört
& Stef, der immer an mich glaubt.

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Zusammenfassung
Pathologische Herzhypertrophie ist ein entscheidender Risikofaktor für die Entwicklung von Herzinsuffizienz und prädisponiert darüber hinaus für Herzrhythmusstörungen und plötzlichen Herztod. Physiologische Herzhypertrophie stellt einen Mechanismus der Adaption des Herzens dar, wobei Hypertrophie im Kontext von Grunderkrankungen wie Hypertension, Aortenstenose, oder aber auch bei genetischen Mutationen wie zum Beispiel der Hypertrophen Kardiomyopathie, maladaptiv ist. Das hier vorgeschlagene Modell „A microenvironmental model of pressure overload-induced cardiac hypertrophy", zeigt die entscheidenden Rollen und wechselseitigen Interaktionen von Kardiomyozyten und nicht-myokardialen Zellen als Reaktion auf pathologische Zustände. Anhaltende kardiovaskuläre Stressfaktoren führen zu einer Aktivierung von Kardiomyozyten und nicht-myokardialen Zellen woraufhin diese zahlreiche pro-hypertrophe, pro-fibrotische, und pro-inflammatorische Mediatoren wie z.B. vasoaktive Hormone, Wachstumsfaktoren, sowie Zytokine freisetzen, die in der Folge die Aktivierung von Signalwegen einleiten, welche gemeinsam Herzhypertrophie verursachen. Das bedeutet, die Aktivierung von mehreren wachstumsassoziierten Signalwegen führt insgesamt zu Herzhypertrophie. Während des fibrotischen Umbaus spielen kardiale Fibroblasten eine zentrale Rolle, wobei auch Endothelzellen, sowie ansässige und infiltrierende Immunzellen diesen Prozess vorantreiben. Wenn man bedenkt, wie sich Veränderungen im Mikroumfeld auf die Herzfunktion auswirken, ist eine wichtige zukünftige Aufgabe, das aus dem Modell erlangte Wissen, in neue pharmakologische Ansatzpunkte zu übertragen. Diese Studie fast Literatur bezüglich der Fortschritte aus der Herzhypertrophie Forschung zusammen und beschreibt und diskutiert die Entwicklung eines komplexen Mikroumfelds sowie der zugehörigen molekularen Mechanismen der Signaltransduktion (Bazgir et al., 2023).

Hintergrund
Herzerkrankungen haben eine hohe Prävalenz in der westlichen Welt, wobei eine dysfunktionale Herzfunktion ausgelöst durch kardiovaskuläre Stressfaktoren eine der primären Ursachen für Morbidität und Mortalität darstellt (Bazgir et al., 2023). Diese Pathogenese ist häufig mit myokardialem Umbau assoziiert, ausgelöst durch Herzhypertrophie. Die zugrundeliegenden Mechanismen im Mikroumfeld sind sehr komplex und obwohl Therapien etabliert sind, scheint die derzeitige Behandlung insuffizient zu sein.

Ziel
Aufgrund des bekannten Zusammenhangs zwischen Herzhypertrophie und Herzinsuffizienz, ist eine entscheidende Herausforderung das Verstehen der molekularen Pathogenese von Herzhypertrophie. Daher ist das Ziel der Studie, den Fokus auf die Prozesse welche im Zusammenhang mit dem Anfang, Fortschreiten und der Pathogenese von Herzhypertrophie stehen zu richten und ein Modell für zukünftige experimentelle Studien vorzuschlagen, wodurch ein besseres Verständnis über die zu Herzhypertrophie führenden Mechanismen erlangt werden kann (Bazgir et al., 2023).

Methodik
Eine Literaturrecherche wurde durchgeführt unter Verwendung der PubMed® Suche, um Moleküle und Mechanismen zu identifizieren welche die Grundlage für die pathologischen Prozesse im Mikroumfeld von Herzhypertrophie darstellen und ein Modell für zukünftige experimentelle Studien vorzuschlagen.

Ergebnisse
"Table 2: Mediators influencing the microenvironment in cardiac hypertrophy" (Bazgir et al., 2023)
Table 3: Pressure overload triggers several actions in cardiac cells
Table 4: Various mediators trigger actions in cardiac cells
Figure 4: *"A microenvironmental model of pressure overload-induced cardiac hypertrophy"* (Bazgir et al., 2023)
Figure 5: *"An overview of the pro-hypertrophic and anti-hypertrophic signaling pathways regulating the hypertrophic response in the cardiomyocyte"* (Bazgir et al., 2023)
Figure 6: *"Schematic illustration of the process of fibrotic scar formation at the cellular level"*
Figure 7: Schematic diagram of how changes in the microenvironment affect cardiac function (Bazgir et al., 2023)

Schlussfolgerung
Das an der Entwicklung von Herzhypertrophie beteiligte Mikroumfeld besteht aus Kardiomyozyten und nicht-myokardialen Zellen, sowie der begleitenden Freisetzung von einer Vielzahl an pro-hypertrophen, pro-fibrotischen, and pro-inflammatorischen Mediatoren (Bazgir et al., 2023).

Kardiale Fibroblasten sind die Hauptakteure während der Entstehung von Fibrose, nichtsdestotrotz sind auch Endothelzellen, welche die sogenannte EndMT durchlaufen können und in einen Myofibroblast-ähnlichen Phänotyp übergehen, in diesem Prozess involviert. Ortsansässige und infiltrierende Immunzellen (Mastzellen, Makrophagen, Neutrophile) verstärken diesen Prozess, während sie gleichzeitig zu Gewebe Inflammation beitragen. Berücksichtigt man all diese Mechanismen im hypertrophen Mikroumfeld, scheint das Zuschneiden einer effizienten Therapie extrem Komplex zu sein, und erfordert multidirektionale Ansätze und ausgeklügelte Strategien, in welche alle Signalwege integriert sein müssen (Bazgir et al., 2023).

Da es nicht möglich ist, jeden zellulären und molekularen Prozess, welcher in verschiedenen Formen der Herzhypertrophie involviert ist zu diskutieren, zielte diese Studie darauf ab, die hauptsächlichen Einflussfaktoren und entsprechend beeinflussten Signalwege des hypertrophen Mikroumfelds zusammenzufassen. Ein für die Zukunft notwendiger Ansatz, wird die präzise Identifikation der Beteiligung von verschiedenen Zelltypen, sowie der von ihnen freigesetzten zellulären Mediatoren und entsprechenden „second messengers" sein. Dies wird es erlauben, die Bekannten, sowie bisher unerkannten molekularen Achsen, während der Erkrankung zu beurteilen. In Anbetracht der hohen Prävalenz von Herzerkrankungen in der westlichen Welt, sollte es zukünftig ein wichtiges Bestreben sein, das erworbene Wissen in neue pharmakologische Ansatzpunkte umzuwandeln, die dabei helfen, den Umbauprozess und die schweren

Konsequenzen, welche Patienten nach der Diagnose von diastolischer oder systolischer Dysfunktion erleiden, zu verlangsamen oder gar zu stoppen (Bazgir et al., 2023).

Abstract
"Pathological cardiac hypertrophy is a key risk factor for the development of heart failure and predisposes individuals to cardiac arrhythmia and sudden death. While physiological cardiac hypertrophy is adaptive, hypertrophy resulting from conditions comprising hypertension, aortic stenosis, or genetic mutations, such as hypertrophic cardiomyopathy, is maladaptive". The proposed model of the microenvironment of cardiac hypertrophy highlights the essential role and reciprocal interactions involving both cardiomyocytes and non-myocardial cells in response to pathological conditions. *"Prolonged cardiovascular stress causes cardiomyocytes and non-myocardial cells to enter an activated state releasing numerous pro-hypertrophic, pro-fibrotic, and pro-inflammatory mediators such as vasoactive hormones, growth factors, and cytokines, i.e., commencing signaling events that collectively cause cardiac hypertrophy"*. The activation of multiple growth-associated signaling pathways collectively causes cardiac hypertrophy. *"Fibrotic remodeling is mediated by cardiac fibroblasts as the central players, but also endothelial cells and resident and infiltrating immune cells enhance these processes"*. Considering how changes in the microenvironment affect cardiac function, *"an important future effort should be to translate the knowledge gained"* from the proposed model *"into new pharmacological targets that help delay or even stop the remodeling process"*. This study summarizes the literature on *"the last decades' advances in cardiac hypertrophy research"* and describes and discusses the development of a *"complex myocardial microenvironment"* and its molecular signaling mechanisms (Bazgir et al., 2023).

Background
"Given the high prevalence of heart disease in the Western world", cardiovascular stresses that cause heart dysfunction are *"one of the primary causes of morbidity and mortality […]"* (Bazgir et al., 2023). This pathogenesis is often associated with myocardial remodelling caused by cardiac hypertrophy. The underlying mechanisms in the microenvironment are extremely complex, and despite established therapies in use it appears that current treatment regimens are insufficient.

Aim
Due to the known association between cardiac hypertrophy and heart failure, it is a pivotal challenge to focus on understanding the molecular pathogenesis of cardiac hypertrophy. Therefore, this study aimed to *"focus on these processes related to the onset, progression, and pathogenesis"* of cardiac hypertrophy, and propose a model for future experimental studies that will provide a better understanding of the mechanisms leading to cardiac hypertrophy (Bazgir et al., 2023).

Methods
A literature study was performed using PubMed® search to identify the molecules and mechanisms that prepare the ground for the pathological hypertrophic

processes in the cardiac microenvironment and propose a model for future experimental studies.

Results

"Table 2.: Mediators influencing the microenvironment in cardiac hypertrophy" (Bazgir et al., 2023)

Table 3.: Pressure overload triggers several actions in cardiac cells

Table 4.: Various mediators trigger actions in cardiac cells

Figure 4: *"A microenvironmental model of pressure overload-induced cardiac hypertrophy"* (Bazgir et al., 2023)

Figure 5: *"An overview of the pro-hypertrophic and anti-hypertrophic signaling pathways regulating the hypertrophic response in the cardiomyocyte"* (Bazgir et al., 2023)

Figure 6: *"Schematic illustration of the process of fibrotic scar formation at the cellular level"* (Bazgir et al., 2023)

Figure 7: Schematic diagram of how changes in the microenvironment affect cardiac function (Bazgir et al., 2023)

Concluding remarks and future directions

"The microenvironment involved in the development of cardiac hypertrophy involves cardiomyocytes and non-myocardial cells, and the accompanying release of numerous pro-hypertrophic, pro-fibrotic, and pro-inflammatory mediators facilitating reciprocal interactions" (Bazgir et al., 2023).

"Cardiac fibroblasts are the main players in the development of fibrosis, nevertheless, endothelial cells that can undergo EndMT toward a myofibroblast-like phenotype are closely involved as well. Resident and infiltrating immune cells (mast cells, macrophages, neutrophils) enhance these processes while simultaneously contributing to tissue inflammation. Thus, considering all these mechanisms in the hypertrophic microenvironment", it appears that *"tailoring an efficient treatment regimen" is "extremely complex"*, requiring multidirectional approaches and sophisticated strategies, in which all signaling components are integrated (Bazgir et al., 2023).

"Since it is not feasible to discuss every cellular and molecular process involved in the development of different types of cardiac hypertrophy", this study *"aimed to outline the main drivers of the hypertrophic microenvironment and the respective signaling pathways being affected. A necessary future approach will be the identification of the precise involvement of different cell types, cellular mediators released by them, and the respective activation of second messengers. This will allow evaluation of the known and thus far unrecognized molecular signaling axes during disease development. Given the high prevalence of heart disease in the Western world, an important future effort should be to translate the knowledge gained into new pharmacological targets that help to delay or even stop the remodeling process and the severe consequences that patients experience after diagnosis of diastolic or systolic dysfunction"* (Bazgir et al., 2023).

Abbreviations

AC, adenylate cyclase; ACE, angiotensin converting enzyme; α-cd actin, alpha-cardiac actin; aFGF, acidic fibroblast growth factor; AGT, angiotensinogen; AKT/PKB, protein kinase B; α-MHC, α-myosin heavy chain; AMP, adenosine monophosphate; ANP, atrial natriuretic peptide; APCs, antigen-presenting cells; α-sk actin, alpha skeletal muscle actin ; α-sm actin, alpha smooth muscle actin ; AT-I, angiotensin I; AT-II, angiotensin II; AT1R, angiotensin II type 1 receptor; ATP, adenosine triphosphate; bFGF, basic fibroblast growth factor; FGF-2, fibroblast growth factor 2; BH4, tetrahydrobiopterin; ß-MHC, ß-myosin heavy chain ; BNP, brain natriuretic peptide; Ca^{2+}, Calcium ion; CaMK, calmodulin-dependent kinase; cAMP, cyclic adenosine monophosphate; CHF, chronic heart failure; CMs, cardiomyocytes; CnAβ, calcineurin Aß; CNP, c-type natriuretic peptide; CR, cytokine receptor ; CT-1, cardiotrophin-1; DCs, dendritic cells; ECM, extracellular-matrix ; EndMT, endothelial-to-mesenchymal transition ; ERK, extracellular signal regulated kinase ; ET-1, endothelin-1; FGFR, FGF receptor; GPCR, G-protein-coupled receptor; gp130, glycoprotein 130; GSK3ß, glycogen synthase kinase-3ß; GTP, guanosine-5'-triphosphate; HCM, hypertrophic cardiomyopathy; HDAC4/5, histone deacetylases; Hi-bFGF, high molecular weight FGF-2; H2O2,hydroxyl and hydrogen peroxide; ICAM-1, intercellular adhesion molecule-1; IGF1, Insulin like growth factor-1; IL-1, Interleukin-1; IL-1b, Interleukin-1b; IP3, inositol-1,4,5-trisphosphate; iPSC, induced pluripotent stem cells;, Janus kinase; JNK, c-Jun N-terminal kinase; LIF, leukemia inhibitory factor; Lo-FGF-2, low molecular weight FGF-2; MAPK, mitogen-activated protein kinase ; MAPKKK, mitogen-activated kinase kinase kinase; MCP-1, monocyte chemoattractant protein-1; MEF2, myocyte enhancer factor 2 ; MEK, mitogen activated ERK activating kinase; MLC, myosin light chain; NADPH, nicotinamide adenine dinucleotide phosphate; NFAT, nuclear factor of activated T cells ; NE, norepinephrine; NF-κB, nuclear factor kappa B ; NO, nitric oxide; NOS, uncoupled NO synthases; NOX, nicotinamide adenine dinucleotide phosphate oxidase ; NRCs, neonatal rat cardiomyocytes; O2-, superoxide anion; $ONOO^-$, peroxynitrite; PDE3A, phosphodiesterase-3a; PAF, platelet-activating factor; PDGF, platelet-derived growth factor; PE, phenylephrine; PI2, prostaglandin I2; PKA, protein kinase-A; PKC, protein kinase-C; PKD, protein kinase-D; PI3K, phosphoinositide 3-kinase; PKGI, cyclic GMP (cGMP)-dependent protein kinase 1; PLC, phospholipase-C; RAAS, renin-angiotensin-aldosterone system; Rac, RAS-related C3 botulinum toxin substrate; Raf, rapidly accelerated fibrosarcoma; RAS, renin-angiotensin system; Ras, rat sarcoma ; ROS, reactive oxygen species; SERCA2, Ca-pump of sarcoplasmic reticulum ; SMAD, Suppressor of Mothers Against Decapentaplegic; Src, sarcoma; STAT, signal transducer and activator of transcription; TGF-ß, transforming growth factor beta; TFs, transcription factors; TNFα, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; LVH, ventricular cardiac hypertrophy; XO, xanthine oxidase; YAP, yes-associated protein.

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1. General Introduction

"Myocardial remodeling associated with cardiac hypertrophy is one of the critical causes in the development of heart failure" (Peter et al., 2016; Zhu et al., 2019). *"The pathogenesis of heart dysfunction is one of the primary causes of morbidity and mortality in elderly people"* (Zhu et al., 2019) (Bazgir et al., 2023).

1.1 Cardiac hypertrophy

"Cardiac hypertrophy is most frequently" a *"compensatory or adaptive process to numerous physiological or pathological conditions (Table 1)"* (Fig. 1) (Schaub et al., 1997). *"Hypertrophic enlargement is characterized by an increase in the cell size of cardiomyocytes"* (Table 1). *"The heart can dynamically change its muscle mass to cope with the stimuli of development, physiological conditions of exercise and pregnancy, or pathological disease stimuli (Table 1)"* (Fig. 1) (Heineke and Molkentin, 2006). *"Increased workload as a consequence of volume or pressure overload due to pathological or physiological stimuli increases tension on the cardiac walls of the heart chambers"* (Fig. 1) (Maillet et al., 2013; Ovchinnikova et al., 2018) (Bazgir et al., 2023).

Table 1: Characteristics of physiological and pathological cardiac hypertrophy

Characteristic	Physiological cardiac hypertrophic	Pathological cardiac hypertrophic
Stimuli	Exercise, pregnancy	i.a. pressure or volume overload
Cardiomyocyte size	Increased	Increased
Concentric or eccentric	eccentric > concentric	concentric or eccentric initially yes/ advanced
Adaptivity	yes	maladaptive
Contractility	preserved or increased	preserved or decreased
Cardiac metabolism		
fatty acid oxidation	increased	decreased
Glycolysis	increased	increased
Structural and functional		
Replacement	no	yes
Interstitial fibrosis	no	yes
Cardiomyocyte apoptosis	no	yes
Capillary network	sufficient	insufficient
Molecular characteristics		
Fetal gene expression	unmodified	upregulated
Contractile linked genes	normal or increased	downregulated
Cardiac function	normal or increased	depressed
Reversible	yes	no
Heart failure	no	yes

Adapted from (Bernardo et al., 2010; Nakamura and Sadoshima, 2018)

"This ultimately triggers stress signals released by different cell types of the microenvironment to compensate for the wall tension increase, resulting in a hypertrophic growth response" (Maillet et al., 2013; Ovchinnikova et al., 2018). *"Individual cardiomyocytes can increase in length and/or width" (Fig. 2) "in response to hypertrophic stimuli depending on the intracellular signaling cascades involved"* (Berenji et al., 2005; Haider et al., 1998) (Bazgir et al., 2023). Collectively, cardiac hypertrophy is the ability of the heart to change its size to cope with various hypertrophy stimuli leading to physiological or pathological hypertrophy controlled by the stimulus (Table 1; Fig. 1) (Maillet et al., 2013).

1.2 Physiological and pathological cardiac hypertrophy

The development of physiological cardiac hypertrophy is described in athletes, during pregnancy (Table 1; Fig. 1), as well as in normally growing children (Shimizu and Minamino, 2016). Physiological hypertrophy exhibits preserved cardiac function and is triggered by pregnancy or exercise it is fully reversible (Table 1; Fig. 1) and suggested to be harmless or even beneficial. A net induction of angiogenesis has been described during physiological hypertrophy. Especially exercise training increases the capillary-to-cardiomyocyte ratio across the heart, as well as the coronary artery diameter and coronary blood flow (Maillet et al., 2013). Thus, an entirely normal structure and function is found in a physiological hypertrophic condition (Table 1; Fig. 1) (Da Costa Martins and De Windt, 2012). *"Triggers of pathological cardiac hypertrophy include extrinsic motives such as pressure overload due to long-standing hypertension or valvular stenosis"* (Table 1; Fig. 1), *"as well as volume overload due to mitral regurgitation or aortic insufficiency (Table 1), loss of contractile mass (myocardial infarction), or intrinsic reasons such as hereditary defects"* (Fig. 1) (Schaub et al., 1997; Shenasa and Shenasa, 2017). *"Although a notable feature of physiological and pathological cardiac hypertrophy is the increase in heart size"* (Fig. 1), *"pathological cardiac hypertrophy involves the loss of myocytes and fibrotic replacement, leading to cardiac dysfunction, heart failure, and/or sudden death"* (Table 1; Fig. 1) (Cohn et al., 1997; Levy et al., 1990; Maron et al., 2022; Weber et al., 1993) (Bazgir et al., 2023).

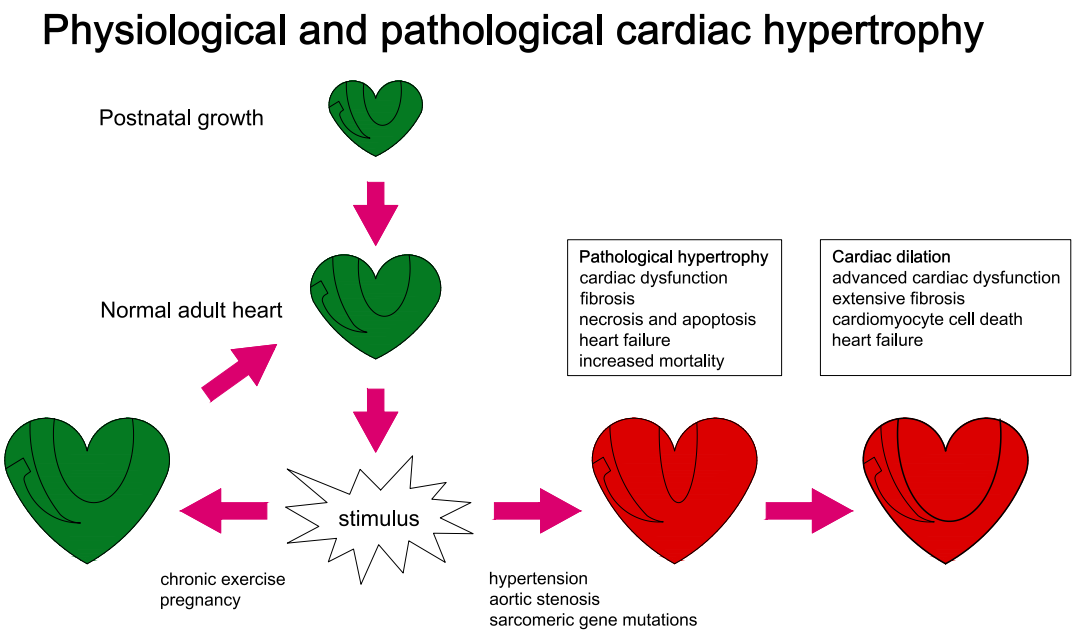

Fig. 1: A schematic overview of physiological and pathological hypertrophy outlining the key differences in initiating stimuli and cellular responses and cardiac function. The heart shows normal growth after birth until adulthood, a condition that is referred to as developmental hypertrophy. Stimuli such as pregnancy or chronic exercise training trigger cardiac hypertrophy that can be classified as physiological, in which the major characteristics comprise reversibility and normal cardiac morphology and function. In contrast, a detrimental cardiac structure and function occur in disease settings such as hypertension and can progress into heart failure**.** RV: right ventricle, LV: left ventricle. Normal/ physiological heart growth is shown in green, and pathological heart growth is shown in red**.** Adapted from (Bernardo et al., 2010).

1.3 Concentric and eccentric cardiac hypertrophy

Cardiac hypertrophy can be sub-classified into concentric and eccentric hypertrophy (Table 1; Fig. 2). This subdivision is dependent on the initiating stimulus and the resulting changes to the cardiomyocyte shape (Fig. 2) (Grossman et al., 1975; Pluim et al., 2000).

Concentric and eccentric cardiac hypertrophy in pathological settings

Concentric hypertrophy is the result of major pathological stimuli, e.g., hypertension, and aortic stenosis that cause pressure overload (Fig. 2) and increase systolic wall stress. In turn, cardiomyocytes grow in width by adding sarcomeres in a parallel pattern and thereby increase relative wall thickness and cardiac mass leading to a concentric appearance (Fig. 2). Concentric hypertrophy, in particular, appears with a small reduction in chamber volume or even no change at all (Fig. 2) (Grossman et al., 1975).

Aortic regurgitation is a major pathological stimulus causing volume overload (Fig. 2) and an increase in diastolic wall stress resulting in eccentric cardiac hypertrophy. Individual cardiomyocytes, in turn, grow in length due to the addition of sarcomeres in series (Fig. 2). Thereby increase in chamber volume and cardiac mass results in dilated chambers with an eccentric appearance (Fig. 2) (Grossman et al., 1975).

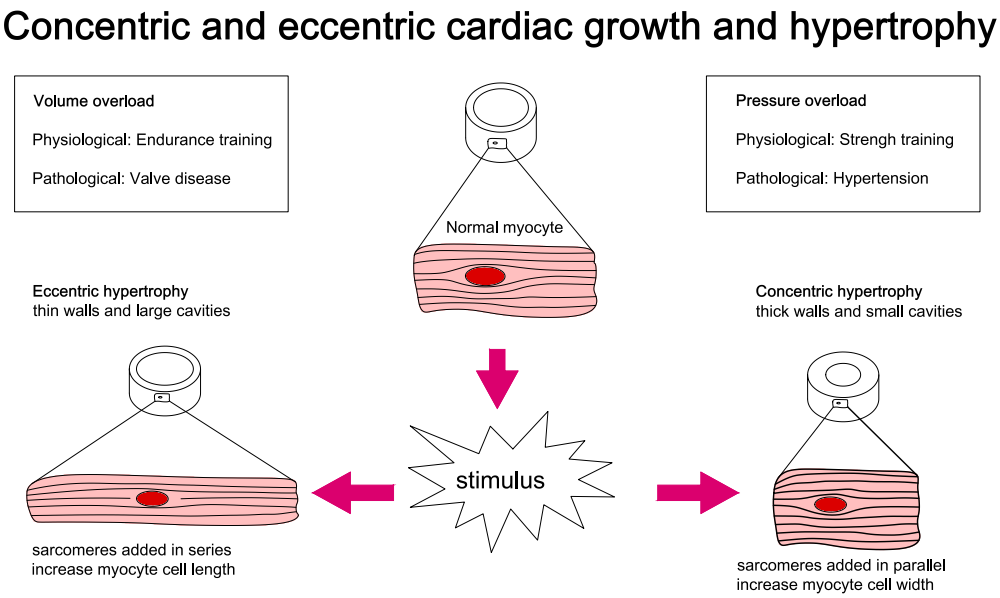

Fig. 2: Concentric and eccentric cardiac hypertrophy. Different forms of cardiac hypertrophy occur in response to pressure or volume overload. Pressure overload results in concentric hypertrophy, a condition characterized by the addition of sarcomeres in parallel which causes the thickening of the left ventricle wall. Volume overload triggers an increase of muscle mass via the addition of sarcomeres in series, a condition referred to as eccentric hypertrophy. Adapted from (Bernardo et al., 2010).

Concentric and eccentric cardiac hypertrophy in physiological settings

Concentric and eccentric cardiac hypertrophy can also result from physiological stimuli (Table 1; Fig. 2). In contrast to pathological conditions concentric cardiac hypertrophy can also arise from physiological stimuli such as weightlifting and wrestling (Fig. 2). This isomeric exercise trainings induce pressure load and concentric cardiac hypertrophy (Fig. 2). Compared to chronic pressure overload caused by pathological hypertension this form of concentric hypertrophy is milder and identified as not pathological (Bernardo et al., 2010). Physiological circumstances such as pregnancy and endurance training (Fig. 2) increase venous return to the heart. The increase in volume load promotes the

development of eccentric hypertrophy (Fig. 2). In this physiological setting of volume overload, individual cardiomyocytes grow in both length and width resulting in proportional changes in wall thickness and chamber enlargement. Thus, non-pathological eccentric hypertrophy appears in a less distinctive form compared to pathological disease setting (Dorn, 2007; Heineke and Molkentin, 2006).

1.4. Characteristics of physiological and pathological cardiac hypertrophy

"Physiological and pathological cardiac hypertrophy" is "associated with distinct molecular *characteristics (Table 1) involving alterations in the expression of fetal genes, contractile- and calcium-handling proteins"* (Nakamura and Sadoshima, 2018). *"A major molecular characteristic of pathological hypertrophy is the re-expression of fetal genes"* (Table 1). *"Pathological settings such as hypertension cause the induction of the stress program that involves increased expression of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and alpha-skeletal actin (α-sk actin)"* (Bernardo et al., 2010). *"In contrast, an important characteristic of physiological hypertrophy is the absence of molecular stress programs"* (Table 1) (Wilkins et al., 2004). *"In addition, cardiac contractile proteins such as alpha- and ß-myosin heavy chain and calcium-handling proteins, e.g., sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) remain unchanged during physiological cardiac hypertrophy, whereas pathological cardiac hypertrophy is closely associated with alterations in the above-named genes and proteins"* (Bernardo et al., 2010) (Bazgir et al., 2023).

"While the events associated with physiological hypertrophy are generally reversible, those associated with pathological cardiac hypertrophy are commonly irreversible and impose a high risk of heart failure (Table 1)" (Fig. 1). *"A common disease stimulus, such as long-standing hypertension usually causes pressure overload"* (Fig. 2) *"and increases systolic wall stress"* (Grossman et al., 1975; Huston and Shah, 2022). *"In this case, individual cardiomyocytes typically grow in width more than in length, leading to the thickening of the cardiac walls, a condition referred to as concentric hypertrophy"* (Fig. 2) (Dorn, 2007; Heineke and Molkentin, 2006). *"Hypertrophic changes have been rationalized employing Laplace´s law, which says wall stress (or tension) is an inverse function of wall*

thickness (tension= (pressure x radius)/ 2x wall thickness). Thus, compensated growth of the cardiac muscle" (Fig. 1) *"is a physiological response to decrease wall tension and thereby maintain cardiac pump function"* (Maillet et al., 2013). *"Prolonged pathological stress"* (Fig. 1), *"however, causes maladaptive changes at the cellular and molecular level resulting in pathological cardiac hypertrophy"* (Table 1; Fig. 1). *"Untreated pathological cardiac hypertrophy predisposes individuals to heart failure, arrhythmia, and sudden death"* (Berenji et al., 2005; Haider et al., 1998) (Bazgir et al., 2023).

Despite the extensive work on distinguishing between the cellular signaling pathways and axes associated with physiological and pathological hypertrophy, more attention needs to be paid to the complexity of cellular communication in the cardiac microenvironment in concert with changes in the signatures they influence. Following, the focus of this study is exclusively on pathological conditions.

2. Cardiac hypertrophy at the cellular level

Cardiac hypertrophy involves actions at the cellular and molecular level of cardiomyocytes and nonmyocytes (Oka and Komuro, 2008). Next to cardiomyocytes, the myocardium is composed of a variety of nonmyocytes comprising, amongst others, fibroblasts, endothelial cells, smooth muscle cells, and immune cells, which all respond to external and internal stress (Nag, 1980; Zak, 1973). As cardiomyocytes exhibit cellular hypertrophy that is accompanied by the reexpression of fetal genes, abnormal Ca2+ handling, oxidative stress, and necrosis or apoptosis that results in cardiomyocyte death (Oka and Komuro, 2008). The entire myocardium undergoes a complex structural remodeling process during cardiac hypertrophy and progression to heart failure that involves rearrangement of muscle fibers, accumulation of extracellular matrix (ECM), fibrosis, cellular death, and angiogenesis (Manabe et al., 2002).

2.1 Cardiomyocytes

Cardiomyocytes are the muscle cells of the heart which represent 30% of the total cells of the heart, however, they account for 70-80% of heart mass (Long, 1996). Generally, most mammalian cardiomyocytes lost their ability for cell

division shortly after birth and enter the G0 phase of the cell cycle. Adult cardiomyocytes are terminally differentiated cells and highly specified cells for the contraction function of the heart. Due to the lack of cell division in these cells, the enlargement of the heart in response to physiological or pathological stimuli (seen in cardiac hypertrophy) is mainly achieved by an increase in cardiomyocyte size rather than number (hyperplasia) (Anversa et al., 1986).

Equipped with contractile units called sarcomeres arranged in series cardiomyocytes are the contracting cells of the myocardium (Bernardo et al., 2010; Heineke and Molkentin, 2006; van Berlo et al., 2013). The contractile force is transmitted between adjacent cardiomyocytes through intercalated discs at their bipolar ends which at the same time ensure cell-cell adhesion. Embedded within the extracellular matrix alongside non-myocytes the fundamental function of cardiomyocytes is the simultaneous rhythmic contraction and thereby pumping blood throughout the circulatory system (Estigoy et al., 2009).

In the case of cardiac hypertrophy, cardiomyocytes undergo an adaptational process to increased hemodynamic stress caused by various factors (Anversa et al., 1986). Cardiomyocytes grow in response to an increased workload that initiates several events including activation of hypertrophic signaling pathways, changes in gene expression program, increase in protein synthesis, and rearrangement of sarcomeric units by integrating contractile proteins (Hoshijima, 2006; Knoll et al., 2003). Increased workload, injury, or intrinsic disease result in the initiation of hypertrophy-related signaling cascades and thereby activate the initially adaptive hypertrophied remodeling. Chronic hypertrophy due to constant pathological stress, however, shifts and exacerbates the initially adaptive remodeling and may result in end-stage heart failure (Teunissen et al., 2004).

One fundamental molecular feature of pathological hypertrophy within cardiomyocytes is the induction of the fetal gene program, which is not activated in normal physiological conditions (Wilkins et al., 2004). The activation of the fetal gene program results in the upregulation of ß-myosin heavy chain, alpha-skeletal-actin, alpha-smooth muscle actin, and atrial natriuretic peptide as well as downregulation of alpha-myosin heavy chain and the sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) (Dorn et al., 2003; McMullen and Jennings, 2007).

2.2 Cardiac fibroblasts

Fibroblasts represent one major group in cardiac tissue accounting for homeostasis under physiological conditions and tissue remodeling in response to stress stimuli (Gregor et al., 2014; Leask, 2015). 27% of all cardiac cells in mice and 64% in rats are Fibroblasts. In humans, non-cardiomyocytes (primarily Fibroblasts) are described to account for 72% of all cells (Banerjee et al., 2007; Vliegen et al., 1991).

Fibroblasts exhibit a specific morphology including a flat, spindle-shaped cell body with multiple processes, and an absent basement membrane (Baudino et al., 2006). During development, the source of the majority of resident cardiac fibroblasts is the embryonic proepicardial organ (Carmona et al., 2010; Snider et al., 2009). Cells out of the proepicardial and primitive epicardial tissue undergo epithelial-mesenchymal transition (EMT) becoming resident fibroblasts and further migrating into the myocardium. On-site they differentiate into interstitial fibroblasts, perivascular fibroblasts, and coronary SMCs (Epstein, 2010; Olivey et al., 2006). During pathological settings, such as cardiac hypertrophy, however, non-epicardial tissues are thought to be the source of a large proportion of cardiac fibroblasts. Noteworthy, one study found that in pressure overload-induced cardiac lesions, up to 70% of cardiac fibroblasts were derived from pathologically induced endothelial-to-mesenchymal transition (EndMT) (Zeisberg et al., 2007). Another study reported that pathological cardiac EndMT is also induced by diabetes (Widyantoro et al., 2010). In addition, during heart disease cells of hematopoietic origin have been reported as a major source of cardiac fibroblasts (van Amerongen et al., 2008; Zeisberg et al., 2007). Finally, activation of adult epicardium has been found to generate fibroblasts in the context of myocardial infarction (Zhou et al., 2011).

Fibroblasts play a central role in both physiological and pathological conditions of cardiac tissue. Due to the expression of extracellular matrix (ECM) receptors cardiac fibroblasts are capable of directly coupling mechanical stimuli into functional responses, thereby regulating the composition and stiffness of the ECM as well as fibrotic response (Gregor et al., 2014; Leask, 2015). Excessive extracellular matrix deposition by cardiac fibroblasts is a key component of heart failure as it leads to fibrosis and pathological cardiac remodeling (Banerjee et al.,

2006). Cardiac fibrosis is mediated by the recruitment of fibroblasts and is associated with deteriorating microvasculature and dysfunction of myocardial structures (Zeisberg et al., 2007). Thus, the development of cardiac fibrosis is tremendously driven by cardiac fibroblasts (Manabe et al., 2002). At the moment, reparative and reactive fibrosis are known as the two types of fibrosis that involve critical actions of cardiac fibroblasts. Reparative fibrosis is associated with cardiomyocyte death and is also characterized as replacement fibrosis. Reactive fibrosis on the other hand results in “interstitial” or “perivascular” fibrosis which is not linked to cardiomyocyte death directly (Anderson et al., 1979; Weber et al., 1989). Thus, cardiac fibroblasts and their central role in fibrosis affect the metabolism and performance of cardiomyocytes and in the end ventricular function (Porter and Turner, 2009). In addition, mechanical stress triggers the activation of cardiac fibroblast resulting in the production and release of bioactive mediators (MacKenna et al., 2000). Thus, the exact way cardiac fibroblasts contribute to cardiac hypertrophy is yet to be defined.

2.3 Cardiac endothelial cells

Endothelial cells (EC) are active players in cardiac physiology and pathology and by number one of the most abundant cell types in the heart (Gogiraju et al., 2019). The cavitary surface of all blood vessels and the heart is lined by endothelial cells which form a continuous monolayer. The Endothelium is equivalent in mass to five normal hearts and in area to half a dozen tennis courts per standard 70 kg man (Henderson, 1991). The heart exhibits two types of endothelial cells: vascular endothelial cells and endocardial endothelial cells. Endocardial endothelial cells line the cardiac cavities whereas all blood vessels are lined by vascular endothelial cells (Brutsaert and Andries, 1992). Vascular endothelial cells exert a critical role during the development of cardiac hypertrophy, remodeling, and failure (Esper et al., 2006). Furthermore, cardiac endothelial cells such as vascular endothelium cells express and release numerous auto- and paracrine substances and thereby communicate with cardiomyocytes. Notably, the secretion of autocrine, juxtacrine, and paracrine substances is used by all cells present in the myocardium to modulate function in neighboring cells (Segers et al., 2018). Besides, the interaction between cardiac endothelial cells

and cardiomyocytes is required for normal cardiac development and growth. Neuregulin, vascular endothelial growth factor (VEGF), and angiopoietin are among the various molecular mechanisms and cellular signals which control that interaction. In addition, these factors maintain the phenotype and survival of cardiomyocytes in the adult heart (Brutsaert, 2003).

Endothelial cells own the ability to produce numerous functional agonists and antagonists, comprising vasodilators and vasoconstrictors, procoagulants and anticoagulants, and inflammatory as well as anti-inflammatory factors. Under physiological conditions, endothelial cells control the balance of these mediators and thereby maintain homeostasis. Pathological conditions such as endothelial dysfunction disturb the balance of these mediators promoting pathological inflammatory processes (Esper et al., 2006).

2.4 Immune cells

It has been shown that by secretion of mediators such as cytokines and growth factors, immune cells in part promote cardiac remodeling (Hinglais et al., 1994; Nicoletti et al., 1996). Frieler and colleagues assumed in 2015 that cardiac injury is followed by a much earlier response of residents and recruited immune cells than thought before. Moreover, immune cells act before cardiac hypertrophy and remodeling, and changes continue throughout the major maladaptive hypertrophic modification that is followed by cardiac dysfunction and heart failure. One major function of immune cells includes their coordination of cardiomyocyte and non-myocyte action in maladaptive remodeling. Aside from cardiomyocyte function immune cells own a critical role as they affect cardiac function by influencing response to injury, in particular scar formation and interstitial fibrosis (Frieler and Mortensen, 2015). However, the role of inflammatory cells in the process of cardiac hypertrophy is yet to be defined.

2.4.1 Cardiac mast cells

First described by Paul Ehrlich, mast cells exert a critical role as multi-effector cells during inflammation (Bischoff, 2007; Mekori and Metcalfe, 2000). The bone marrow serves as a place of origin for mast cells where they arise from multipotent progenitor cells. To become mature mast cells, these precursor cells

have to migrate into several tissues (Kirshenbaum et al., 1999). Furthermore, restricted to peripheral tissues, mature mast cells do not circulate in the blood, but maintain the ability to proliferate (Galli, 2000; Marone et al., 2002). Especially, connective tissue-rich organs including lungs, cardiovascular tissues, gastrointestinal tract, skin, uterus, and prostate exhibit mast cells (Galli, 1993; Metcalfe and Boyce, 2006).

The protease enzymes tryptase and chymase serve as classifications of mature mast cells in humans resulting in tryptase-positive (MCt), chymase-positive (MCc), or tryptase and chymase-positive (MCtc) mast cells. Although, mast cell heterogeneity can be observed (Gurish and Boyce, 2006; Prussin and Metcalfe, 2006) tryptase and chymase positive mast cells (MCtc) represent 90% of the mast cells present in the heart (Weidner and Austen, 1993).

A study using posttransplant endomyocardial biopsies performed a quantitative analysis of mast cells and fibrosis. Here, they demonstrated that mast cells participate in interstitial and perimyocyte fibrosis of transplanted hearts through degranulation of release products that are toxic to the heart. In addition, the number of mast cells was shown to be critical for the volume of fibrosis, and detection of more severe rejection episodes was found related to increased mast cell numbers (Li et al., 1992). Thus, mast cells are critical players in various pathological processes including inflammation and cardiovascular complication such as arrhythmia and graft rejection (Balakumar et al., 2008). Plus, mast cells serve as a source of numerous mediators, including cytokines, growth factors, chemokines, proteases, and other mediators (Mekori and Metcalfe, 2000). Angiogenesis (Rakusan et al., 1990), formation of atrial natriuretic peptide (ANP) (Proctor et al., 1991) and angiotensin II (AT II) (Frangogiannis et al., 1998; Silver et al., 2004) are among the numerous physiological functions of cardiac mast cells. Beyond that mast cells have long been understood as cells with mainly inflammatory properties, but through the elaboration of several cytokines (e.g., IL-4, IL-8, TNF-a) in early 1990 it was becoming evident (Bradding et al., 1992; Moller et al., 1993; Walsh et al., 1991), that unlike originally thought, these cells might exhibit a more complex role (Galli, 1993; Marone et al., 1989). Consistent with several studies this suggests a significant role for mast cells in cardiac

hypertrophy and heart failure (Batlle et al., 2006; Hara et al., 2002; Joseph et al., 2003; Shiota et al., 2003).

2.4.2 Monocytes & macrophages

The healthy as well as the injured cardiac tissue exhibits a heterogenous population of macrophages and is found in both human and mouse hearts (Azzawi et al., 2005). Most macrophages within the heart are established embryonically from the yolk sac and fetal monocyte progenitors independent of bone-marrow-derived monocytes (Epelman et al., 2014). Although it is commonly accepted that circulating blood monocytes give rise to macrophages. Several studies demonstrated that mainly local proliferation serves to maintain tissue-resident macrophage numbers in a steady-state heart (Ginhoux et al., 2010; Hashimoto et al., 2013; Schulz et al., 2012; Yona et al., 2013). The surface expression of Ly6C and chemokine C-C motif receptor-2 (CCR2) divide the heterogenous monocyte subsets, comprising classical Ly6ChighCCR2high monocytes and non-classical Ly6ClowCCR2low monocytes (Geissmann et al., 2003). Ly6Chigh monocytes descend from Ly6CC progenitors in the bone marrow. Ly6Chigh monocytes are released into the blood, relying on the expression of CCR2 (Serbina and Pamer, 2006). Ly6Clow monocytes arise from Ly6Chigh monocytes through a nuclear receptor subfamily-4-dependent (NR4A1) transcriptional program (Hanna et al., 2011). In that context, as Ly6Clow monocytes/macrophages express more CX3CR1 than Ly6Chigh cells, the chemokine receptor CX3CR1 can be used to distinguish between different monocyte/macrophage populations (Geissmann et al., 2003; Geissmann et al., 2010). Moreover, during inflammation, the CX3CR1 contributes to cell recruitment via chemotaxis and mediates adhesion (Auffray et al., 2009; Hochheiser et al., 2013; Imai et al., 1997).

Several studies indicate that within the first week of pressure overload Ly6ChighCCR2high and Ly6ClowCX3CR1high monocytes and macrophages infiltrate hypertrophic hearts by using CCR2 and CX3CR1 (Liao et al., 2018; Patel et al., 2018; Patel et al., 2017; Weisheit et al., 2014; Weisheit et al., 2021). Other studies reported that almost always macrophages can be identified near collagen-producing Myofibroblasts (Leicester et al., 2004; Ramm et al., 1998;

Thompson et al., 2008), and according to others there is strong evidence for reciprocal interactions (Friedman, 2008). In addition, several actions including clearance of dead cells and debris, secretion of growth factors and cytokines, control of fibroblast activation, as well as protease production for degradation of ECM are among the regulatory actions of monocytes and macrophages (Kagitani et al., 2004; Ren et al., 2011; Wynn and Barron, 2010). Thus, inflammatory cells, especially cardiac macrophages can be considered major players driving fibrotic changes in the microenvironment of cardiac hypertrophy.

2.4.3 Neutrophils

The first responders to infection and injury and the most numerous circulating leukocytes in human blood comprise the neutrophil granulocytes (Kolaczkowska and Kubes, 2013), which have been described as innate immune cells that are readily mobilized, and thereby exert a major role in the defense of bacterial and fungal pathogens (Nathan, 2006). In addition, neutrophils have been implicated in the pathophysiology of myocardial ischemia, and reperfusion which is accompanied by microvascular and parenchymal injury (Engler, 1989; Lucchesi et al., 1989). Neutrophils are short-lived, terminally differentiated cells, with a lifespan that is generally measured in terms of hours and suggested blood circulation time of several days (Kennedy and DeLeo, 2009; Pillay et al., 2010; Summers et al., 2010). During homeostasis these cells continuously undergo replenishment, however infection or serious tissue injury is followed by an augmented provision, and then producing neutrophils involves almost the entire bone marrow. Several areas comprising macrophages in the liver, bone marrow stroma, and marginal zone of the spleen have been described to mediate the homeostatic removal of neutrophils from the circulation, which at the same time must match with production (Gordy et al., 2011; Summers et al., 2010).

Pattern recognition receptors (PPRs) on tissue-resident cells sense pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) during an infection or tissue damage, as well as recruit neutrophils via the production of chemokines such as CXCL1 and CXCL2 (Kolaczkowska and Kubes, 2013). Additionally, PAMPs and DAMPs may be implicated in the induction of recruitment as well as proinflammatory activation

via the direct activation of neutrophils (Hayashi et al., 2003). Thus, chemotactic factors which are presented in a temporally and spatial manner recruit neutrophils into injured tissues irrespective of existing infection (Billadeau, 2008; McDonald et al., 2010). Having arrived in tissues, neutrophils concomitantly mediate mononuclear cell activities and unleash a variety of substances such as reactive oxygen species (ROS) which potentially trigger further tissue injury (Nathan, 2006; Soehnlein and Lindbom, 2010; Soehnlein et al., 2009). Moreover, oxygen radicals, proteases, and arachidonic acid metabolites comprise the variety of cytotoxic products released by activated neutrophils (Engler, 1989; Lucchesi et al., 1989; Weiss, 1989).

Even though the view on cardiac hypertrophy development and progression to heart failure has traditionally been associated with hemodynamic and neurohormonal disorders, awareness has increased that inflammation also exerts a critical role (Kamo et al., 2015; Mann, 2002). Thus, these lines of evidence all indicate that neutrophils may also be involved in the pathophysiological processes occurring in the microenvironment of cardiac hypertrophy.

2.5 Sympathetic neurons

Central and peripheral components compose the sympathetic circuit, and the interface between these systems is represented by the peripheral sympathetic ganglia. The sympathetic chain exhibits postganglionic sympathetic neurons, which receive central inputs of cholinergic preganglionic spinal cord neurons located in the intermediolateral column, and in turn transmit to target structures including heart, kidneys, and vasculature in the periphery (Coote and Chauhan, 2016).

Sympathetic neurons densely innervate the heart by norepinephrine (NE) release and activation of ß-adrenergic receptors (ß-ARs). To match the blood flow requirements of peripheral organs, sympathetic neurons operate physiologically as a short-term enhancer of the heart rate, conduction velocity, and cardiac contractility (Sampson and Kass, 2010). Thus, the continuous functional adaption of the heart through acute (e.g., chronotropic, inotropic, and lusitropic) and chronic (i.e. regulation of gene expression) effects of neuronal inputs on target

cardiomyocytes is provided via myocardial sympathetic innervation ensuring optimal electrical and contractile performance (Franzoso et al., 2016; Larsen et al., 2016; Pianca et al., 2019; Prando et al., 2018; Shan et al., 2010; Zaglia et al., 2013).

Several cardiac diseases including myocardial hypertrophy, ischemia/infarction (MI), and heart failure involve a dysfunctional neurogenic control of cardiac activity. Increased incidences of arrhythmias comprise the characteristic of these disease conditions, which all are associated with the increased sympathetic drive or reduced sympathetic neuron transmission (Gardner et al., 2016; Hasan et al., 2006; Herring et al., 2019; Kaye et al., 2000; Kimura et al., 2007; Miyauchi et al., 2003; Schafers et al., 1998; Zhou et al., 2004). A critical role has been attributed to the sympathetic nervous system especially in the regulation of blood pressure, in which before hypertension onset increased sympathetic drive has been observed in human and animal models, respectively (Davis et al., 2020; Grassi et al., 2015). In addition, sympathetic neurons have been identified as active drivers changing the properties of cardiomyocytes (Larsen et al., 2016), and a study reported pathological hypertrophy in adult hypertensive SHR hearts (Bell et al., 2004). In conclusion, heart failure (Schwartz et al., 2015; Tu et al., 2014), post-myocardial infarction (Ajijola et al., 2015), and hypertension, both in humans (Esler et al., 2010; Grassi et al., 2015; Habecker et al., 2016; Joyner et al., 2008; Mancia and Grassi, 2014) and in the spontaneously hypertensive rat (SHR) (Heaton et al., 2007; Shanks et al., 2013) comprise conditions that share the common hallmark of cardiac sympathetic hyperactivity. Thus, increased norepinephrine (NE) release due to increased activity of cardiac sympathetic neurons seems to exert a central role in various cardiovascular diseases, and therefore needs consideration in the context of the microenvironment of cardiac hypertrophy.

3. Mediators and their corresponding intracellular signaling pathways

Mechanical stretch is an important cause of cardiac hypertrophy (Frey et al., 2004b; Ruwhof and van der Laarse, 2000). Besides mechanical loading, a range of mediators involved in cardiomyocyte hypertrophy has been identified comprising, amongst others, vasoactive peptides, catecholamines, growth

factors, and cytokines. The various hypertrophic mediators have been found to activate numerous different signaling pathways (Hefti et al., 1997). Thus, a key aspect of cardiac hypertrophy research relies on the investigation of signaling pathways, gene expression analysis, and production of certain proteins and transcription factors, that influence or are by some means accountable for cardiac remodeling (Stansfield 2014). *In vivo* experiments in the past were unable to distinguish between the relative contribution of a single mediator (Long, 1996). But, the use of primary cardiomyocyte cultures provided the platform for controlled studies where isolated cardiomyocytes can be treated with single or multiple factors (Piper et al., 1982). Fortunately, the in vitro modeling of cardiac hypertrophy for further pathway analysis has vastly improved over the recent years and many signaling pathways have been identified to play major roles during physiological as well as pathological cardiac hypertrophy development (Kastner et al., 2020).

3.1 Growth factors

The five growth factors EGFs, FGFs, IGFs, PDGFs, and TGFs comprise the classic peptide growth factor family. Each family in turn has multiple members with individual properties, such as induction of cell growth and proliferation. Already in 1996 Long found that FGF, TGFß, IGF, and PDGF induce cardiac hypertrophy in *vitro* systems (Long, 1996).

3.1.1 Transforming growth factor-ß (TGF-ß)

TGF-ß-1, TGF-ß-2, and TGF-ß-3 comprise the three isoforms of TGF-ß and, all exhibit distinct but overlapping functions in immunity, inflammation, and tissue repair. In addition, TGF-ß exerts a central role in the activation of fibroblasts and further differentiation into myofibroblasts (Leask and Abraham, 2004). Bound to a latent TGF-ß binding protein (LTBP), TGF-ß is initially produced as a latent complex within the interstitium. Altered pH physiochemically activates TGF-ß as well as proteases, enzymes, and integrin-mediated mechanisms (Hyytiainen et al., 2004; Munger et al., 1999). The three forms of TGF-ß bind to three types of receptors found in most mammalian cell types. Interestingly, no signaling function was found concerning the type III receptors (Brand and Schneider, 1995).

Notably, the type-I and the type-II receptors are distantly related to serine/threonine kinases (RSTK). Once activated, the binding of TGF-ß by the primary receptor (type-II) further enables it to bind to the type-I receptor. In this heterodimeric complex, the type-II receptor phosphorylates the type-I receptor leading to signal transduction (Massaous and Hata, 1997). The TGF-ß type-I receptor (TGF-ßR1) in turn phosphorylates receptor-regulated Smads (R-Smads: Smad2 and Smad3) that further associate with a common mediator Smad (co-Smad: Smad4). This complex translocates into the nucleus, associates with DNA binding proteins, and becomes active as a transcription factor (Yoshimura et al., 2010).

Locally generated, TGF-ß has been linked to tissue proinflammatory processes as a major stimulator (Border and Noble, 1994). Noteworthy, several studies in the past found increased expression of myocardial TGF-ß in cardiac hypertrophy and fibrosis (Takahashi et al., 1994; Tomita et al., 1998; Villarreal and Dillmann, 1992).

3.1.2 Fibroblast Growth Factor (FGF)

The two prototypes of the FGF gene family are FGF-1 (aFGF) and FGF-2 (bFGF). To direct their secretion through membranes, neither FGF-1 nor FGF-2 use a classic signal sequence (Friesel and Maciag, 1995). Assumedly, the prototype FGFs form disulfide-bonded homodimers for secretion and it seems that exocytosis is involved (Bastagli et al., 1995). All FGFs associate with the extracellular matrix at the outer cell surface especially with glycosaminoglycan heparin and heparan sulfate proteoglycan. This provides a potential storage site and, upon injury or activation of matrix-degrading enzymes, FGFs may be released. FGF-1 and FGF-2 exhibit identical effects; however, FGF-1 is found to be 30-100 times less potent. In addition, both are found in cardiomyocytes and non-myocytes within the heart (Kardami and Fandrich, 1989).

All FGFs mediate their biological functions through transmembrane tyrosine kinase receptors (RTKs) (Szebenyi and Fallon, 1999). The FGF receptor-1 (FGFR-1) is the predominant receptor present in the heart (Hughes, 1997; Liu et al., 1995; Sugi et al., 1995). Noteworthy, during normal cardiac development, the presence and functioning of the FGFR-1 receptor is essential (Mima et al., 1995).

In the adult heart, although, FGFR-1 expression persists at reduced levels (Liu et al., 1995). Consistent to present cell surface receptors is the presence of FGF-2 which implies release into the extracellular milieu. FGF-2 release appears regardless of any absent classical hydrophobic export signal peptide (Szebenyi and Fallon, 1999). Possible mechanisms for releasing FGF-2 may involve Na+/K+ ATPase (Florkiewicz et al., 1998; Mignatti et al., 1992; Oh and Lee, 1998) and/or passive processes (Bikfalvi et al., 1997).

FGF-2 was found, despite its name, to influence various cellular functions in different cell types including cell proliferation, differentiation, survival, adhesion, migration, motility and apoptosis, and processes such as limb formation, vasculogenesis, wound healing, tumorigenesis, angiogenesis, and blood vessel remodeling (Szebenyi and Fallon, 1999). In cardiomyocytes, FGF-2 induces DNA, RNA, and protein synthesis and exerts potent cardioprotective functions (Detillieux et al., 2003).

FGF-2 has also been linked to undesirable effects including induction of cardiac hypertrophy in response to AT-II administration and pressure overload in animal models (Kardami et al., 2004).

The single Fgf2 gene is alternatively translated as a high molecular weight (Hi-FGF-2) and a low molecular weight (Lo-FGF-2) isoform (Liao et al., 2009). The Lo-FGF-2 (18 kDa) or Hi-FGF-2 (21-23 kDa in rat and mouse (Pasumarthi et al., 1996); in human 21-34 kDa (Touriol et al., 2000)) result from alternative translation from the same messenger RNA from downstream conventional methionine (AUG) or upstream leucine (CUG) sites (Florkiewicz and Sommer, 1989). Due, to its nuclear localization sequence the Hi-FGF-2 isoform is localized predominantly in the cell nucleus, whereas the Lo-FGF-2 isoform is found in the cytoplasm and the ECM (Liao et al., 2009). To date, especially cardiovascular studies focused on the role of Lo-FGF-2 as it has been believed that only the Lo-FGF-2 isoform can exit the cell and activate the transmembrane tyrosine kinase FGF-2 receptor (Detillieux et al., 2003; Kardami et al., 2004). However, according to reports the Hi-FGF-2 isoform may be released into the extracellular matrix (Piotrowicz et al., 1997; Taverna et al., 2003).

3.1.3 Receptor tyrosine kinase signaling (RTK signaling)

Growth factors, with exception of TGF-ß and IGF-II, bind to transmembrane receptor tyrosine kinases (RTKs) (Ullrich and Schlessinger, 1990). Binding of FGF, EGF, and PDGF to RTKs results in receptor dimerization. Thereby, the two cytoplasmic domains can cross-phosphorylate each other on multiple tyrosine residues (Heldin, 1995). Enzyme-linked receptors with a single transmembrane domain are generally activated by dimerization. Various intracellular signaling proteins bind to high-affinity binding sites represented by autophosphorylated tyrosine. Despite varied structures and functions, these proteins usually share two non-catalytic modular binding domains that are highly conserved. Since they were first discovered in a tyrosine kinase encoded by the Rous sarcoma virus oncogene Src these binding domains are termed SH2 and SH3 (for Src homology). All of these proteins bind to specific phosphorylated sites on the activated receptor, detecting surrounding features of the polypeptide chain, concomitant to the phosphotyrosine (Cohen et al., 1995).

3.2 Vasoactive hormones and catecholamines

Anabolic responses and cardiomyocyte growth reportedly result from circulating vasoactive peptides (AT II and ET-1) and catecholamines. Each mediator binds to its specific receptor that belongs to the G-protein linked superfamily of homologs heptahelical transmembrane proteins. Composed of an a-, ß- and y-subunit, G-proteins represent a large family of heterotrimeric GTP-binding regulatory proteins and comprise Gq, Gi, and Gs (Gudermann et al., 1996).

3.2.1 Angiotensin-II (AT II)

AT-II as the main effector molecule of the renin-angiotensin system is accountable for pressure and volume homeostasis (Bernstein and Berk, 1993). The kidney synthesizes and secretes renin into the blood, in turn, renin hydrolysis the decapeptide angiotensin-I (AT-I) from the N-terminus of angiotensinogen. The carboxypeptidase angiotensin-converting enzyme (ACE) converts AT-I into the octapeptide AT-II (Fig. 3). Notably, within the human heart a chymotrypsin-like protease (chymase) has been identified, and though to represent the main pathway for converting AT-I into AT-II (Urata et al., 1990).

AT-II is a pleiotropic vasoactive substance that exerts indirect and direct physiological activities on cardiac tissue. The indirect effects of AT-II combine a variety of local and systemic actions including stimulation of vasoconstriction, an increase of aldosterone secretion, central sympathetic outflow enhancement, catecholamine release from the adrenal medulla, and promotion of vasopressin release (Timmermans et al., 1993. AT-II binds to its specific cardiomyocyte plasma membrane-bound receptor coupled to guanine nucleotide-binding proteins and thereby directly affects cardiac function (Baker and Aceto, 1989; Baker et al., 1984; Baker and Singer, 1988). The Gq-coupled AT-II type 1 receptor (AT1) is the primary signaling pathway of AT-II (Touyz and Schiffrin, 2000). According to reports, the AT1 receptor is upregulated in hypertrophic and ischemic conditions (Lambert et al., 1995; Meggs et al., 1993; Suzuki et al., 1993a), and found downregulated in end-stage human heart failure (Regitz-Zagrosek et al., 1995; Rogg et al., 1996). It has been suggested that prolonged elevated levels of AT-II found in cardiac hypertrophy and during heart failure may be in part accountable for the AT1 receptor downregulation (Makita et al., 1992; Regitz-Zagrosek et al., 1997). Consequential, AT-II stimulates short- and long-term effects including positive chronotropic and inotropic effects, protein synthesis (Dostal et al., 1992), and has hypertrophic effects on cardiomyocyte and is considered to be a growth factor (Timmermans et al., 1993. Even though most of the cardiovascular effects of AT-II are mediated through the AT1 receptor various other receptor subtypes have been identified and supposedly the AT-II type 2 receptor (AT2) may as well be important, as both are upregulated in numerous cardiac diseases. Beyond, AT-II exerts influence on cardiac non-myocytes resulting in the development of cardiac fibrosis and remodeling (Lopez et al., 1994; Suzuki et al., 1993a; Tsutsumi et al., 1998).

3.2.1.1 The renin-angiotensin-system (RAS)

Much evidence indicates that the renin-angiotensin system (RAS) exists in two distinct forms: a circulating and a local system in multiple organs and that local tissue RAS inherits a central role in organ damage including cardiac hypertrophy. Angiotensinogen, renin, ACE, AT1, and AT2 comprise the major components of

the classical RAS, and all are expressed in the heart (Fig. 3) (Baker et al., 1992; Lee et al., 1993).

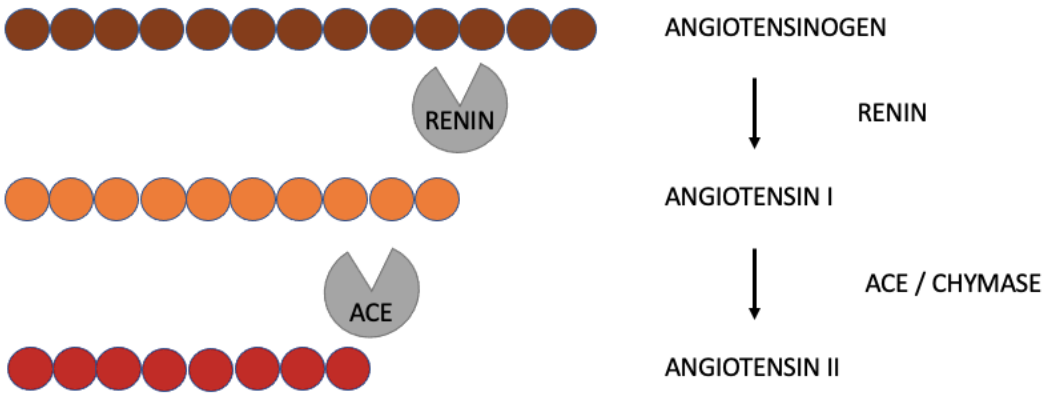

Fig. 3: The Renin-Angiotensin-System (RAS) exists in two distinct forms: a circulating and a local system in multiple organs. The local tissue RAS inherits a central role in organ damage including cardiac hypertrophy. All major components of the classical RAS are expressed in the heart such as angiotensinogen, renin, ACE, AT1, and AT2. In addition, the protease chymase represents another pathway for converting AT-I into AT-II within the human heart. Adapted from (Bader, 2010).

It has been found that AT-II causes hypertension and cardiac hypertrophy via angiotensin receptors in the kidney (Crowley et al., 2006). Consistent, another study found that AT-II is causing end-organ damage known as heart failure and renal failure in hypertension (Siragy, 2008). In addition, AT-II has long been recognized to promote cardiac hypertrophy (Dostal and Baker, 1992) and remodeling (Pfeffer et al., 1997) and has led to the use of angiotensin-converting enzyme inhibitors (Pfeffer et al., 1992) and AT 1 receptor antagonists (Pitt et al., 1997) in patients with myocardial infarction and heart failure. Other clinical studies demonstrated in addition to a decrease in blood pressure, effective reduction of cardiac fibrosis and remodeling through blockade of the renin-angiotensin system in patients (Hoogwerf, 2010).

Thus, the treatment of hypertension and associated end-organ damage with ACE inhibitors and angiotensin receptor blockers (ARBs) seems to be beneficial. Albeit, renal and cardiac failure seem to progress, indicating incomplete blockade of RAS by current treatment regimes. Local AT-II synthesis, extracellular or intracellular, could be accountable for incomplete blockade of RAS by ARBs and ACE inhibitors resulting in disease progress (Kumar et al., 2007).

3.2.2 Endothelin-1 (ET-1)

Three structurally similar peptides comprise the endothelins, and all exhibit a length of 21 amino acids. Endothelin receptor type A (ET_A) and endothelin receptor type B (ET_B) become activated with equal affinity by endothelin 1 (ET-1) and ET-2, while ET-3 has a lower affinity for ET_A (Dhaun and Webb, 2019). Participation of the endothelin system has been described in cardiac physiology and pathology, respectively. In addition, the predominant cardiac endothelin is ET-1, which is produced by a variety of cells, comprising cardiomyocytes, endothelial cells, and cardiac fibroblasts (Gray et al., 1998; Sakai et al., 1996; Yanagisawa et al., 1988), although the main sources of ET-1 are vascular endothelial cells (Kohan et al., 2011). Besides, cardiomyocytes and fibroblasts both exhibit the ET_A and ET_B receptors, but 90% of the endothelin receptors on cardiomyocytes comprise the ET_A subtype (Fareh et al., 1996; Sakai et al., 1996). Plus, in rat hearts, the ET_A receptor is predominant as well and identified to be coupled to both the Gq and Gi subfamily of G-proteins (Hilal-Dandan et al., 1994). Originally, identified as a vasoconstricting factor in 1988 (Yanagisawa et al., 1988), ET-1 has been found to mediate hypertrophic, fibrotic, pro-inflammatory, and inotropic actions, and thereby contributes to heart failure development (Gray and Webb, 1996). Noteworthy, it has been reported that the expression of the precursor of ET-1, prepro-ET-1, is increased in the process of hypertension-induced progression of cardiac dysfunction in hypertrophied hearts (Koyanagi et al., 2008). In addition, studies with patients and animal models reported increased ET-1 levels in circulation and tissue of failing hearts that correlate with the severity of the disease (Lerman et al., 1992; Loffler et al., 1993). Beyond, chronically elevated levels of GPCR agonists ET-1 and AT-II have been found in diseases, including the myocardium (Francis et al., 1990; Yorikane et al., 1993). Thus, the primary involvement of Gq-protein coupled receptor (GPCR) signaling can be considered a key characteristic of pathological hypertrophic responses (Clerk et al., 2007; Frey and Olson, 2003; Heineke and Molkentin, 2006; Moreira-Goncalves et al., 2015).

3.2.3 Catecholamines

For a long time, catecholamines are considered to play an active role in the development of both physiological and pathological cardiac hypertrophy (Bristow, 2000. The sympathetic nervous system is connected with the cardiovascular system *via* adrenergic receptors (ARs), which exert an essential regulatory role regarding myocardial function. In addition, ARs are members of G protein–coupled receptor (GPCR) superfamily (Hein and Kobilka, 1997). The three major AR subfamilies comprise α1-AR, α2-AR, and β-AR. The mammalian heart exhibits at least 6 types of ARs (three α1-AR: α1A, α1B, α1D and three β-AR: β1, β2, and β3). Notably, the ß1-ARs are predominating, and account for approximately 80% of total ß-ARs in the healthy heart (Barki-Harrington et al., 2004; Salazar et al., 2007; Woodcock et al., 2008; Xiang and Kobilka, 2003). ARs have been described to couple to Gαq, Gαs, and Gαi, thereby modulating adenylyl cyclase (AC), phospholipase C (PLC), and ion channels (Rockman et al., 2002). In particular, Gαq signaling is activated *via* α1A, α1B, and α1D-ARs, β1-ARs are coupled to Gαs, and β2-AR activate both Gαs and Gαi (Exton, 1985; Garcia-Sainz et al., 1999; Rockman et al., 2002).

The receptors that couple to Gαs primarily signal *via* AC thereby regulating contractility. It has been found that chronically activated Gαs signaling pathways result in cardiac hypertrophy, fibrosis, and heart failure. In addition, cardiac-specific Gαs overexpressing transgenic mice show increased heart rate and contractility in response to catecholamine stimulation, however, eventually display cellular hypertrophy, fibrosis, and necrosis as histological evidence of myocardial damage development (Gaudin et al., 1995; Iwase et al., 1996). In addition, α1-ARs are coupled to Gαq signaling, and thereby activate an extensive spectrum of signaling pathways comprising, amongst others PLC, protein kinase C (PKC), Ca^{2+} channels, and MAPK (Piascik and Perez, 2001). Furthermore, in animals, cardiomyocyte hypertrophy is stimulated through chronic activation of α1-AR and β-AR. The model of choice to study the signaling pathways involved in hypertrophy stimulation *via* α1-AR and β-AR has been neonatal rat ventricular myocytes (Adams and Brown, 2001; Simpson, 1983). Thus, the signaling pathways in the process of inducing hypertrophy *via* activation of α1-AR are complex and seem to involve activation of extracellular signal-regulated protein

kinase (ERK) and PI3K through Gq, PKC, and Ras, as well as activation of calcineurin through Ca^{2+} and calmodulin. Both pathways activate transcription factors followed by changes in gene expression (Clerk and Sugden, 2000; Sugden, 2001). Moreover, elevated catecholamines plasma levels and increased adrenergic drive can be identified in heart failure patients, a condition that is initially beneficial as it increases contractility. But, the prolonged adrenergic drive has detrimental effects whereby ß-adrenergic receptors desensitize and become downregulated (Bristow, 2000). Norepinephrine concentrations found in failing human hearts show that is exceptionally cardiotoxic as it is involved in cardiomyocyte injury. Additionally, the cytotoxicity appears to be mediated through ß-adrenergic receptors rather than a-adrenergic receptors as norepinephrine is mildly ß1-receptor selective (Mann et al., 1992).

Thus, cardiac hypertrophy and cardiomyocyte apoptosis is promoted via chronic catecholamines stimulation, which also leads to reduced contractility (Xiang and Kobilka, 2003). Aside from that, a reduction of βAR contractile responsiveness as well as increasing Gαi signaling has been identified as a hallmark of heart failure (Tilley and Rockman, 2006).

3.3 G-protein coupled Receptor signaling

G proteins can be divided into two main subgroups: heterotrimeric G proteins and small-molecular-weight monomeric G proteins (small G proteins).

3.3.1 Heterotrimeric G proteins

Heterotrimeric G proteins consist of three subunits (α, β, and γ) and couple to GPCR. The binding of an agonist to the GPCR leads to the dissociation of the Gα and Gβγ subunits, followed by the activation of downstream signaling pathways (Gutkind, 1998; Rockman et al., 2002). Isoforms of the heterotrimeric G proteins are largely determined by the isoform of the α subunits: Gs, Gi, and Gq (e.g., Gαq, Gα11) (Neer, 1995; Simon et al., 1991). In particular, the vasoactive peptides, Angiotensin II (Ang II), endothelin 1 (ET-1), and catecholamines bind to seven-transmembrane receptors that are coupled to and activate heterotrimeric G proteins (GPCR). The ligand-bound GPCRs thereupon stabilize in an active conformation and through their intracellular domains

stimulate heterotrimeric guanine nucleotide-binding regulatory proteins (G-proteins). Notably, GPCRs lack catalytic activity, but the dissociation of G proteins into Gα and Gßy subunits is promoted by the interaction of the receptor with an agonist. In turn, the Gα and Gßy subunits amplify downstream signals by modulation of effector molecules, including phospholipases, adenylyl cyclizes, and ion channels (Clapham and Neer, 1997. These active effector enzymes and ion channels furthermore regulate second messenger molecule production that induces different signaling pathways and cellular responses (Molkentin and Dorn, 2001).

The ligands Angiotensin II (AT-II), endothelin 1 (ET-1), and catecholamine norepinephrine (NE) bind to GPCR: Ang II receptor type 1 (AT1 receptor), endothelin receptors (ETA and ETB) and α1-adrenergic receptors (ARs), respectively. This causes activation of Gαq/11 and downstream signaling proteins, including phospholipase C (PLC), MAPKs, PKC, and protein kinase A (PKA) (D'Angelo et al., 1997; Mende et al., 1998). In particular, Gq/11 signaling activates phospholipase C (PLC), which catalyzes the synthesis of inositol 1,4,5-triphosphate (Ins(1,4,5) P3) and DAG (van Berlo et al., 2013). The production of Ins(1,4,5)P3 induces intracellular Ca2+ release to then activate calcium/calmodulin-dependent protein kinase (CaMK) or calcineurin, which mediates cardiomyocyte growth. As calcium-dependent protein phosphatase, Calcineurin dephosphorylates the nuclear factor of activated T cells (NFAT) transcription factors. Dephosphorylated NFAT in turn relocates into the nuclear to form complexes with cofactors such as GATA4 or myocyte enhancer factor-2 (MEF-2). These complexes further transactivate the transcription of hypertrophic target genes that are known to be maladaptive (Heineke and Molkentin, 2006). Interestingly, the critical role of Gaq/11 signaling in mediating pathological cardiac hypertrophy has been highlighted by transgenic mouse studies. Here, cardiac hypertrophy associated with cardiac dysfunction and premature death was developed by cardiac-specific transgenic mice overexpressing Gaq (D'Angelo et al., 1997; Mende et al., 1998. Other studies revealed that using mice lacking G-proteins (Gaq11) in cardiomyocytes and cardiac-specific transgenic mice expressing an inhibiting peptide specific for Gq-coupled receptor signaling show

no hypertrophy or the response to pressure overload was relevantly attenuated (Akhter et al., 1998; Wettschureck et al., 2001).

The catecholamines norepinephrine and adrenaline can also induce protein kinase A (PKA) via activation of adenylyl cyclase (AC) signaling resulting in increased cardiomyocyte apoptosis and necrosis (Heineke and Molkentin, 2006). Gαs stimulates adenylyl cyclase as a consequence of ß-AR activation, whereas activation of α1-AR stimulates effector phospholipase C through G αq. Thus, different G-protein complexes involve different effector molecules in cells for transmitting signals (Molkentin and Dorn, 2001).

3.3.2 Small G proteins (GTPases)

The family of small G proteins can be subdivided into 5 groups including Ras, Rho, ADP ribosylation factors, Rab, and Ran) (Aikawa et al., 1999; Aoki et al., 1998; Chiloeches et al., 1999; Clerk et al., 2001; Clerk and Sugden, 2000; Ramirez et al., 1997). Small G proteins, e.g., Ras act as molecular switches that link receptors to downstream signaling cascades. Ras, like the other monomeric and trimeric G-proteins, cycles between two conformational states where it is active when GTP is bound and inactive when GDP is bound. The activity of Ras and its relatives is regulated by two classes of signaling proteins that influence the transition between either active or inactive state (Boguski and McCormick, 1993). Inactivation of Ras is brought about by hydrolysis of bound GTP by GTPase activating proteins (GAPs). In contrast, guanine nucleotide exchange factors (GEFs) promote the exchange of bound GDP for GTP and thereby activate Ras (Sun and Tonks, 1994).

Ras and Rho have been implicated in the development of cardiac hypertrophy and can be activated in cardiomyocytes in response to mechanical stress as well as binding of AT-II, ET-1, and phenylephrine (PE) (Aikawa et al., 1999; Aoki et al., 1998; Chiloeches et al., 1999; Clerk et al., 2001; Clerk and Sugden, 2000; Ramirez et al., 1997). Already in *1994, Abdellatif et al.* suggested that Ras activity regulates “the basic transcriptional machinery” in the ventricular muscle (Abdellatif et al., 1994). In addition, it was shown that cardiac-specific transgenic mice developed pathological cardiac hypertrophy when expressing a constitutively active form of Ras or over-expressed Rab1a (Hunter et al., 1995;

Wu et al., 2001). Furthermore, it was shown that Rho-kinase was significant for pressure overload-induced pathological cardiac hypertrophy in rats but not in swimming-induced physiological cardiac hypertrophy using the Rho kinase Inhibitor Fasudil (Balakumar and Singh, 2006).

Thus, Ras is known to activate multiple signaling pathways. Molecules that transmit signals after interaction with GTP-bound Ras are referred to as Ras effectors (Marshall, 1996). Through interaction on a particular site on Ras, each of these effectors may be activated by Ras-GTP. In particular, PI3K seems to be one of these effectors (Feig et al., 1996).

3.4 PI3K(p110y) signaling

The PI3K(p110y) appears to have detrimental effects on the heart and, in contrast to the p110α (coupled to RTKs), the isoform is coupled to GPCRs comprising Gαs/Gαi/Gαq, e.g. adrenergic receptors, AT-II receptors, and ET-1 receptors (Oudit et al., 2004). Interestingly, the enhanced contractile function was found in experimental setups using PI3K(p110y) knockout mice. This led to the belief that PI3K(p110y) is a negative regulator of cardiac contractility (Crackower et al., 2002). In addition, another study using chronic ß-AR activation showed that PI3K(p110y) knockout mice were protected from heart failure, displaying less hypertrophy, fibrosis, and a better cardiac function compared to controls (Oudit et al., 2003). Furthermore, it is speculated that cardiomyocyte contractility is reduced by PI3K(p110y) through regulation of the activity of phosphodiesterase's (PDEs) (Kerfant et al., 2007; Patrucco et al., 2004). Thus, the second messenger cAMP mediates Ca2+ release from the sarcoplasmic reticulum in turn inducing contraction. It is known that PDE hydrolysis cAMP and therefore using a PDE inhibitor increases intracellular cAMP levels that in turn improve contractile function. However, the safety of therapeutic strategies using PDE inhibitors in heart failure patients is yet to be investigated (Osadchii, 2007).

3.5 MAPK signaling in cardiac hypertrophy

Initiating of the MAPK signaling cascade in cardiomyocytes is brought about activation of GPCRs, receptor tyrosine kinases (IGF-1, fibroblast growth factor receptors), receptor serine/ threonine kinases (transforming growth factor-ß

(TGF-ß)), cardiotropin-1 (gp130 receptor), and by stress stimuli such as stretch (Sugden and Clerk, 1998b). For example, signal transmission from Ras to the nucleus involves a relay system of three distinct cascades of protein phosphorylation. Each cascade again has three levels of defined reactions: (1) MAPKKKs phosphorylate MAPKKs on serine threonine residues; (2) MAPKKs are dual-specificity protein kinases that phosphorylate the MAPKs on threonine and a tyrosine residue in a *Thr-X-Tyr* motif; and (3) once activated, the MAPKs phosphorylate serine or threonine residues in numerous nuclear and extranuclear substrates (Denhardt, 1996; Seger and Krebs, 1995). Phosphorylation in a distinct motif defines the three mammalian MAPK families. The motifs comprise *Thr-Glu-Tyr* for the extracellular signal-regulated kinase (ERKs), *Thr-Phe-Tyr* for the c-jun amino-terminal kinase (JNKs), and *Thr-Gly-Tyr* for the p38/MAPKs (Treisman, 1996). Once activated, ERKs, JNKs, and p38 further phosphorylate downstream targets, comprising multiple transcription factors that in turn induce reprogramming of cardiac gene expression. The two MAPK kinases (MAPKK) MEK1 and MEK2 function as upstream activators of ERK1 and ERK2 by directly phosphorylating a dual site in the ERK kinases activation loop. MKK4 and MKK7 directly activate JNKs, whereas the MAPKKs MKK3 and MKK6 directly activate p38 kinases. In addition, MEK5 directly activates ERK5 (Garrington and Johnson, 1999). A complex network of several MAPKK kinases (MAPKKK) upstream of the MAPKKs sense stress signals differently. MAPKKKs can sense stress directly or become regulated by small G-proteins such as Ras, Rho, Rac, and CDC42 or MAPKKK kinases (Yamamoto et al., 2003).

Numerous studies using cultured cardiomyocytes showed that in response to the binding of agonists to GPCRs, (that couple to Gαq: Angiotensin-II type 1 receptor, endothelin-1 receptors, and α1- adrenergic receptors) all three MAPKs are activated. In addition, ERK, JNK, and p38/MAPK are activated in cultured cardiomyocytes by mechanical stress and pressure overload, as well as in failing human hearts (Cook et al., 1999; Esposito et al., 2001; Komuro et al., 1996; Pearson et al., 2001; Purcell et al., 2007; Sadoshima et al., 1995; Sugden and Clerk, 1998a; Takeishi et al., 2001; Yamazaki et al., 1993). Thus, the role of Ras, Ras effectors, and the molecules of the MAPK cascade in cardiac signal

transduction has been addressed by numerous studies (Abdellatif et al., 1994), but the exact role of MAPKs has remained unclear.

3.5.1 ERK1/2 – essential regulators in hypertrophy

A series of cytosolic and nuclear substrates is phosphorylated by ERK protein kinases (Chen et al., 2001). In a study by Clerk et al in response to agonists known to induce pathological heart growth (AT-II, ET-1, and NE), ERK 1/2 was activated. In contrast, in response to IGF1 as a mediator of physiological cardiac hypertrophy, no activation was found (Clerk et al., 2006). In addition, stimulation of isolated cardiomyocytes with hypertrophic agonists that signal through Gq protein-coupled receptors showed that ERK 1/2 activation was crucial for protein synthesis which is a known requirement for cell growth (Wang and Proud, 2002). According to these findings, another study implicated ERK 1/2 in the development of cardiac hypertrophy since using mice subjected to pressure overload and with the expression of a dominant negative mutant of Raf-1 (a MAPK kinase kinase downstream of Gαq) found that cardiac hypertrophy was attenuated (Harris et al., 2004). But, a physiological rather than pathological phenotype was found in transgenic mice that expressed a cardiac-specific constitutively active MAPK kinase 1 (MEK1). These mice developed concentric cardiac hypertrophy with enhanced systolic cardiac function and no interstitial fibrosis. This phenotype is conformable with the physiological form of compensated hypertrophy and so far, has not been described to turn into heart failure (Bueno et al., 2000). In contrast to compensated hypertrophy in vivo induced by MEK1-ERK1/2, pathological cardiac remodeling, and premature death occurred when the upstream regulator of this pathway, Ras, was overexpressed (Hunter et al., 1995). Ras can directly activate Raf-1 that in turn activates MEK1-ERK1/2. Additionally, Ras can also activate the JNK as part of another MAPK cascade branch, the PI3K, as well as other intracellular signaling pathways (Molkentin and Dorn, 2001). Thus, numerous settings of cardiac hypertrophy and failure found activation of ERK1/2 (Muslin, 2008. But, yet it remains unclear whether ubiquitously expressed ERK 1/2 (Boulton et al., 1991) is a critical mediator of hypertrophic responses (Muslin, 2008).

3.6 Sensing biomechanical stress signals

Next to ligand-receptor interactions at the cell membrane that further initiate signaling events, cardiomyocytes exhibit an internal sensory apparatus that enables them to directly detect mechanical deformation or stretch. The conversion of mechanical forces into biomechanical signals is the fundamental process of Mechanotransduction. Integrins represent one such apparatus linking the extracellular matrix to the intracellular cytoskeleton (Ross and Borg, 2001).

Comprised of an α and ß subunit, Integrins are plasma membrane-spanning heterodimers binding extracellular matrix components including fibronectin, collagen, or laminin. Through signaling proteins that reside within the focal adhesion complex inside the cell, the ß subunit can transmit information with the cytoplasmic tail comprising composition and stretching of the extracellular matrix. Non-receptor tyrosine kinases such as focal adhesion kinase (FAK) or integrin-linked kinase (ILK) compose integrin-associated complexes that in turn recruit signaling proteins including Rho GTPases, PI3K, and protein kinase C (PKC) (Johnston et al., 2009; Shai et al., 2002) as well as other downstream effectors such as Ras (Ross and Borg, 2001). Studies using a cardiac-specific ablation of Itgb1 (known to be responsible for encoding the ß1 subunit) or a global deletion of Itgb3 (encoding for ß3 subunit) found exacerbated hypertrophic diseases when induced by pressure overload (Johnston et al., 2009; Shai et al., 2002). In addition, another study implicated melusin, an integrin-interacting molecule, as a sensor of mechanical stress in cardiomyocytes (Brancaccio et al., 2003).

Furthermore, at the level of the cardiac Z-disc within each sarcomere, another sensing apparatus has been described. Anchored to specific proteins at the Z-disc and through a complex of transducing proteins, the small LIM-domain protein MLP (muscle LIM protein) in particular, is thought to function as an internal stretch sensor (Knoll et al., 2002). In particular, melusin was found to be crucial for the phosphorylation (inactivation) of glycogen synthase kinase-3ß (GSK3ß), MLP, however, was suggested to transduce signals via the calcineurin-NFAT pathway (Brancaccio et al., 2003; Heineke et al., 2005). Thus, both apparatuses use attached signaling molecules for transmitting biomechanical stress signals.

In addition, originally identified in chicken skeletal muscle myocytes, the transient receptor potential (TRP) channels (Patel et al., 2010), which have been described

as possible stretch-sensitive signaling mediators permeating calcium and other cations, were later identified in essentially all tissues and cell types. Thus, growth signaling in the heart may be mediated *via* a stretch-activated calcium current and its downstream effectors such as the calcineurin-nuclear factor of activated T cells (NFAT) signaling (Musaro et al., 1999). The TRP canonical (TRCP) subfamily consists of TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7. GPCR signaling generated diacylglycerol (DAG) has been described to activate TRPC3, TRPC6, and TRPC7. DAG has also been shown to activate TRPC1, TRPC4, and TRPC5, in addition to the depletion of intracellular calcium stores (Patel et al., 2010). Furthermore, stretching has been found to activate TRPC1, TRPC4, TRPC5, and TRPC6, indicating that these TRP channels might thus act as stretch sensors and participate in downstream signaling resulting in a hypertrophic growth response of the heart. Nevertheless, TRPC1 and TRPC6 have been implicated in regulating cardiac hypertrophy, and both have been identified to be directly activated via stretch (Maroto et al., 2005; Seth et al., 2009; Spassova et al., 2006; Wu et al., 2010).

However, in response to biomechanical stress, membrane-embedded receptors such as angiotensin II type 1 directly associate with Janus kinase-2 (JAK2). G proteins translocate into the cytosol and further activate extracellular signal-regulated kinase (ERK), resulting in hypertrophy induction (Zou et al., 2004).

3.7 Cytokines

Interleukin-6 (IL-6), leukemia inhibitory factor LIF and cardiotrophin-1 (CT-1), and other members of the IL-6 family of cytokines are multifunctional molecules that contribute to inflammation and cardiac hypertrophy (Elson et al., 2000; Heinrich et al., 1998).

IL-6 expression in the heart is upregulated in several conditions including hypoxia/ischemia (Hishinuma et al., 1999; Roy et al., 2006) and especially during the progression of hypertrophy due to pressure overload, myocardial infarction, and congestive heart failure (Baines and Molkentin, 2005; Briest et al., 2003; Kaneko et al., 1997; Sano et al., 2000; Yamauchi-Takihara and Kishimoto, 2000). Cardiac IL-6 expression is upregulated by multiple factors comprising the inflammatory cytokines IL-1ß and TNFα (Nakaoka et al., 2003), LPS (Tsutamoto

et al., 1998), neurohormones such as norepinephrine (Chen et al., 1998) and Ang II (Sano et al., 2001), as well as intracellular reactive oxygen species (Jacoby et al., 2003; Sarkar et al., 2004). However, in the context of physiological, adaptive exercise-induced cardiac hypertrophy IL-6 release is apparently not increased (Jin et al., 1996). In the human heart, both cardiac fibroblasts and cardiomyocytes produce IL-6 (Antonicelli et al., 2005; Aoyama et al., 2000). In addition, elevated serum levels are found in conditions such as cardiac hypertrophy, congestive heart failure as well as acute myocardial infarction (Testa et al., 1996; Tsutamoto et al., 1998). It has been described that after binding to its receptor and subsequent formation of the gp130 receptor complex, IL-6 activates the Janus-kinase-signal transducer. Furthermore, results from transgenic mice models indicate the importance of the gp130 signaling pathway in cardiomyocyte hypertrophy and cardiac development. A continuously activated gp130 characterizes mice that overexpress IL-6 and the IL-6 receptor in the heart which results in cardiac hypertrophy (Hirota et al., 1995). In contrast, mice develop a lethal hypoplastic ventricular myocardium in response to a disrupted gp130 gene (Yoshida et al., 1996).

In addition, postnatal murine cardiomyocytes have been found to abundantly express the LIF receptor and its ligand (Aoyama et al., 2000; Latchman, 2000), and others found that LIF mediates both hypertrophic and cytoprotective responses in adult cardiomyocytes in vitro (Haspel and Darnell, 1999; Wang et al., 2001). In addition, LIF has been described to trigger actions such as increasing cardiomyocyte growth and expression of fetal genes (upregulated c-fos, β-MHC, and ANF) (Latchman, 2000; Matsui et al., 1996). Although, others reported that the myocardial hypertrophy induced by LIF is different from the alpha-adrenergic responses mediated by G protein-coupled receptors, and characterized by a predominant increase in myocardial cell length with the addition of new sarcomeric units in series without a concomitant increase in cell width (Kuwahara et al., 2000; Wang et al., 2001).

Likewise, CT-1 induces myocardial hypertrophy similar to LIF, in which sarcomeres become added in series increasing myocardial cell length (Wang et al., 2001). Both, LIF and CT-1 have been described to activate the major gp130 downstream signaling cascades JAK/STAT, MEK/ERK, and PI3K/Akt (Fuchs et

al., 2003; Kaneko et al., 1997). In addition, a significant increase of CT-1 mRNA and protein along with gp130 expression has been demonstrated in the phase of transition from left ventricular hypertrophy to congestive heart failure (Talwar et al., 2000). Furthermore, several experimental studies indicate that CT-1 is functioning as a potent cardiac survival factor, as well as a promotor for cardiomyocyte proliferation and hypertrophy in vitro and in vivo (Jougasaki et al., 2000; Kato et al., 2000; Sheng et al., 1996; Villegas et al., 2000). Moreover, others report that fibroblast proliferation, migration, and collagen synthesis are induced by CT-1 (Freed et al., 2003; Fuchs et al., 2003; Kaneko et al., 1997). Beyond that, AT-II has been found to trigger increased expression of IL-6, LIF, and CT-1 in cardiac fibroblasts, in which especially LIF and CT-1, in turn, activate gp130-linked downstream signaling (Sano et al., 2001).

Thus, the pathogenesis of left ventricular hypertrophy and dysfunction is associated with activating cytokines such as Interleukin-6 (IL-6) as they mediate proliferation, negative inotropic effects, and myocardial hypertrophy (Jeron et al., 2002).

3.8 Calcium signaling

Calcium is essential in the regulation of cardiac contractile function, growth, and gene expression (Frey et al., 2000a). Calcineurin and calcium/calmodulin-dependent protein kinases (CaMKs) comprise the best-described calcium-dependent signaling proteins, in which the serine-threonine phosphatase calcineurin exhibits a catalytic A and regulatory B subunit. Two regulatory genes (*B1, B2*) have been identified for the subunit B, whereas three genes encode for the catalytic A subunit: *calcineurin-Aα* (*CnAα*), *calcineurin-Aß* (*CnAß*), *calcineurin-Aγ* (*CnAγ*). However, expression in human, mouse, and rat hearts has only been shown for *CnAα* and *CnAß* (Klee et al., 1998; Molkentin and Dorn, 2001). Sustained elevations of intracellular calcium activate calcineurin, which enables binding to its primary downstream effector, the nuclear factor of activated T cell (NFAT) transcription factors. Subsequently, calcineurin mediates the dephosphorylation of NFAT, which is normally found hyperphosphorylated and sequestered in the cytoplasm (Crabtree and Olson, 2002). A robust hypertrophic response has been described in transgenic mice after cardiac-specific activation

of calcineurin or its downstream effector NFAT (Molkentin et al., 1998). In addition, genetic inhibition of calcineurin or NFAT in several rodent models revealed that the calcineurin/NFAT pathway is necessary for a full hypertrophic response (Wilkins and Molkentin, 2002). Furthermore, some studies suggest the involvement of this pathway in regulating pathological remodeling and failure as they reported increased levels of calcineurin or phosphatase activity in failing or hypertrophic human hearts (Haq et al., 2001; Lim and Molkentin, 1999; Ritter et al., 2002).

3.9 Reactive oxygen and nitrogen species

Signaling that involves modification of biomolecules by oxidation/reduction is referred to as redox signaling, which has been identified to influence many physiological processes in the heart as well as contribute to pathological cardiac remodeling (Burgoyne et al., 2012; Hafstad et al., 2013). Although many studies described redox signaling either within cardiomyocytes (Burgoyne et al., 2012; Santos et al., 2011) or endothelial cells (Alom-Ruiz et al., 2008) data suggest that both direct and indirect mechanisms resulting from redox signaling within and between endothelial cells and cardiomyocytes are responsible for functional communication between these cells (Zhang and Shah, 2014). The redox crosstalk occurring between cardiomyocytes and endothelial cells may comprise several mechanisms such as direct diffusion of reactive oxygen species (ROS) and NO; indirect effects on cardiomyocytes function through ROS affecting the extracellular matrix (ECM) in the heart (Murdoch et al., 2014); and ROS modifying paracrine release of cytokines and growth factors from endothelial cells (Zhang et al., 2010). The reactive species providing redox signaling involve reactive oxygen species (ROS) such as superoxide anion (O^{-}_{2}), hydroxyl (OH), and hydrogen peroxide (H_2O_2), and reactive nitrogen species including nitric oxide (NO) and peroxynitrite ($ONOO^{-}$). The latter results from the reaction of (O^{-}_{2}) with NO (Pacher et al., 2007).

3.9.1 Reactive oxygen species (ROS)

Reactive oxygen species (ROS) cause modulation of intracellular signaling, and thereby also drive cardiac remodeling. Although different sources of ROS are

present in the heart, for redox signaling the NADPH oxidases (NOXs) are especially important. Multiple cell types such as cardiomyocytes, fibroblasts, endothelial cells, and inflammatory cells express NOX isoforms, but Nox2 and Nox4 comprise the two main isoforms expressed in the heart (Nabeebaccus et al., 2011). Typical triggers of Nox2 activation involve G-protein-coupled receptor agonists comprising AT-II, ET-1, α-adrenergic agonists, as well as cytokines such as TNF-α and mechanical forces. These stimuli initiate O^{-}_{2} production by inducing the translocation of four cytosolic regulatory subunits (p47phox, p67phox, p40phox, and Rac1), which bind to the flavocytochrome (Brown and Griendling, 2009). Besides, in response to pressure overload, Nox4 levels increase in cardiomyocytes, and ischemia/hypoxia, starvation, or even TGF-ß lead to increased Nox4 levels in several cell types, such as cardiomyocytes, endothelial cells, and potentially fibroblasts (Zhang et al., 2013). However, rather than generating O^{-}_{2}, Nox4 has been described to predominantly generate H_2O_2 (Takac et al., 2011).

3.9.2 Nitric oxide (NO)

Endothelial cells exert a key role in the regulation of vasomotor activity via the release of vasoactive substances comprising vasodilator nitric oxide (NO) (Kuo et al., 1992) and vasoconstrictor ET-1 (Yanagisawa et al., 1988). In addition, several aspects of physiological myocardial function are modulated by NO comprising excitation-contraction coupling, myocardial relaxation, diastolic function, the Frank-Starling response, heart rate, ß-adrenergic inotropic response, and myocardial energetics and substrate metabolism (Shah and MacCarthy, 2000). Moreover, in various cardiovascular diseases, including hypertension, elevated oxidative stress is responsible for impaired NO-mediated vasodilation, which has been considered the hallmark of endothelial dysfunction (Giles, 2006; Kuo and Hein, 2013). Furthermore, the heart exhibits different nitric oxide synthases (NOSs), such as endothelial NOS (eNOS) and neuronal NOS (nNOS). Worth knowing, eNOS is primarily localized on endothelial cells, and less found in caveolae of cardiomyocytes. nNOS on the other hand is mostly found in the cardiac sarcoplasmic reticulum (SR) and potentially mitochondria (Hare, 2004). Thus, constitutive NOSs generate NO under physiological conditions in

the heart (Hare, 2004). In contrast, inducible NOS (iNOS) may serve as an additional source under pathological conditions (Carnicer et al., 2013). Stimulation of soluble guanylate cyclase and thereby generation of guanosine monophosphate (cGMP) and posttranslational modification of effector proteins, e.g., S-nitrosylation of cysteine residues, comprise potential ways of NO influencing cellular function. Noteworthy, NO has been described to exert anti-hypertrophic effects in cardiomyocytes (Calderone et al., 1998) and the entire heart (Dawson et al., 2005; Ichinose et al., 2004; Ruetten et al., 2005; Scherrer-Crosbie et al., 2001). Here, increased intracellular cGMP/PKG1 activity through inhibition of the calcineurin/NFAT pathway has been reported as one anti-hypertrophic action of NO (Fiedler et al., 2002).

However, excessive O_2^- levels interact extremely rapidly with NO, resulting in peroxynitrite ($ONOO^-$) formation, thereby disrupting physiological NO signaling (Hare, 2004; Nediani et al., 2011). Thus, the interactions of ROS generated by NOX proteins with NOS-derived NO have been indicated to be particularly important for redox signaling in the development of heart failure (Nediani et al., 2011; Zhang et al., 2013; Zhang et al., 2012)

3.10 Natriuretic peptides

The first member of the natriuretic peptides family discovered in 1981 was the atrial natriuretic peptide (ANP) (de Bold et al., 1981; Kangawa and Matsuo, 1984; Levin et al., 1998). A few years later, the other two members comprising brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) were identified (Sudoh et al., 1988; Sudoh et al., 1990). All three natriuretic peptides share similarities as they consist of a 17-amino-acid ring structure and are encoded by genes including three exons in their active forms (He et al., 2006; Potter et al., 2009). In addition, initially synthesized as a pre-hormonal form, natriuretic peptides become biologically active as they are cleaved into the carboxy-terminal forms (ANP, BNP-32, CNP-22), and respective amino-terminal ends. The latter characterizes the circulating form of natriuretic peptides, which have been described as more stable (He et al., 2006; Matsuo et al., 2019; Potter et al., 2009). The principal source of CNP production is the endothelium (He et al., 2006; Matsuo et al., 2019; Potter et al., 2009), whereas cardiomyocytes secrete atrial

natriuretic peptide (ANP) and brain natriuretic peptide (BNP) (Wong et al., 2017). While ANP is commonly synthesized in the heart atria, the ventricles are the primary location of BNP synthesis. In addition, ANP and BNP have been described as markers for cardiac differentiation, and during cardiac development, the expression of these peptides is under tight spatiotemporal regulation. After birth, several pathological conditions of the heart show upregulated expression of ventricular ANP and BNP, and patients with cardiac hypertrophy or congestive heart failure display markedly elevated plasma concentrations of these peptides (Mukoyama et al., 1991). Furthermore, ANP and BNP exhibit multiple functions including diuretic, natriuretic, and vasorelaxant effects (Nakao et al., 1996). Aside from that, evidence indicates that ANP and BNP also act as paracrine mediators which thereby exert antihypertrophic and antifibrotic effects in the heart. Moreover, both peptides exert their hormonal and paracrine effects *via* activation of their common receptor guanylyl cyclase-A (GC-A) which is coupled to an increase in the intracellular concentration of cGMP (Nakao et al., 1996).

Additionally, both in vitro and in vivo hypertrophy of the ventricular chamber is associated with the induction of several embryonic genes, including the reexpression of atrial natriuretic peptide (ANP), which is known as a fetal heart marker protein (Boheler and Schwartz, 1992; Knowlton et al., 1991; Shubeita et al., 1990). Thus, one of the most conserved and well-characterized markers of the hypertrophic response comprises ANP induction, which has been identified in all forms of hypertrophy (Chien et al., 1991; Chien et al., 1993).

4. Aims

A hallmark of life is the capability of responding to stimuli thereby adapting to altered circumstances in our environment, and throughout life, we are constantly maintaining these compensational processes. Also, individual cells and tissues undergo these adaptional procedures because of various signals that surround them. In the context of cardiac hypertrophy, the cardiac tissue is exposed to a variety of stress signals. Particularly for the induction of cardiomyocyte hypertrophy, mechanical stress seems to be the most upstream trigger, followed by a variety of secreted molecules including vasoactive hormones (AT II, ET-1, catecholamines), growth factors (TGF-ß, FGF), cytokines (IL-6, CT-1) which

trigger reciprocal interactions of cardiomyocytes, fibroblasts, endothelial cells, and immune cells. If we want to understand the molecular triggers and mechanisms leading to cardiac hypertrophy it is essential to focus on the crosstalk between cardiomyocytes and nonmyocytes in the heart´s microenvironment. In this context, *"the fact that immune cells, fibroblasts, and endothelial cells collectively outnumber cardiomyocytes by a significant margin as the resident cells in the heart"* need consideration regarding future therapeutic investigations, *"making this viewpoint increasingly important as a crucial element in the study of the intercellular communications and the treatment of heart disease"* (Bazgir et al., 2023). Due to the known association between cardiac hypertrophy and heart failure, it is a pivotal challenge to focus on understanding the molecular pathogenesis of cardiac hypertrophy. Therefore, this study aimed to *"focus on these processes related to the onset, progression, and pathogenesis"* of cardiac hypertrophy, and propose a model for future experimental studies that will provide a better understanding of the mechanisms leading to cardiac hypertrophy (Bazgir et al., 2023).

5. Material and methods

A literature study was performed using PubMed® search to identify the molecules and mechanisms that prepare the ground for the pathological hypertrophic processes in the cardiac microenvironment and propose a model for future experimental studies.

6. Results

Mediators influencing the microenvironment in cardiac hypertrophy (Table 2)

Preferentially ventricular cardiomyocytes appear to store AT II in secretory granules (Sadoshima and Izumo, 1996). Mechanical stress triggers AT II secretion out of this storage into the culture medium (Sadoshima et al., 1993). Also, cardiac endothelial cells secrete angiotensin II (ATII) (Brutsaert, 2003). Another example of an endothelium-derived small molecule is endothelin-1 (ET-1) (Moravec et al., 1989; Wang et al., 2022). Cardiac endothelial cells secrete endothelin-1 (ET1) (Brutsaert, 2003). *"Aside from endothelial cells, ET-1 is also*

expressed in non-endothelial cells such as fibroblasts and cardiomyocytes" amongst others (Gray et al., 1998). Fibroblasts secrete paracrine mediators such as TGF-ß and ET-1 (Gray et al., 1998; Harada et al., 1997; Pellieux et al., 2001). Studies on cardiac synaptosomes found clear indications that *"locally produced AT II […] activates the AT1 receptor resulting in increased"* noradrenaline *"release"* (Mackins et al., 2006). FGF-1 and FGF-2 both exist within the heart in cardiomyocytes and non-myocytes (Kardami and Fandrich, 1989). FGF-2 is expressed by numerous cell types in the adult myocardium including cardiomyocytes and fibroblasts (Detillieux et al., 2003; Rao et al., 2020). FGF-2 is predominantly expressed by fibroblasts (Bogoyevitch et al., 1993; Pellieux et al., 2001). Endothelial cells have been reported to secrete bFGF in vitro (Vlodavsky et al., 1987). Endothelial cells and smooth muscle cells use a non-lethal disruption of the plasma membrane thereby also releasing FGF-2 (Cheng et al., 1997; Ku and D'Amore, 1995; McNeil et al., 1989). The potent angiogenic and mitogenic polypeptide bFGF is localized to the majority of mast cells (Qu et al., 1995). Mast cells release bFGF (Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006). *"Hi-FGF-2 is preferentially accumulated and released by cardiac fibroblasts which induce paracrine cardiomyocyte hypertrophy"* (Pellieux et al., 2001). Cardiomyocytes, cardiac fibroblasts, and endothelial cells secrete TGF-ß (Kuwahara et al., 2002) and endothelin-1 (Heiden et al., 2014). Also in a healthy heart, cardiomyocytes, fibroblasts, and endothelial cells release TGF-ß (Bujak and Frangogiannis, 2007; Euler, 2015). In addition, TGFß-1 is released upon mast cell degranulation (Lindstedt et al., 2001; Mekori and Metcalfe, 2000; Pennington et al., 1992; Prussin and Metcalfe, 2006). Also, in the context of injury repair, here, myofibroblasts and infiltrating immune cells secrete TGF-ß (Lindahl et al., 2002; Wipff et al., 2007). Cardiomyocytes and cardiac fibroblasts both release IL-6 (Ancey et al., 2002; Ancey et al., 2003). *"Cardiomyocytes and cardiac fibroblasts both express leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1)"* (Feng et al., 2022; King et al., 1998; Kuwahara et al., 1999). *"[…] cardiomyocytes […] express autocrine-acting CT-1 […]"* (Guseh and Rosenzweig, 2017; Wollert et al., 1996). *"[…] Mast cells release […] cytokines including IL-1 and IL-6"* (Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006). Another release product of mast cells includes TNFα (Frangogiannis et al., 1998;

Gilles et al., 2003; Gordon and Galli, 1990; Kaartinen et al., 1996). *"[…] endothelial cells express adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) […]"* (Esper et al., 2006). Cardiomyocytes, fibroblasts, and endothelial cells produce ECM components (Bowers et al., 2010). In addition, myofibroblasts produce extracellular matrix components and release pro-hypertrophic mediators including TGF-ß (Desmouliere et al., 1993; Ragazzini et al., 2022). Also, myofibroblasts can produce a wide range of ECM proteins, comprising interstitial collagens, proteoglycans, glycoproteins, and proteases (Kanekar et al., 1998). One major mediator *"released upon mast cell degranulation in the heart is histamine"* (Dvorak, 1986). Also, chemotactic factors for eosinophils and basophils are released by mast cell degranulation (Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006). Cardiomyocytes secrete anti-hypertrophic peptides including ANP and BNP (Kuhn, 2015; Lee et al., 2015). *"One major mediator produced and secreted by endothelial cells is NO"* (Esper et al., 2006). Another major factor secreted by cardiac endothelial cells is nitric oxide (NO) (Brutsaert, 2003). Also, endothelial cells secrete the active mediator CNP. *"Together, NO and […] CNP contribute to the suppression of cardiac hypertrophy by up-regulating cyclic GMP (cGMP)-cGMP dependent protein kinase 1 (PKGI) signaling"* (Kuhn, 2015). *"The heart […] exhibits a local RAS that may mediate autocrine, paracrine, and intracrine effects"* (Campbell, 1987; Dinh et al., 2001; Lindpaintner and Ganten, 1991). All RAS components *"including angiotensinogen (AGT), renin, ACE, AT1, and AT2 are expressed in the heart"* (Baker et al., 1992; Lee et al., 1993). All parts of the heart express AGT as well as cultured cardiomyocytes and fibroblasts (Campbell and Habener, 1986). *"[…] mast cells are"* an additional *"source of renin"*, which is *"released upon […] degranulation"* (Mackins et al., 2006; Silver et al., 2004). *"Moreover, cardiac endothelial cells"* carry out enzymatic activities *"like angiotensin-converting enzyme (ACE) and human chymase activity"* (Froogh et al., 2020; Urata et al., 1994). Also, mast cells release the proteolytic enzyme chymase that is activated upon degranulation, and independently of the angiotensin-converting enzyme (ACE), catalyzes the conversion of angiotensin I to angiotensin II (McEuen et al., 1995) (Bazgir et al., 2023).

Table 2.: Mediators influencing the microenvironment in cardiac hypertrophy

Vasoactive peptides	**Secretion from/ Location**	**References**
AT-II	cardiomyocyte	(Ramos-Kuri et al., 2021; Sadoshima and Izumo, 1996)
AT-II	endothelial cell	(Brutsaert, 2003)
ET-1	cardiomyocyte	(Gray et al., 1998; Heiden et al., 2014)
ET-1	fibroblast	(Forrester et al., 2018; Gray et al., 1998; Harada et al., 1997; Heiden et al., 2014; Pellieux et al., 2001)
ET-1	endothelial cell	(Brutsaert, 2003; Duangrat et al., 2023; Gray et al., 1998; Heiden et al., 2014; Moravec et al., 1989; Wang et al., 2022)
Catecholamines	**Secretion from/ Location**	**References**
NE	sympathetic nerve ending	(Mackins et al., 2006; Seravalle and Grassi, 2022)
Growth factors	**Secretion from/ Location**	**References**
FGF (aFGF, bFGF)	cardiomyocyte	(Detillieux et al., 2003; Kardami and Fandrich, 1989; Kardami and Koleini, 2022; Rao et al., 2020)
FGF (aFGF, bFGF)	non-myocyte	(Kardami and Fandrich, 1989)
FGF-2 (bFGF)	fibroblast	(Bogoyevitch et al., 1993; Detillieux et al., 2003; Kardami and Koleini, 2022; Pellieux et al., 2001; Rao et al., 2020)
FGF-2 (bFGF)	endothelial cell	(Cheng et al., 1997; Dolivo, 2022; Ku and D'Amore, 1995; McNeil et al., 1989; Vlodavsky et al., 1987)
FGF-2 (bFGF)	mast cell	(Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006; Qu et al., 1995)
High-FGF-2 (Hi-bFGF)	fibroblast	(Pellieux et al., 2001)
TGF-ß	cardiomyocyte	(Bujak and Frangogiannis, 2007; Euler, 2015; Kuwahara et al., 2002)
TGF-ß	fibroblast	(Bujak and Frangogiannis, 2007; Euler, 2015; Gray et al., 1998; Harada et al., 1997; Kuwahara et al., 2002; Pellieux et al., 2001)
TGF-ß	endothelial cell	(Bujak and Frangogiannis, 2007; Euler, 2015; Kuwahara et al., 2002)
TGF-ß	mast cell	(Lindstedt et al., 2001; Mekori and Metcalfe, 2000; Pennington et al., 1992; Prussin and Metcalfe, 2006)
TGF-ß	myofibroblast	(Desmouliere et al., 1993; Lindahl et al., 2002; Wipff et al., 2007)
Cytokines	**Secretion from/ Location**	**References**
IL-6, CT-1, LIF	cardiomyocyte	(Ancey et al., 2002; Ancey et al., 2003; Feng et al., 2022; Guseh and Rosenzweig, 2017; King et al., 1998; Kuwahara et al., 1999; Wollert et al., 1996)
IL-6, CT-1, LIF	fibroblast	(Ancey et al., 2002; Ancey et al., 2003; Feng et al., 2022; King et al., 1998; Kuwahara et al., 1999)
IL-6	mast cell	(Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006)
IL-1	mast cell	(Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006)

TNFα	mast cell	(Frangogiannis et al., 1998; Gilles et al., 2003; Gordon and Galli, 1990; Kaartinen et al., 1996; Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006)
Various other components	**Secretion from/ Location**	**References**
VCAM-1, ICAM-1	endothelial cell	(Esper et al., 2006)
ECM components	cardiomyocyte	(Bowers et al., 2010)
ECM components	fibroblast	(Bowers et al., 2010)
ECM components	endothelial cell	(Bowers et al., 2010)
ECM components	myofibroblast	(Desmouliere et al., 1993; Kanekar et al., 1998; Ragazzini et al., 2022)
Histamine	mast cell	(Dvorak, 1986)
Chemotactic factors	mast cell	(Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006)
Anti-hypertrophic peptides	**Secretion from/ Location**	**References**
ANP, BNP	cardiomyocyte	(Kuhn, 2015; Lee et al., 2015)
NO	endothelial cell	(Brutsaert, 2003; Esper et al., 2006)
CNP	endothelial cell	(Kuhn, 2015)
Enzymatic activities	**Secretion from/ Location**	**References**
Local RAS	cardiac tissue	(Campbell, 1987; Dinh et al., 2001; Lindpaintner and Ganten, 1991)
AGT, renin, ACE, AT1, AT2	cardiac tissue	(Baker et al., 1992; Lee et al., 1993)
AGT	cardiomyocyte	(Campbell and Habener, 1986)
AGT	fibroblast	(Campbell and Habener, 1986)
Renin	mast cell	(Mackins et al., 2006; Silver et al., 2004)
ACE	endothelial cell	(Froogh et al., 2020; Urata et al., 1994)
Chymase (alternative ACE)	endothelial cell	(Urata et al., 1994)
Chymase (alternative ACE)	mast cell	(McEuen et al., 1995; Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006)

Adapted from (Bazgir et al., 2023)

Pressure overload triggers several actions in cardiac cells (Table 3)

The expression of several RAS components *"is upregulated in cardiomyocytes in vitro in response to stretch"* (Malhotra et al., 1999; Sadoshima et al., 1993). Several other studies have suggested *"that hemodynamic overload activates the local RAS and outlined the crucial role of the AT 1 receptor"* in load-induced *"cardiac hypertrophy"* (Cohn et al., 2001; Fan et al., 2019; Griendling et al., 1996; Kojima et al., 1994; Komuro et al., 1990; Komuro and Yazaki, 1993; Lindholm et al., 2002; Pitt et al., 2000; Sadoshima et al., 1992; Sadoshima et al., 1993; Watanabe et al., 2021; Yamazaki et al., 1995a). A local AT II storage in cardiomyocytes has been reported, and mechanical stress triggers AT II

secretion out of this storage into the culture medium inducing cardiomyocyte hypertrophy by autocrine mechanisms (Sadoshima et al., 1993). AT II and ET-1 can also trigger the release of ANP and BNP from cardiomyocytes, although the primary regulation pathway of ANP and BNP synthesis is cardiomyocyte stretch (de Lemos et al., 2003; Nishikimi and Nakagawa, 2022). Pressure overload seems to be a strong trigger for the upregulation of leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1) expression in the adult human myocardium (Pan et al., 1998; Pemberton et al., 2005). Pressure overload rather triggers resident cardiac fibroblasts originating from the epicardium and endocardium to undergo rapid expansion and activation than hematopoietic precursor-derived fibroblasts (Moore-Morris et al., 2014). Mechanical stress activates fibroblasts, forcing them into a phenotype change which results in becoming myofibroblasts (Powell et al., 1999; Sun et al., 2022; Tomasek et al., 2002). *"In response to pressure overload"*, endothelial cells as well as fibroblasts are *"capable of changing […] phenotype"*. Endothelial cells use endothelial-to-mesenchymal transition (EndMT) to differentiate into myofibroblast-like cells resulting in extracellular matrix production. That way next to fibroblasts endothelial cells may as well contribute to cardiac fibrosis (Zeisberg et al., 2007). *"[…] pressure overload initiates endothelial cells of the intramyocardial arteries"* to express *"intercellular adhesion molecule (ICAM)-1"*, which results in the accumulation of macrophages adjacent to these *"ICAM-1 expressing arteries in the perivascular space"* (Kuwahara et al., 2003). *"[…] neutrophilic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase gets activated in response to pressure overload injury"* (Li et al., 2002), *"resulting in […] degranulation of neutrophils and thereby release of pro-fibrotic proteases as well as reactive oxygen species (ROS)"* (Ciz et al., 2012) (Bazgir et al., 2023).

Table 3.: Pressure overload triggers several actions in cardiac cells

Trigger	Action	Secretion from/ Location	References
mechanical stress/ pressure overload	upregulation of RAS components	cardiomyocytes	(Malhotra et al., 1999; Sadoshima et al., 1993)

	activation of local RAS	cardiac tissue	(Cohn et al., 2001; Fan et al., 2019; Griendling et al., 1996; Kojima et al., 1994; Komuro et al., 1990; Komuro and Yazaki, 1993; Lindholm et al., 2002; Pitt et al., 2000; Sadoshima et al., 1992; Sadoshima et al., 1993; Watanabe et al., 2021; Yamazaki et al., 1995a)
	AT II secretion from AT II storage	cardiomyocytes	(Sadoshima et al., 1993)
	secretion of ANP & BNP	cardiomyocytes	(de Lemos et al., 2003; Nishikimi and Nakagawa, 2022)
	IL-6, CT-1, LIF upregulation	cardiac tissue	(Pan et al., 1998; Pemberton et al., 2005)
	activation, accumulation of resident fibroblasts	fibroblasts	(Moore-Morris et al., 2014)
	phenotype change	fibroblasts to myofibroblasts	(Powell et al., 1999; Sun et al., 2022; Tomasek et al., 2002)
	phenotype change	endothelial cells to myofibroblasts	(Zeisberg et al., 2007)
	accumulation of macrophages	ICAM-1 expressing endothelial cells	(Kuwahara et al., 2003)
	activation of neutrophilic NADPH oxidase, release of pro-fibrotic proteases and ROS	neutrophils	(Ciz et al., 2012; Li et al., 2002)

Various mediators trigger actions in cardiac cells (Table 4)

Studies showed that in presence of AT II fibroblasts secrete paracrine mediators such as growth factors and cytokines including TGF-ß and ET-1 (Gray et al., 1998; Harada et al., 1997; Pellieux et al., 2001). *"Increased"* expression *"of LIF, IL-6, and CT-1 in cardiac fibroblasts in response to AT-II"* (Sano et al., 2000). AT II and ET-1 can also trigger the release of ANP and BNP from cardiomyocytes, although the primary regulation pathway of ANP and BNP synthesis is cardiomyocyte stretch (de Lemos et al., 2003; Nishikimi and Nakagawa, 2022). Plus, other data showed that AT II has direct effects on fibroblast proliferation, collagen and ECM protein synthesis, and expression of fibroblast growth factor 2 (FGF-2 or bFGF) (Jiang et al., 2007). Plus, *"AT-II, ET-1, and FGF-2 itself have been reported to stimulate FGF-2 gene expression"* (Detillieux et al., 2003; Jimenez et al., 2004). According to findings, TGF-ß, similar to mechanical stress,

"promotes fibroblast proliferation and extracellular matrix production, especially collagen and fibronectin, whereas degradation of these components is reduced" (Border and Noble, 1994). In addition, TGF-ß has been found to promote fibroblast to myofibroblast differentiation which expresses a smooth muscle actin (Sappino et al., 1990). It has been found that TGF-ß triggers endothelial cells to undertake EndMT (Zeisberg et al., 2007). By injury, FGF-2 is released from its "storage site" thereby potentially activating cell surface receptors (Detillieux et al., 2003; Rao et al., 2020). According to reports, *"FGF-2 increases both fibroblast and myofibroblast proliferation"* (Fortier et al., 2021; Galzie et al., 1997; Hoerstrup et al., 2000). Hi-FGF-2 is released from cardiac fibroblasts and exerts autocrine activity thereby triggering the release of pro-hypertrophic CT-1 (Aoyama et al., 2000; Freed et al., 2003; Pellieux et al., 2001). *"Mast cells are"* an additional *"source of renin"*, which is *"released upon […] degranulation"* (Mackins et al., 2006; Silver et al., 2004). It has been found that this local renin release results in Angiotensin II formation in striking distance of AT1 receptor expressing cardiac sympathetic nerve endings (Reid et al., 2004; Rodriguez-Gonzalez et al., 2020; Seyedi et al., 1997). Mast cells also release the proteolytic enzyme chymase that is activated upon degranulation, and independently of the angiotensin-converting enzyme (ACE), catalyzes the conversion of angiotensin I to angiotensin II (McEuen et al., 1995). In addition, others observed 2-fold increases in chymase levels in human ventricles than atria and that chymase carries out 80% of AT-II formation in the left ventricle (Urata et al., 1993; Urata et al., 1994). *"In response to various stimuli activated endothelial cells express adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) which"* attracts and further promotes *"infiltration of immune cells into the myocardium"* (Esper et al., 2006). Endothelial cell activation and *"subsequent expression of adhesion molecules"* enable the *"transmigration of neutrophils"* (Filippi, 2019; Woodfin et al., 2009). Moreover, *"inflammatory mediators such as TNF-a, IL1ß, and mast cell-derived histamine enhance this process"* (Asako et al., 1994; Mackay et al., 1993; Sahni et al., 2005). Neutrophils *"attract monocytes and dendritic cells (DCs)"* via the generation of *"chemotactic signals, thereby influencing the differentiation of macrophages into a predominantly pro- or anti-inflammatory state"* (Bennouna et al., 2003; Chertov et

al., 1997; Tsuda et al., 2004). *"Neutrophils […] produce cytokines such as TNF-a that drive macrophage and dendritic cell differentiation"* (Bennouna et al., 2003; Tsuda et al., 2004; van Gisbergen et al., 2005). *"Locally produced AT-II thus activates the AT1 receptor at sympathetic nerve endings, resulting in increased NE release"* (Mackins et al., 2006). *"Several mediators including AT-II, ET-1, a-adrenergic agonists, TNF-α, and mechanical forces trigger Nox2 activation. Via induction of four cytosolic regulatory subunits (p47^{phox}, p67^{phox}, p40^{phox}, and RAC1), these mediators initiate O_2^- production"* (Brown and Griendling, 2009). *"Excessive O_2^- levels interact extremely rapidly with NO, resulting in peroxynitrite ($ONOO^-$) formation, thereby disrupting physiological NO signaling"* (Hare, 2004; Nediani et al., 2011). *"GPCR stimulation with hypertrophic agonists, including AT-II and PE on cultured neonatal rat cardiomyocytes indicated an increase in calcineurin enzymatic activity,* which was induced by increased calcineurin Aß (CnAβ) mRNA and protein, compared to CnAα or CnAγ*"* (Taigen et al., 2000; Zhou et al., 2022) (Bazgir et al., 2023).

Table 4.: Various mediators trigger actions in cardiac cells

Trigger	Action	Secretion from/ Location	Reference
AT II	release of TGF-ß, ET-1	fibroblasts	(Gray et al., 1998; Harada et al., 1997; Pellieux et al., 2001)
AT II	increased expression of IL-6, CT-1, LIF	fibroblasts	(Sano et al., 2000)
AT II & ET-1	release of ANP, BNP	cardiomyocytes	(de Lemos et al., 2003; Nishikimi and Nakagawa, 2022)
AT II	fibroblast proliferation, ECM production, expression of FGF-2	fibroblasts	(Jiang et al., 2007)
AT, ET-1 & FGF-2	stimulation of FGF-2 gene	fibroblasts	(Detillieux et al., 2003; Jimenez et al., 2004)
TGF-ß	proliferation, ECM production	fibroblasts	(Border and Noble, 1994)
	phenotype change	fibroblasts to myofibroblasts	(Sappino et al., 1990)
	EndMT	endothelial cells to myofibroblasts	(Zeisberg et al., 2007)
injury	FGF-2 release	cardiac tissue	(Detillieux et al., 2003; Rao et al., 2020)
FGF-2	increase of proliferation	fibroblasts and myofibroblast	(Fortier et al., 2021; Galzie et al., 1997; Hoerstrup et al., 2000)

Hi-FGF-2	CT-1 release	fibroblasts	(Aoyama et al., 2000; Freed et al., 2003; Pellieux et al., 2001)
alternative RAS (renin & chymase)	AT II formation	mast cells	(Mackins et al., 2006; McEuen et al., 1995; Reid et al., 2004; Rodriguez-Gonzalez et al., 2020; Seyedi et al., 1997; Silver et al., 2004; Urata et al., 1993; Urata et al., 1994)
various stimuli	expression of VCAM-1, ICAM-1, attraction of immune cells	endothelial cells	(Esper et al., 2006)
endothelial cell activation, adhesion molecules	transmigration of neutrophils	endothelial cells	(Filippi, 2019; Woodfin et al., 2009)
TNF-a, IL-1ß, histamine	enhanced transmigration of neutrophils	endothelial cells	(Asako et al., 1994; Mackay et al., 1993; Sahni et al., 2005)
chemotactic signals	attraction of macrophages and dendritic cells	neutrophils	(Bennouna et al., 2003; Chertov et al., 1997; Tsuda et al., 2004)
TNF-a	differentiation of macrophages & dendritic cells	neutrophils	(Bennouna et al., 2003; Tsuda et al., 2004; van Gisbergen et al., 2005)
AT-II	increased norepinephrine release	sympathetic neurons	(Mackins et al., 2006)
AT-II, ET-1, NE, TNF-a	initiation of O2- production	cardiomyocytes, endothelial cells	(Brown and Griendling, 2009)
excessive O2- levels	interaction with NO, formation of ONOO-	cardiomyocytes, endothelial cells	(Hare, 2004; Nediani et al., 2011)
AT-II & PE	increase in calcineurin enzymatic activity	cardiomyocytes	(Taigen et al., 2000; Zhou et al., 2022)

7. Discussion

7.1 An interplay of different cells in hypertrophic remodeling

"The heart consists of various cell types, including myocytes, endothelial cells, fibroblasts, vascular smooth muscle cells, sympathetic neurons, and immune cells, which collectively account for a synchronized cardiac function" (Ding et al., 2022; Hefti et al., 1997; Zhang and Shah, 2014). *"However, it has been shown that […] cardiomyocytes in particular account for the majority of heart mass, increase in size and reprogram transcription in the process of cardiac hypertrophy"* (Peter et al., 2016; Schaub et al., 1997). Crosstalk *"between cardiomyocytes and non-myocytes leads to the secretion of bioactive mediators, which operate in an autocrine and paracrine manner (Table 2). This is followed*

by microenvironmental stimulation of different cell types and the activation of various signaling pathways within the cells" (Fig. 4,5) (Hefti et al., 1997; Takeda and Manabe, 2011). *"Altogether these complex processes result in cardiomyocyte hypertrophy, fibroblast hyperplasia, interstitial tissue composition change, and remodeling of the ventricular chambers"* (Jane-Lise et al., 2000) (Bazgir et al., 2023).

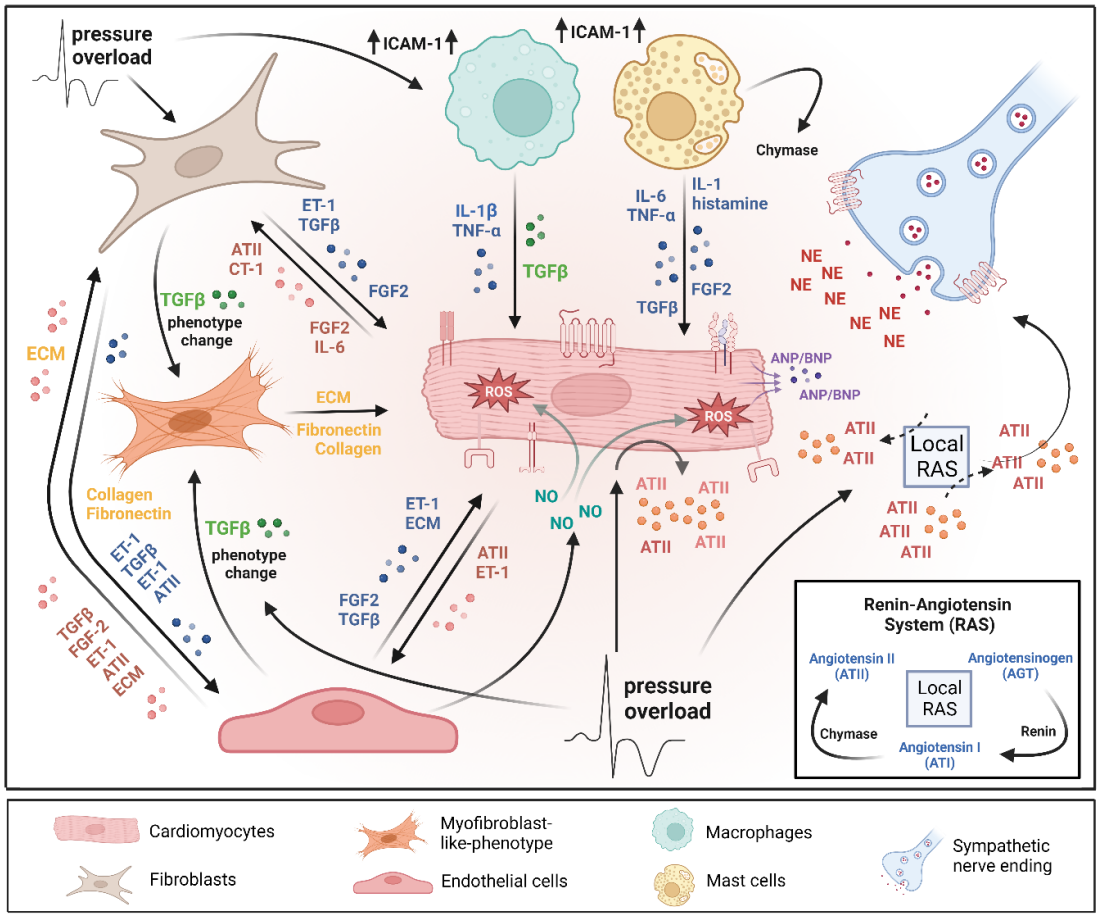

Fig. 4: ***"A microenvironmental model of pressure overload-induced cardiac hypertrophy.*** *The model also illustrates multiple cell types' substantial roles and reciprocal interactions in the myocardium. In response to pressure overload cardiomyocyte and non-myocardial cells are transformed into an 'activated state', releasing numerous pro-hypertrophic, pro-fibrotic, and pro-inflammatory mediators. In addition, vasoactive hormones, various growth factors, cytokines, and the local renin-angiotensin system (RAS) act in an autocrine and/or paracrine fashion. Collectively, the above-mentioned mechanisms orchestrate effects that contribute to pathological remodeling processes leading to cardiac hypertrophy, fibrosis, and inflammation". AT II: angiotensin II; CT-1: Cardiotrophin-1; ECM: extracellular matrix; ET-1: endothelin-1; FGF-2: fibroblast growth factor 2; ICAM-1: Intercellular Adhesion Molecule 1; IL-1: interleukin-1; IL-6: interleukin-6; NE: norepinephrine; TGF-ß: transforming growth factor-ß; TNFα: tumor necrosis factor-α"* (Bazgir et al., 2023).

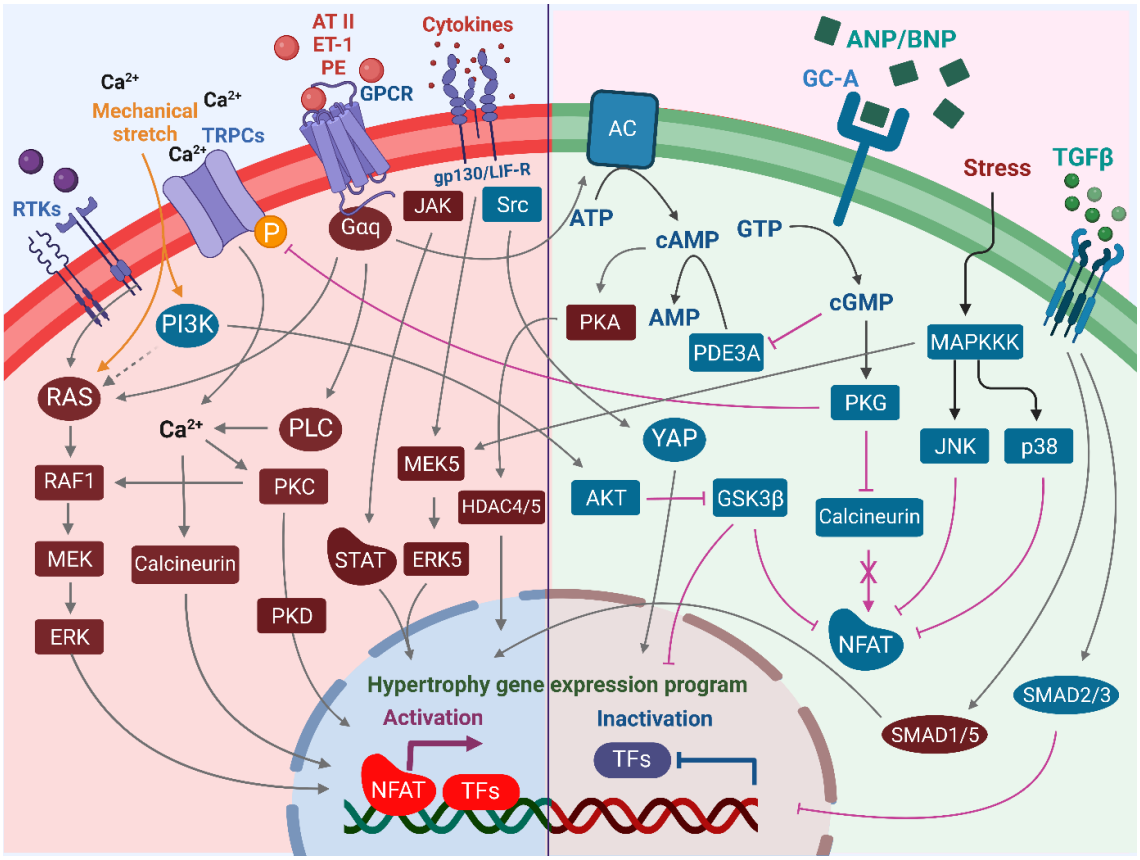

Fig. 5: ***"An overview of the pro-hypertrophic (left panel) and anti-hypertrophic (right panel) signaling pathways regulating the cardiac hypertrophic response in the cardiomyocyte.*** *Increased intracellular Ca^{2+} levels mediated by TRPCs and Ca^{2+} import promote pro-hypertrophic transcriptional signaling events via calcineurin-NFAT and activation of PKC. PLC may contribute to these axes in the activation of alpha-adrenergic receptor signaling. Although canonical MAPK signaling via RTKs including FGFR-1 promotes pro-hypertrophic signaling, the PI3K-AKT axis plays an opposing role in hypertrophic signaling via inhibition of GSK3β and activation of YAP transcriptional activity. Increased secretion of cytokines promotes transcriptional activation of the pro-hypertrophic gene program in the nucleus not only via JAK-STAT but also the MEK5-ERK5 axis. On the other hand, increased pressure overload in cardiac tissue promotes secretion of ANP and BNP by cardiomyocytes, leading to vasodilation and an antihypertrophic response in cells via an increase in intracellular cGMP levels, which leads to activation of PKG, which in turn mediates reduced hypertrophic growth. Activation of JNK and p38 stress signaling events in the cardiomyocyte, although leading to cardiomyopathy and heart failure, results in inhibition of NFAT through phosphorylation that prevents its nuclear localization and pro-hypertrophic transcriptional activation events, thereby blocking the calcineurin axis. Increased secretion of TGFβ during increased pressure stress can lead to mixed responses, with canonical TGFβ-SMAD2/SMAD3 signaling leading to anti-hypertrophic responses, whereas activation of noncanonical SMAD1/SMAD5 leads to pro-hypertrophic responses"* (Bazgir et al., 2023).

Fibroblast remodeling. *"Pressure overload triggers resident cardiac fibroblasts originating from the epicardium and endocardium to undergo rapid expansion and activation"* (Table 3), *"rather than previously reported hematopoietic precursor-derived fibroblasts or endothelial-to-mesenchymal transition (EndMT) as a contributing source"* (Fig. 4,6) (Kanisicak et al., 2016; Moore-Morris et al., 2014). *"Despite this, the exact origins of cardiac fibroblasts as well as the delineation of*

their characteristics and plasticity remain a field of current investigation and controversy" (Tallquist and Molkentin, 2017). *"Like cardiomyocytes, fibroblasts respond to external stress stimuli, but in a slightly different manner. Mechanical stress promotes fibroblast differentiation"* into a myofibroblast phenotype (Table 3; Fig. 4,6) (Powell et al., 1999; Sun et al., 2022; Tomasek et al., 2002), *"which has been shown to develop from tissue-derived fibroblasts rather than endothelial or smooth muscle cells"* (Kanisicak et al., 2016) (Bazgir et al., 2023).

In addition, TGF-ß has been found to promote fibroblast to myofibroblast differentiation (Table 4; Fig. 4) which expresses α-skeletal actin (Sappino et al., 1990).

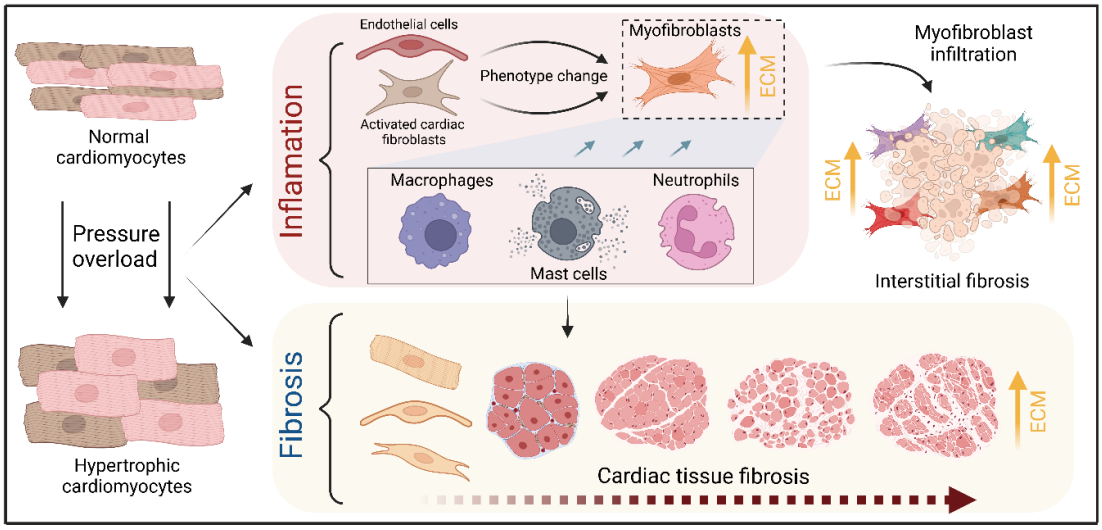

Fig. 6: ***"Schematic illustration of the process of fibrotic scar formation at the cellular level.*** *The myocardium develops cardiomyocyte hypertrophy under pressure overload, triggering concomitant inflammatory processes and fibrotic scar formation. The evidence discussed in the text suggests a central role for resident fibroblasts, nonetheless cardiac endothelial cells may also contribute to myofibroblast-like cells and drive cardiac fibrosis. Resident and infiltrating immune cells, including mast cells, macrophages, and neutrophils, enhance this phenotype change by releasing TGF-ß while mediating tissue inflammation via cytokines such as TNFα, IL-6, and IL-1. These mechanisms increase the number of myofibroblasts and the accumulation of collagen, which accelerates fibrotic scar formation in the microenvironment of cardiac hypertrophy"* (Bazgir et al., 2023).

Noteworthy, by actively producing extracellular matrix (ECM) components and release of *"pro-hypertrophic mediators, including TGF-ß (Table 2)",* myofibroblasts are *"engaged in a wide range of pathological conditions",* especially *"fibrosis and tissue remodeling"* (Fig. 6) (Desmouliere et al., 1993; Ragazzini et al., 2022) (Bazgir et al., 2023). Notably, myofibroblasts do not reside in normal cardiac tissue except the valve leaflets (Manabe et al., 2002).

Consistent with data, *"enhanced release of ECM by myofibroblasts contributing to mechanical stiffness accompanied by increasing fibrosis evolves into severe consequences causing cardiac diastolic dysfunction"* (Fig. 7) (Chaturvedi et al., 2010). Besides, others reported that *"progressing fibrosis can affect systolic function by building a barrier between […] cardiomyocytes, thereby provoking a defective electrical coupling"* of cardiomyocytes (Spach and Boineau, 1997). *"Additionally, an increased level of ECM, such as collagen, can disrupt the oxygen diffusion capacity leading to hypoxia in the affected myocytes, a process that may further enhance pathological remodeling"* (Fig. 7) (Sabbah et al., 1995). *"In conclusion, cardiac fibroblasts react to pressure overload-induced injury with activation, accumulation, and excessive extracellular matrix deposition"* (Fig. 4,6). *"The resulting conditions including mechanical stiffness, myocyte uncoupling, and ischemia comprise key contributors to heart failure"* (Fig. 7) (Moore-Morris et al., 2014). *"These lines of evidence also emphasize the identification of […] cardiac hypertrophy as an independent risk factor for arrhythmias, myocardial infarction, and sudden death"* (Fig. 7) (Levy et al., 1990) (Bazgir et al., 2023).

Endothelial cell activation. *"In response to pressure overload, cardiac endothelial cells, similar to cardiac fibroblasts are capable of changing […] phenotype"* (Table 3; Fig. 4). *"It has been reported that endothelial cells can undergo an EndMT, differentiate into myofibroblast-like cells, and thereby contribute to cardiac fibrosis"* (Fig. 4,6) (Zeisberg et al., 2007). *"Others outlined that EndMT recruits circulating hematopoietic progenitors to the heart thereby generating significant numbers of cardiac fibroblasts"* (reviewed in (Cheng et al., 2021)). However, data seems contradictory as others found clear indications that contribution to cardiac fibroblast numbers arises from tissue-resident fibroblasts (Fig. 6) (Kanisicak et al., 2016; Moore-Morris et al., 2014). *"Altogether, left ventricular myocardial tissue of end-stage cardiac failure patients revealed dramatically increased expression levels of EndMT-related genes"* (Xu et al., 2015), *"indicating"* that "*further investigation"* is necessary to *"clarify the exact contribution of EndMT"* (Bazgir et al., 2023).

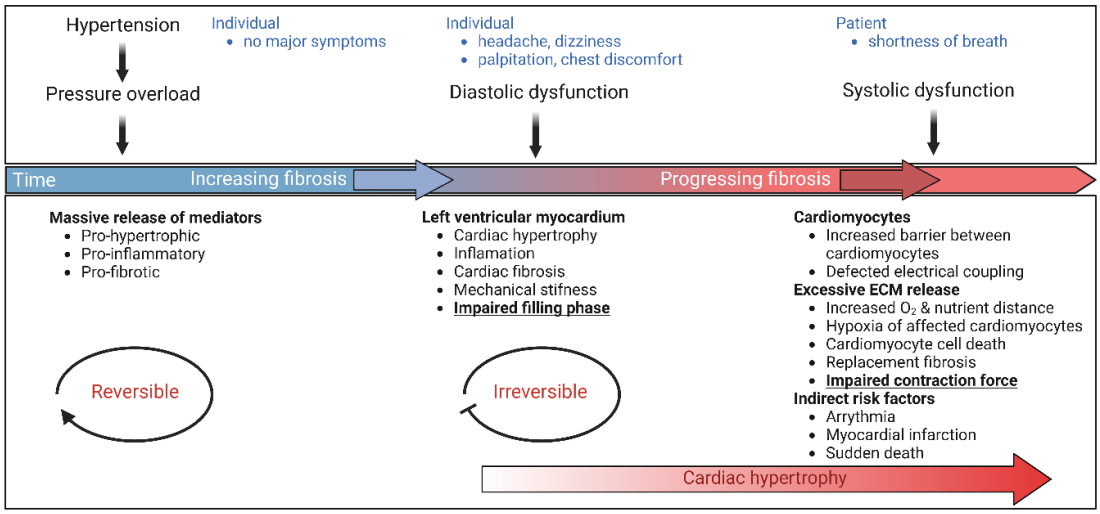

Fig. 7: Schematic diagram of how changes in the microenvironment affect cardiac function. "*Hypertension, a common cardiovascular disease, causes pressure overload followed by a massive release of pro-hypertrophic, pro-fibrotic, and pro-inflammatory mediators. At this stage, when individuals do not experience symptoms, hypertension, and its accompanying microenvironmental complications may be reversible with strategies such as lifestyle modification",* but *"without any intervention, this could evolve into cardiac hypertrophy and fibrotic remodeling. Increasing fibrosis leads to mechanical stiffness and impaired filling phase, both prominent features of diastolic dysfunction. Common symptoms include headache, dizziness, palpitations, and chest discomfort. Notably, this phase is not reversible and requires pharmacological treatment. Late diagnosis or inadequate treatment leads to progressive fibrosis and detrimental changes at the molecular level, such as a barrier between cardiomyocytes, impaired electrical coupling, hypoxia of affected cardiomyocytes"*, and resulting cardiomyocyte cell death. *The subsequent decreased contractile force characterizes systolic dysfunction while having severe consequences as individuals suffer from shortness of breath. Biomarker identification in a diagnostic screening approach could help detect early onset diastolic dysfunction in affected individuals, setting the platform for early management and preventive course of action to avoid the subsequent detrimental outcomes of the developing condition"* (Bazgir et al., 2023).

Beyond that, endothelial cells seem to exert a substantial role in the microenvironment of cardiac hypertrophy via the release of various mediators (Fig. 4). It has been reported that endothelial cells similar to cardiomyocytes and fibroblasts secrete TGF-ß (Kuwahara et al., 2002) and endothelin-1 (Fig. 4) (Heiden et al., 2014). Described as a canonical pathway, the TGF-ß/Smad3 signaling contributes to the progression of cardiac fibrosis (Kuwahara et al., 2002). In addition, others reported that TGF-ß triggers endothelial cells to undertake EndMT (Table 4; Fig. 4) (Zeisberg et al., 2007). Additionally, endothelial cells have been reported to secrete bFGF in vitro (Vlodavsky et al., 1987). Plus, others found that endothelial cells and smooth muscle cells use a non-lethal disruption of the plasma membrane thereby also releasing FGF-2 (Cheng et al., 1997; Ku and D'Amore, 1995; McNeil et al., 1989). Indicating that

alongside fibroblasts, endothelial cells participate in cardiac scar tissue formation (Fig. 6) as active players, thereby enhancing cardiac stiffness and promoting cardiac dysfunction.

"One major mediator produced and secreted by endothelial cells is NO (Table 2)" (Fig. 4). *"Among the numerous functional influences of NO are cardiac-related functions, including key regulator of vasodilation, reduction of permeability and thrombogenesis, and inhibition of inflammation"* (Esper et al., 2006). *"Another active mediator secreted by endothelial cells is CNP (Table 2). Together, NO and […] CNP contributes to the suppression of cardiac hypertrophy by up-regulating cyclic GMP (cGMP)-cGMP-dependent protein kinase 1 (PKGI) signaling"* (Kuhn, 2015), *"by inhibiting calcineurin"* (Fig. 5). Another example of an endothelium-derived small molecule next to NO and CNP is ET-1 (Table 2) (Moravec et al., 1989; Wang et al., 2022). Originally identified as an endothelium-derived vasoconstrictor (Yanagisawa et al., 1988), ET-1 *"contributes to cardiac hypertrophy and fibrosis as a major growth factor. Aside from endothelial cells, ET-1 is also expressed in non-endothelial cells such as fibroblasts and cardiomyocytes (Table 2)"* (Fig. 4). *"Functioning in an autocrine and paracrine manner, ET-1 seems to have important effects during"* cardiomyocyte hypertrophy (Gray et al., 1998). *"ET-1 exhibits a positive inotropic effect"* (Moravec et al., 1989) as well as cardiomyocyte hypertrophy responses (Drawnel et al., 2013) (Bazgir et al., 2023).

"Moreover, cardiac endothelial cells" carry out enzymatic activities *"like angiotensin-converting enzyme (ACE) and chymase (Table 2)"* (Fig. 4), *"which may contribute to changes in local levels of AT-II"* (Froogh et al., 2020; Urata et al., 1994). *"Besides fibroblasts, endothelial cells may also contribute to cardiac fibrosis"* (Fig. 6). Apart from that, *"in response to various stimuli, activated endothelial cells express adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM) which"* attracts and further promotes *"infiltration of immune cells into the myocardium"* (Table 4; Fig. 4) (Esper et al., 2006) (Bazgir et al., 2023).

Thus, *"major factors secreted by cardiac endothelial cells (Table 2) comprise nitric oxide (NO), endothelin-1 (ET1), prostaglandin I2 (PI2), and angiotensin II (ATII) which directly influence cardiac metabolism, growth, contractile*

performance, and rhythmicity of the adult heart" (Brutsaert, 2003) (Bazgir et al., 2023). Combined, these lines of evidence all identify a central regulatory role for endothelial cells by secretion of autocrine and paracrine mediators. Plus, an essential role in maintaining cardiac function as well as promoting pathological remodeling of the cardiac microenvironment.

Immune cells in the cardiac microenvironment

"The pathogenesis of pressure overload and heart failure has been suggested to be in close context with the activation of inflammatory cells and release of inflammatory mediators" (Fig. 4) (Liu et al., 2021) (Bazgir et al., 2023).

Cardiac mast cells. *"The identification of the presence of mast cells in the heart tissue of animals"* (Ghanem et al., 1988), *"and human"* (Assem and Ghanem, 1988; Dvorak, 1986; Estensen, 1984; Forman et al., 1985; Ingason et al., 2019; Marone et al., 1986; McGovern, 1956; Pepler and Meyer, 1961), *"as well as the discovery of mast cells as the source of an array of mediators (Table 2)"* (Mekori and Metcalfe, 2000), *"clearly emphasizes the crucial participation of innate immune cells, especially cardiac mast cells, in cardiac hypertrophy and remodeling"* (reviewed in (Balakumar et al., 2008; Liu et al., 2021)) (Bazgir et al., 2023).

Several reports in the past noticed that TGFß-1 is released upon mast cell degranulation (Lindstedt et al., 2001; Mekori and Metcalfe, 2000; Pennington et al., 1992; Prussin and Metcalfe, 2006), and that the potent angiogenic and mitogenic polypeptide bFGF is localized to the majority of mast cells (Table 2) (Qu et al., 1995), indicating cardiac mast cells as active players promoting cardiac fibrosis and scar tissue formation in the cardiac microenvironment. Another study reported that especially cardiac mast cells participate in the induction of cardiac hypertrophy and cardiac fibrosis, known as the key steps in the transition to heart failure.

Here, *"activated cardiac mast cells were identified in spontaneously hypertensive rats as a major source of growth factors"* (Fig. 4), *"such as TGF-ß and bFGF, in areas of myocardial fibrosis"* (Shiota et al., 2003). *"This is consistent with findings that the release of TGF-1 provokes an increase in collagen production alongside*

the differentiation of fibroblasts to myofibroblasts" (Fig. 4) (Petrov et al., 2002), *"and indicates that cardiac mast cells also contribute to the key steps of cardiac tissue fibrosis"* (Fig. 6) (Weber, 2000) (Bazgir et al., 2023).

"Another major mediator that is released upon mast cell degranulation in the heart is histamine (Table 2)" (Dvorak, 1986). *"Histamine is a neurohormonal mediator that binds to histamine H1, H2, and H3 receptors, thereby inducing various cellular functions"* (Hough, 2001; Leurs et al., 2005), *"as well as cardiac hypertrophy"* (Fig. 4) (Barka et al., 1987; Levick, 2022). *"Notably, cardiomyocytes express the histamine H2 receptor"*, which is coupled to Gs proteins, *"which are coupled to the beta receptor and Gs proteins"* (Du et al., 1993; Eckel et al., 1982; Hattori, 1999; Hill et al., 1997; Matsuda et al., 2004). *"Consistently, histamine triggers positive inotropic effects"* (Eckel et al., 1982; Huang et al., 2022; Kirch et al., 1992). *"In contrast, blocking the histamine H2 receptors decreases cardiac output"* (Kirch et al., 1992). *"The application of famotidine, a histamine H2 receptor antagonist, in chronic heart failure (CHF) patients, was found to decrease left ventricular remodeling"* (Kim et al., 2006) (Bazgir et al., 2023).

"Another characteristic of mast cells involves their strategic location often at a perivascular site, thereby exerting regulatory functions" upon "*endothelial cells"*. In addition, "*mast cells synthesize several endothelial cell activators comprising, amongst others, the platelet-activating factor (PAF), IL-1ß, IL-4, and tumor necrosis factors alpha (TNF-α)"* (Bradding et al., 1992; Galli, 1993; Ohkawara et al., 1992). Several other *"studies […] indicated mast cell degranulation as a major source of TNFα (Table 2)"* (Fig. 4) (Frangogiannis et al., 1998; Gilles et al., 2003; Gordon and Galli, 1990; Kaartinen et al., 1996). *"Even though many cardiac cells have been described to generate TNF-α"*, evidently *"cardiac mast cells"* seem to *"constitutively express TNF-α"* (Frangogiannis et al., 1998; Gilles et al., 2003). In addition, Shiota et al. found that stimulation of cardiac mast cells activates TNF-a/NF-kB/IL-6 cascades (Shiota et al., 2003). *"Activation of the TNFα/NF-κB axis leads to the activation of p38-MAPK"* (Fig. 5), *"collectively causing hypertrophy and dysfunction of the heart"* (Barnes and Karin, 1997; Sugden and Clerk, 1998b) (Bazgir et al., 2023).

"Moreover, mast cells release other cytokines including IL-1 and IL-6 (Table 2)" (Fig. 4) (Mekori and Metcalfe, 2000; Prussin and Metcalfe, 2006). Especially the

IL-6 family of cytokines use the common transducing component gp130 and may thereby take an *"active role in cardiac hypertrophy induction via the JAK/STAT pathway"* (Fig. 5) (Plenz et al., 2001; Yamauchi-Takihara et al., 1996). *"Although several studies suggest that cardiac mast cells are"* an additional *"source of renin",* which is *"released upon […] degranulation (Table 2)"* (Mackins et al., 2006; Silver et al., 2004), *"the major source of renin in the myocardial microenvironment is complex"* (Dostal and Baker, 1999; Krop and Danser, 2008) (Bazgir et al., 2023).

Evidence suggests that AT II production in the heart is significantly driven by circulating renin. Studies performing nephrectomy in rats support this hypothesis observing that cardiac levels of renin and AT II correlate well with plasma levels before and after the procedure (Booz et al., 1999; Campbell et al., 1993). Despite this, the majority of cardiac AT II production seems to occur in situ irrespective of the component's origin (van Kats et al., 1998).

In addition, mast cells have been found to release the proteolytic enzyme chymase (Table 2) which is activated upon degranulation. Chymase is capable of catalyzing the conversion of angiotensin I to angiotensin II, independently of the angiotensin-converting enzyme (ACE) (Fig. 4) (McEuen et al., 1995) (Bazgir et al., 2023). In addition, others observed 2-fold increases in chymase levels in human ventricles than atria and that chymase carries out 80% of AT-II formation in the left ventricle (Urata et al., 1993; Urata et al., 1994).

In conclusion, the *"mast cell"* release products *"renin and chymase may serve as an alternative way to upregulate AT II levels in the"* cardiac microenvironment (Table 4) (Bazgir et al., 2023).

The latter is consistent with findings that components of local origin generate tissue AT II. It has been found that cleavage of AGT to AT II may be brought about by enzymes such as cathepsin D and chymase instead of renin and ACE depending on the tissue (Kumar and Boim, 2009). Moreover, local AT II synthesis (e.g., extracellular or intracellular) may be part of the reason why renin-angiotensin system (RAS) blockade by angiotensin receptor blockers (ARBs) and ACE inhibitors is incomplete (Kumar et al., 2007). This is consistent with another study that found a higher mast cell density in ventricular tissues from heart failure patients. Here, they also identified higher expression levels of ACE mRNA and

chymase mRNA in heart failure patients than in the control myocardium (Batlle et al., 2006). Combined, cardiac mast cells seem to be active pathology drivers contributing significantly to the progression of left ventricular dysfunction by activation of a local RAS. Notably, it has been reported that chronically activated RAS is associated with the presence of inflammatory cells and fibroblasts, a process that is preceding vasculature remodeling and is followed by cell recruitment and collagen deposition (Weber, 2004). Cardiac mast cells seem to represent a group of effector cells that are well-engineered residents of the microenvironment. With their toolbox of pro-hypertrophic, -fibrotic, and -inflammatory mediators, these cells are ready to act and respond to various stimuli thereby impacting all cardiac cells and are central drivers of cardiac remodeling.

Monocytes & Macrophages. *"Healthy and injured cardiac tissues possess heterogeneous populations of macrophages, in both humans and mice"* (Fig. 4) (Azzawi et al., 2005). *"Most macrophages within the heart are established embryonically from the yolk sac and fetal liver progenitors, similar to tissue macrophages of the liver or brain. Local proliferation in contrast to monocyte recruitment serves to maintain resident macrophage subsets"* (Epelman et al., 2014; Heidt et al., 2014) (Bazgir et al., 2023). The expression and dependence of CCR2 identify cardiac macrophages of adult monocyte versus embryonic origin (Epelman et al., 2014).

"In the absence of disease, self-renewal serves to maintain local tissue macrophage populations" (Hashimoto et al., 2013). *"Despite this, in response to pressure overload or ischemic injuries, the majority of macrophages"* are recruited and differentiated from blood monocytes (Molawi et al., 2014) (Bazgir et al., 2023). Thus, CCR2+ and CCR- classify cardiac macrophages into recruited proinflammatory monocytes/ macrophages (CCR+) as well as resident macrophages (CCR-) (Bajpai et al., 2018; Dick et al., 2019; Epelman et al., 2014; Patel et al., 2018).

"Cardiac macrophages are key effector cells mediating tissue remodeling and fibrosis" (Fig. 6) (Mosser and Edwards, 2008) (Bazgir et al., 2023). Several studies reported that monocytes and macrophages release mediators such as IL-

1ß, TNF-α, and TGF-ß, amongst others (Fadok et al., 1998; Huynh et al., 2002).

In addition, *"the initial and significant event for vascular lesion formation results from inflammatory cytokine- and growth factor-producing migrating macrophages"* (Fig. 4) (Ross, 1999). According to reports, *"accumulation of macrophages has been found in the perivascular space, where they co-localize with fibroblasts collectively producing collagen during cardiac hypertrophy"* (Fig. 6) (Hinglais et al., 1994; Nicoletti et al., 1996). *"Consistent with this, other studies have found that pressure overload initiates endothelial cells of the intramyocardial arteries to exhibit intercellular adhesion molecule (ICAM)-1"* (Table 3), *"and that accumulation of macrophages occurs adjacent to"* these "*ICAM-1 expressing arteries in the perivascular space"* (Fig. 4) (Kuwahara et al., 2003). Plus, it has been reported that a potent monocyte chemoattractant, the monocyte chemoattractant protein (MCP)-1, is synthesized by vascular cells and monocytes (Capers et al., 1997), and primarily regulates the recruitment of macrophages to the vessels (Reape and Groot, 1999). A study using a *"continuous infusion of angiotensin II (AT II) or norepinephrine into hypertensive rats demonstrated that MCP-1 induction was associated with adventitial macrophage accumulation in the aortic wall"* (Capers et al., 1997) (Bazgir et al., 2023).

Moreover, others found preceding myocardial TGF-ß upregulation and fibroblast proliferation, that myocardial MCP-1 expression and perivascular macrophage infiltration rapidly induced within day 1 after pressure overload, peaking at day 3. The same study demonstrated that macrophage accumulation as well as fibroblast proliferation and TGF-ß induction was inhibited using an MCP-1 monoclonal neutralizing antibody (Kuwahara et al., 2004). Noteworthy, it has been found that pressure overload induces ICAM-1 in a similar time course to that found for MCP-1, and that functional blocking ICAM-1 also reduced accumulation of macrophages and proliferative fibroblasts as well as inhibiting the TGF-ß expression upregulation (Kuwahara et al., 2003). Thus, the upregulated macrophage numbers in response to MCP-1 and ICAM-1 indicate that pressure overload triggers inflammatory changes in the cardiac microenvironment. Another study that used transverse aortic constriction (TAC)

found that cardiac macrophages undergo a two-phase response during pressure overload-induced cardiac hypertrophy (Liao et al., 2018). Their data showed a significant increase of CCR2- cardiac macrophages within the first week, and infiltration of Ly6ChighCX3CR1+CCR2+ classic monocytes at four weeks (Liao et al., 2018). In conclusion, in the first phase, pressure overload seems to trigger resident tissue macrophages (CCR-) to proliferate, while in the second phase infiltration of bone-marrow-derived monocytes occurs. In addition, TAC has been described to trigger two phases of cardiac response, compensatory cardiac hypertrophy at 7-10 days with preserved contractile function, and a decompensated phase with progression to heart failure at 2-4 weeks. According, the dynamic changes in cardiac macrophage numbers in response to TAC correlate well with these two major phases of cardiac hypertrophy (Liao et al., 2018). Thus, during the adaptive response to pressure overload resident cardiac macrophages proliferate, while the transition to decompensation is associated with the infiltration of monocytes (Liao et al., 2018).
Thus, *"collectively this suggests that"* residents, as well as recruited macrophages, take active *"part in the early response to stress preceding hypertrophic remodeling"* (Bazgir et al., 2023).

Neutrophils. *"Under normal reparative conditions, neutrophil granulocytes are recruited"* into *"areas of acute inflammation where they perform functions such as"* elimination *"of dead cells and matrix debris"* (Fig. 6) (Bratton and Henson, 2011; Sreejit et al., 2020). *"As key components of the inflammatory response, neutrophils also act on the recruitment, activation, and programming of antigen-presenting cells (APC)".* Noteworthy, neutrophils *"attract monocytes and dendritic cells (DCs)"* via generation of *"chemotactic signals, thereby influencing the differentiation of macrophages into a predominantly pro- or anti-inflammatory state"* (Table 4) (Bennouna et al., 2003; Chertov et al., 1997; Tsuda et al., 2004) (Bazgir et al., 2023).
Thus, as neutrophils are one of the body's main cellular components *"for the destruction of microorganisms, there is also the possibility that these cells damage"* cells and tissues of the host (Bui et al., 2022; Henson and Johnston, 1987; Weiss, 1989). According to these findings, neutrophils may have

detrimental effects on cardiac tissue, when recruited to sites of pressure overload injury (Fig. 6) (Bazgir et al., 2023).

"Several studies have reported that in response to" pressure overload-induced hypertrophy, the first Leukocytes appearing *"in the myocardium within 3 days after injury are neutrophils"* (Fig. 6) (Weisheit et al., 2014; Weisheit et al., 2021). Endothelial cell activation and *"subsequent expression of adhesion molecules"* enable the *"transmigration of neutrophils"* (Table 4; Fig. 6) (Filippi, 2019; Woodfin et al., 2009). Moreover, *"inflammatory mediators such as TNF-α, IL1ß, and mast cell-derived histamine enhance this process"* (Table 4) (Asako et al., 1994; Mackay et al., 1993; Sahni et al., 2005) (Bazgir et al., 2023).

Several studies with different experimental set-ups observed similar findings regarding alterations of immune cells, such as macrophages and neutrophils in the myocardium in response to pressure overload induced cardiac hypertrophy. In a study using a TAC mouse model, flow cytometry and fluorescence microscopy revealed that cardiac neutrophils peaked in 3 days after TAC surgery, whereas macrophages peaked in 6 days (Weisheit et al., 2014).

Consistent, others found next to ICAM-1 containing coronary arteries in the left and right ventricle, that macrophage and neutrophil infiltration appeared in the first 3 days after injury using a mouse model with inter-renal aortic banding. Noteworthy, they found that these alterations of macrophage and neutrophil content occurred ahead of perivascular fibrosis (10 days), and cardiomyocyte hypertrophy (28 days) (Higashiyama et al., 2007) (Bazgir et al., 2023).

"Neutrophils have been described to produce cytokines such as TNF-α that drive macrophage and dendritic cell differentiation" (Table 4) (Bennouna et al., 2003; Tsuda et al., 2004; van Gisbergen et al., 2005). *"In addition, others found that neutrophilic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase gets activated in response to pressure overload injury"* (Li et al., 2002), *"resulting in […] degranulation of neutrophils and thereby release of pro-fibrotic proteases"* (Fig. 6) *"as well as reactive oxygen species (ROS)"* (Table 3) (Ciz et al., 2012) (Bazgir et al., 2023).

Sympathetic neurons. *"Sympathetic neurons which innervate the heart and release norepinephrine (NE) also express the endothelin receptor A (ET-A)"*

(Isaka et al., 2007; Lehmann et al., 2014b). ET-1 led to an enormous *"NE release in cocultured cardiomyocytes and sympathetic neurons with exaggerated"* cardiomyocyte hypertrophy compared to monoculture cardiomyocytes. In contrast, less adverse structural remodeling and cardiac dysfunction were found in *"mice lacking the ET-A receptor exclusively in sympathetic neurons"* when subjected to pathological pressure overload (Lehmann et al., 2014a) (Bazgir et al., 2023).

In addition, significant *"amounts of renin released in the cardiac microenvironment upon cardiac mast cell degranulation"* (Table 4) (Mackins et al., 2006), *"result in both AT-II formation"* (Table 4) *"within striking distance of AT1 receptor-expressing cardiac sympathetic nerve terminals and enhanced NE release"* (Fig. 4) *"and arrhythmias"* (Fig. 7) (Reid et al., 2004; Rodriguez-Gonzalez et al., 2020; Seyedi et al., 1997). *"The fact that these events can be prevented by mast cell-stabilizing agents confirms the central role of cardiac mast cell-derived renin in AT1 receptor signaling. Locally produced AT-II thus activates the AT1 receptor at sympathetic nerve endings, resulting in increased NE release"* (Fig. 4) (Table 4) (Mackins et al., 2006) (Bazgir et al., 2023).

7.2 Mediators of cardiac remodeling

"Mechanical stretch and neurohumoral mechanisms identify the most proximal stimuli for initiating hypertrophic signaling pathways" (Fig. 4) (Heineke and Molkentin, 2006). *"Due to hemodynamic overload, cardiomyocytes undergo mechanical stress and thereby release autocrine and paracrine signaling factors such as growth factors, hormones, cytokines, and chemokines (Table 2)"* (Bernardo et al., 2010. *"Furthermore, mechanical stress is sensed by both cardiac fibroblasts resulting in the production and release of signaling mediators"* (Fig. 4) (MacKenna et al., 2000), *"and cardiac endothelial cells, which communicate with cardiomyocytes by secretion of autocrine and paracrine mediators"* (Kuhn, 2015; Paulus and Tschope, 2013). *"Cardiomyocytes sense these ligands through a multitude of G-protein-coupled receptors, growth factor receptors, and cytokine receptors"* (Fig. 4,5) (Heineke and Molkentin, 2006). *"Orchestrated mechanisms of the induction, maintenance, and progression of cardiac hypertrophy, particularly left ventricular hypertrophy, underlie a series of*

events that follows the activation of cardiomyocytes upon pressure overload/mechanical stress" (Bazgir et al., 2023).

Activation of the local renin-angiotensin system (RAS). *"In addition to the"* classic *"circulating renin-angiotensin system (RAS)"* (Campbell, 1987; Peach, 1977), *the heart"*, similar to many tissues, exhibits a local RAS that may mediate *"autocrine, paracrine, and intracrine effects"* (Fig. 4) (Campbell, 1987; Dinh et al., 2001; Lindpaintner and Ganten, 1991). *"Components of […] RAS, including angiotensinogen (AGT), renin, ACE, AT1 and AT2 are expressed in the heart"* (Baker et al., 1992; Lee et al., 1993). Consistent with data, the expression of several RAS components *"is upregulated in cardiomyocytes in vitro in response to stretch"* (Table 3) (Malhotra et al., 1999; Sadoshima et al., 1993), indicating that mechanical stress may activate a local RAS thereby increasing the amount of AT-II in the cardiac microenvironment. Several other studies have suggested *"that hemodynamic overload activates the local RAS and highlighted the crucial role of the AT 1 receptor"* in load-induced *"cardiac hypertrophy"* (Table 3) (Cohn et al., 2001; Fan et al., 2019; Griendling et al., 1996; Kojima et al., 1994; Komuro et al., 1990; Komuro and Yazaki, 1993; Lindholm et al., 2002; Pitt et al., 2000; Sadoshima et al., 1992; Sadoshima et al., 1993; Watanabe et al., 2021; Yamazaki et al., 1995a). *"Thus, mechanical stress can be considered the major upstream trigger that activates the local RAS and leads to increased AT-II levels throughout the microenvironment"* (Bazgir et al., 2023).

Reactive oxygen species (ROS). *"Reactive oxygen species (ROS) such as superoxide anion (O^{-}_{2}), hydroxyl (OH), and hydrogen peroxide (H_2O_2), and reactive nitrogen species including nitric oxide (NO) and peroxynitrite ($ONOO^{-}$) classify reactive species involved in redox signaling. The latter results from the reaction of O^{-}_{2} with NO"* (Pacher et al., 2007). Data indicate *"that both, direct and indirect mechanisms, resulting from redox signaling within and between endothelial cells and cardiomyocytes" account "for functional communication between these cells"* (Zhang and Shah, 2014). *"Moreover, redox signaling not only influences many physiological processes in the heart but also plays an important role in pathological cardiac remodeling"* (Burgoyne et al., 2012; Hafstad

et al., 2013). Although, several sources of ROS have been described in cardiac cells, *"such as mitochondria (Tsutsui et al., 2009), xanthine oxidase (XO) (Nishino et al., 2008), uncoupled NO synthases (NOS) (Carnicer et al., 2013), and NADPH oxidases (Noxs)"* (Zhang et al., 2013). *"The interactions of NOX proteins with NOS-derived NO have been highlighted to be particularly important for redox signaling in the development of heart failure"* (Fig. 4) (Nediani et al., 2011; Zhang et al., 2013; Zhang et al., 2012) (Bazgir et al., 2023).

"An increase in the cardiac generation of ROS and therefore an increase in oxidative stress has been implicated in pressure-overload-induced left ventricular cardiac hypertrophy (LVH) and heart failure" (Fig. 4) (Chien, 1999; Dhalla et al., 2000; Nakamura and Sadoshima, 2018; Sugden and Clerk, 1998a). Consistently, *"the development of cellular hypertrophy and remodeling has been found to implicate increased ROS production, and activation of the mitogen-activated protein kinase (MAPK) superfamily, where redox-sensitive protein kinases, are known to be partly responsible. Moreover, cardiomyocyte apoptosis and necrosis may be due to increased oxidative stress"* (Fig. 7), *"which is described to be associated with the transition from compensated pressure-overload hypertrophy to heart failure. Furthermore, alterations in the redox-sensitive activity of several key proteins including sarcolemma ion channels and exchangers and sarcoplasmic reticulum calcium release channels, which collectively account for excitation-contraction coupling, contribute for myocardial contractile dysfunction"* (Fig. 7). *"Beyond that, consequent generation of peroxynitrite ($ONOO^-$) as a result of increased inactivation of NO has been attributed to indirect effects of ROS, leading to coronary vascular endothelial dysfunction and peroxynitrite-induced inhibition of myocardial respiration"* (Shah and MacCarthy, 2000) (Bazgir et al., 2023).

"Several mediators including AT-II, ET-1, a-adrenergic agonists, TNF-α, and mechanical forces trigger Nox2 activation. Via induction of four cytosolic regulatory subunits ($p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and RAC1), these mediators initiate O_2^- production" (Table 4) (Brown and Griendling, 2009), *"indicating that pressure overload subsequently increases O_2^- levels"* (Fig. 4). *"Excessive O_2^- levels interact extremely rapidly with NO, resulting in peroxynitrite ($ONOO^-$) formation"* (Table 4), *"thereby disrupting physiological NO signaling"* (Hare, 2004; Nediani et

al., 2011). *"Hence, pressure overload shifts the balance towards increased ROS" (Fig. 4), "a condition that suppresses the physiological functions of NO. Consistently, O_2^- has long been recognized to be implicated in severe cardiovascular diseases. Moreover, reports indicate that NOS may generate O_2^- instead of NO, a condition referred to as uncoupled NOS. The switch to O_2^- generation appears as a consequence of tetrahydrobiopterin (BH4) depletion (usually through oxidation to BH2) or as NOS enzymes undergo post-translational modification"* (Chen et al., 2010). *"Consistent, increased levels of O2- and ONOO- may be implicated in an amplifying mechanism that aggravates NOS uncoupling through the oxidation of BH4"* (Landmesser et al., 2003). *"Hence, as outlined above, several studies indicate that reactive oxygen species should be considered as group of key mediators driving pathological remodeling in the microenvironment of cardiac hypertrophy* (Fig. 4), *especially regarding pressure overload"* (Bazgir et al., 2023).

Endogenous storage pools of AT-II in secretory granules. *"AT-II secretion into the culture medium upon mechanical stress of isolated cardiomyocytes has been observed and provides some evidence supporting the concept of increased local concentrations of AT-II"* (Table 3) (Sadoshima et al., 1993). *"Potential autocrine and paracrine regulatory mechanisms of AT-II may activate the AT1 receptor on cardiomyocytes and surrounding cells (Table 2)"* (Kala et al., 2023; Sadoshima and Izumo, 1996). *"This in turn has been proposed to induce the release of autocrine and paracrine mediators, including vasoactive peptides, growth factors, cytokines, and ECM components, such as collagen"* (Table 4; Fig. 4) (Gray et al., 1998; Harada et al., 1997; Jiang et al., 2007; Pellieux et al., 2001). *"Potentiated or sustained AT1 receptor activation is likely associated with cardiomyocyte hypertrophy, fibroblast hyperplasia, and fibrosis"* (Fig. 7) (Harada et al., 1998a; Harada et al., 1998b; Sadoshima and Izumo, 1993). *"Alternative mechanisms have been proposed to contribute to the activation of the AT1 receptor upon binding of AT-II"* (Tóth et al., 2018), *"including membrane stretch and mechanoactivation that can in turn promote distinct conformational rearrangements in the receptor, leading to alternative signaling outcomes"* (Hunyady and Turu, 2004; Wang et al., 2018) (Bazgir et al., 2023).

"Several proteins have been implicated as sensors of mechanical stretches, such as muscle LIM proteins, integrins, and their associated signaling pathways" (Brancaccio et al., 2003; Knoll et al., 2002). *"Network models have been developed to predict how these mechano-sensitive proteins work together to coordinate cardiomyocyte hypertrophy"* (Saucerman et al., 2019; Tan et al., 2017). *"Mechanisms that integrate these events and propagate the stress signal to the AT1 receptor after activation by mechanical stress remain areas of active investigation. Interestingly, despite the absence of AT-II/AT1 signaling, cardiac hypertrophy, systolic dysfunction, and fibrosis occurred in response to pressure overload"* (Fig. 7) (Harada et al., 1998a) (Bazgir et al., 2023).

The two faces of the TGF-ß signaling. AT-II-activated fibroblasts stimulate paracrine cardiomyocyte hypertrophy upon TGF-ß and ET-1 release *"(Table 2)"* (Gray et al., 1998). TGF-ß may as well act autocrine. According to findings, TGF-ß, similar to mechanical stress, *"promotes fibroblast proliferation and extracellular matrix production"* (Table 4; Fig. 4), *"especially collagen and fibronectin, whereas degradation of these components is reduced"* (Border and Noble, 1994). *"Several studies report that the canonical TGF-ß/SMAD2/3 signaling pathways"* (Fig. 5) *"induce the expression of genes related to collagen, fibronectin, and other ECM proteins"* (Bujak et al., 2007; Ryer et al., 2006; Verrecchia et al., 2001; Yang et al., 2003), *"which concomitantly contribute to cardiac fibrosis"* (Fig. 4) (Kuwahara et al., 2002). Experiments with pressure-overload rats using *"a TGF-ß neutralizing antibody inhibited fibroblast activation and proliferation, and diastolic dysfunction"* (Kuwahara et al., 2002). *"These data suggest TGF-ß as a central target and the inhibition of TGF-ß as beneficial. In line with this, cardiac fibrosis was attenuated in SMAD3 deficient mice subjected to cardiac pressure overload, but interestingly cardiac hypertrophy and cardiac dysfunction were aggravated"* (Divakaran et al., 2009). *"Also, another rat model revealed that worsened cardiac remodeling and increased mortality correlate with a reduction of ECM using a TGF-ß neutralizing antibody after myocardial infarction"* (Frantz et al., 2008) (Bazgir et al., 2023).

Transforming growth factor beta *"(TGF-ß)-activated kinase 1 (TAK1) binds directly to type II (TBRII) TGFß receptors. Identification of this interaction links*

TAK1 to the TGF-ß signaling cascade, implicating an additional way of hypertrophy induction in cardiomyocytes by TGF-ß signaling" (Watkins et al., 2006). *"Thus, aside from contributing to cardiac fibrosis, the non-canonical TGF-ß/TGF-ß activated kinase 1 (TAK 1) signaling pathway has also been reported to promote cardiac hypertrophy"* (Fig. 5) (Zhang et al., 2000) (Bazgir et al., 2023).
In conclusion, different experimental setups reveal varied consequences in response to inhibiting TGF-ß. *"Altogether, TGF-ß is released from cardiomyocytes, fibroblasts, and endothelial cells in the healthy heart (Table 2)"* (Bujak and Frangogiannis, 2007; Euler, 2015) *"and in the context of injury and repair also from myofibroblasts and infiltrating immune cells"* (Lindahl et al., 2002; Wipff et al., 2007). *"Thus, TGF-ß seems to be involved in adaptive or maladaptive processes most likely depending on the context, and may locally trigger interactions between different cell types such as cardiomyocytes and fibroblasts"* (Fig. 4) *"and thereby impact cardiac hypertrophy, fibrosis, and the development of heart failure"* (Fig. 7) (Bazgir et al., 2023).

Endothelin-1 effects. *"Endothelin-1 (ET-1) is an endothelium-derived vasoconstrictor of 21 amino acids. Later, two additional homologs (ET-2 and ET-3) were identified. ET-1 is released from vascular endothelium and other cells including cardiomyocytes (Fig. 4) after cleavage from a large precursor peptide"* (Chowdhury et al., 2019; Suzuki et al., 1993b). *"ET-1 is the predominant endothelin in the heart and is identified as a potent hypertrophic stimulus in neonatal cardiomyocytes"* (Jankowich and Choudhary, 2020; Shubeita et al., 1990). *"ET-1 is the ligand to two GPCRs: ET-A and ET-B. 90% of the endothelin receptors on cardiomyocytes belong to the ET-A subtype"* (Fig. 5) (Kedzierski and Yanagisawa, 2001). *"In rat hearts, the ET-A is predominant and identified to be coupled to both the Gq and Gi subfamily of G-proteins"* (Fig. 5) (Hilal-Dandan et al., 1994) (Bazgir et al., 2023).
"In addition, a characteristic pattern of gene expression is induced by ET-1 in ventricular neonatal rat cardiomyocytes (NRC) including immediate early genes (c-FOS, c-JUN, EGR-1), early genes (ANF, β-MHC, α-sk actin), and later on, ventricular MLC-2 and α-cd actin" (Sugden and Bogoyevitch, 1996). *"The Gq-RAS-RAF-ERK pathway may be involved in these transcriptional changes"* (Fig.

5). *"Furthermore, ET-1 activates the Ras-MEKK1-SEK-JNK pathway contributing to the hypertrophy-associated gene expression program field"* (Bogoyevitch et al., 1996). *"ET-1 causes cell damage in cardiomyocytes in vivo, and experiments with long-term treatment with the ET-A receptor blocker BQ-123 showed improved survival of rats with heart failure"* (Sakai et al., 1996) (Bazgir et al., 2023).

"The release of ANP and BNP from cardiomyocytes can also be triggered by AT-II and ET-1" (Table 4), *"though cardiomyocyte stretch is the main regulatory mechanism for ANP and BNP production"* (Table 3) (de Lemos et al., 2003; Nishikimi and Nakagawa, 2022) (Bazgir et al., 2023).

FGF-2 effects in scar formation. *"In general, considering the epigenetic state and very low proliferative potential of adult cardiomyocytes, consensus exists that there is only a small ability to regenerate injured myocardium through the proliferation of cardiomyocytes"* (Anversa and Nadal-Ginard, 2002; Auchampach et al., 2022; Du et al., 2022; Pasumarthi and Field, 2002). *"Instead, scar formation occurs through infiltrating highly proliferative fibroblasts"* (Fig. 4, 6) (Greenberg, 2001; Venugopal et al., 2022). *"A key player is FGF-2 (bFGF), which is expressed by numerous cell types in the adult myocardium. FGF-2 is released upon cardiac injury from its "storage site" (Table 2)"* (Table 4) *"thereby potentially activating cell surface receptors, such as FGFR"* (Fig. 5) (Detillieux et al., 2003; Rao et al., 2020). *"Moreover, AT-II, ET-1, and FGF-2 itself have been reported to stimulate FGF-2 gene expression"* (Table 4) (Detillieux et al., 2003; Jimenez et al., 2004). *"Accordingly, FGF-2 increases both fibroblast and myofibroblast proliferation"* (Table 4) (Fortier et al., 2021; Galzie et al., 1997; Hoerstrup et al., 2000), *"therefore contributing to both"* increased *"scar formation and stiffness during cardiac injury"* (Fig. 6) (Bazgir et al., 2023).

"Noteworthy, FGF-2 exists as isoform with a high molecular weight (Hi-FGF-2) and low molecular weight (Lo-FGF-2)" (Liu et al., 1993), *"thus it is important to determine the potential effects of both in the context of cardiac hypertrophy and tissue remodeling. In the past, several in vitro studies revealed evidence for an important role of FGF-2 in cardiac hypertrophy"* (Fig. 4). *"Consistent with reports Lo-FGF-2 alters the gene profile of contractile proteins from 'adult' to 'fetal'*

programs when added to cultured neonatal cardiomyocytes" (Parker et al., 1990), *"a distinct characteristic that is attributed to pressure overload-induced cardiac hypertrophy in vivo"* (Bazgir et al., 2023).

"Although data seems contradictory as others reported that cardiomyocyte hypertrophy is stimulated only by Hi-FGF-2, both in vivo and in vitro" (Jiang et al., 2007; Santiago et al., 2011). Consistently, *"Hi-FGF-2 accumulates preferentially in response to stress stimuli"* (Fig. 4), *"including AT-II"* (Peng et al., 2002) *"and oxidative stress"* (Tong et al., 2020; Vagner et al., 1996). *"This is further supported by others who found that Hi-FGF-2 is preferentially accumulated and released by cardiac fibroblasts which induce paracrine cardiomyocyte hypertrophy (Table 2)"* (Pellieux et al., 2001). *"Once released, Hi-FGF-2 may directly interact and activate the tyrosine kinase receptor FGFR-1"* (Fig. 5) (Gualandris et al., 1994), *"and downstream"* mitogen-activated protein kinase *"signaling"* (Bogoyevitch et al., 1993; Pellieux et al., 2001). *"Lo-FGF-2 exhibits cardioprotective effects, especially against post-ischemic cardiac dysfunction"* (Liao et al., 2009). *"One mechanism for the effects of Lo-FGF-2 is its potent angiogenic activity that may increase resistance to ischemic injury and cardioprotection"* (Detillieux et al., 2003; Jiang et al., 2002; Jiang et al., 2004). "In conclusion, these data imply that Hi-FGF-2 is a contributor in cardiac hypertrophy, fibrosis, and heart failure" (Fig. 7), *"while Lo-FGF-2 seems to exert opposite functions as component of adaptional responses in the injured myocardium"* (Santiago et al., 2014) (Bazgir et al., 2023).

"FGF-2 null mice had a marked reduction of the hypertrophic response in cardiomyocytes in response to pressure overload" (Schultz et al., 1999). However, questions remain about whether entirely blocking FGF-2 is therapeutically beneficial. *"Considering data highlighting the role of FGF-2 in the progression of many cancer types"* (Dow and deVere White, 2000; Halaban, 1996; Kumar-Singh et al., 1999; Morrison et al., 1994; Reed et al., 1995), *"blocking of FGF-2 may have beneficial effects as shown in reports on the elimination of tumor angiogenesis"* (Auguste et al., 2001). *"But, in the context of ischemic heart disease, inhibition of FGF-2 may be detrimental, since an angiogenic effect by Lo-FGF-2 upregulation may be desirable"* (Detillieux et al., 2003; Jiang et al., 2002; Jiang et al., 2004). To date, the available data

emphasizes the many biological functions of FGF-2. *"Although data"* is suggesting *"functions for Hi-FGF-2 and Lo-FGF-2 in the myocardium, further investigation are certainly needed to understand a) the precise […] targeting one or the other isoform, b) the effect on exact organ/ cell, and c) to define the precise function of the isoforms in the context of cardiomyocyte hypertrophy and fibrosis. Additionally, unwanted effects of Hi-FGF-2 and Lo-FGF-2 need to be considered"*. Plus, next to FGF-2, also *"TGF-ß, AT-II, catecholamines, and other molecules […] orchestrate the response to hemodynamic stress"* (Fig. 4), *"[…] targeting just one mediator may not be"* successful (Bazgir et al., 2023).

The most prominent downstream effector of FGF-2 signaling, ERK, *"plays a predominant role in the development of both physiological and pathological cardiac hypertrophy"* (Fig. 5). Upon activation through pressure overload and mediators, the cytosolic functions of ERK are believed to *"promote the development of physiological hypertrophic conditions"*, while *"nuclear transcriptional activations mediated by ERK promote a pathological hypertrophic response"* in cardiomyocytes (Fig. 5) (Lorenz et al., 2009; Tomasovic et al., 2020). *"Hypertrophic stimuli such as angiotensin II, ET-1, cytokines, catecholamines, and biomechanical stress may also contribute to detrimental ROS formation in cardiomyocytes, and additional autophosphorylation of ERK1/2 has been reported to trigger pathological ERK1/2-mediated cardiac hypertrophy"* (Fig. 5) (Laskowski et al., 2006; Ruppert et al., 2013). Subsequently, *"these changes can […] activate several hypertrophic signaling mediators that are regulated by ERK1/2"* (Takimoto and Kass, 2007; Tomasovic et al., 2020) (Bazgir et al., 2023).

The *"hyperactivation of ERK1/2 activity is most frequently"* associated with hypertrophic cardiomyopathies *"caused by genetic abnormalities"* (Alcalai et al., 2008; Towbin, 2014). Although *"genetic variant-induced hyperactivation of ERK is closely linked to pathogenic remodeling"*, treatment with simvastatin can normalize ERK activation, restore contractility, and protect against fibrosis in animal models (Patel et al., 2001; Robinson et al., 2018) (Bazgir et al., 2023).

A *"study reported different cardiac hypertrophic responses"* in *"mice that completely lacked ERK1/2 protein in the heart and mice that expressed an*

activated MEK1 in the heart". In mice lacking ERK1/2, inhibiting MEK-ERK1/2 *"causes eccentric cardiac growth with elongated cardiomyocytes".* On the other hand, the overexpression of an active MEK1 mutant that activates MEK1-ERK1/2 signaling *"appears to be responsible for the concentric type of hypertrophy with thicker cells"* (Kehat et al., 2011). *"Thus, increased pre- versus afterload"* has been *"described to result in typical hypertrophic responses"*, and ERK1/2 appears to play a central role in *"partially regulating the underlying molecular mechanisms*. The induction of *"ERK1/2 translocation to the nucleus in adult rat myocytes"* corresponds to *"reduced myocyte lengths and increased width under both baseline and chronic pacing conditions"* (Davis et al., 2016), *"pointing to the critical role played by ERK signaling in balancing concentric and eccentric hypertrophic growth"* (Fig. 5) (Bazgir et al., 2023).

Cytokines and inflammasome in cardiac remodeling. Members of the Interleukin-6 (IL6) family of cytokines *"are key molecules for local regulation of hypertrophic responses in cardiomyocytes"* (Fig. 4). *"Pressure overload acts as a strong trigger for the upregulation of genes related to leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1) in the adult human myocardium"* (Table 3) (Pan et al., 1998; Pemberton et al., 2005). Consistently, cardiomyocytes and cardiac fibroblasts both express leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1) *"(Table 2)"* (Feng et al., 2022; King et al., 1998; Kuwahara et al., 1999). *"The release of Hi-FGF-2 from cardiac fibroblasts (Table 2) has been suggested to act in an autocrine way and trigger the release of pro-hypertrophic CT-1"* (Table 4) (Aoyama et al., 2000; Freed et al., 2003; Pellieux et al., 2001). *"Moreover, cardiomyocytes also express autocrine-acting CT-1, and CT-1 induces hypertrophy of cardiomyocytes in vitro"* (Guseh and Rosenzweig, 2017; Wollert et al., 1996) (Bazgir et al., 2023).

"Increased production and release of LIF, CT-1, and IL-6 in cardiac fibroblasts in response to AT-II can contribute to cardiomyocyte hypertrophy by paracrine activation of the gp130-linked downstream signaling" (Table 4; Fig. 5) (Sano et al., 2000). *"Interestingly, IL-6 contributes to the induction of massive collagen release by cardiac fibroblasts in response to AT-II and norepinephrine stimulation"* (Briest et al., 2003; Sarkar et al., 2004), *"consistent with a pro-*

hypertrophic response". However, another study reported that *"LIF stimulates several beneficial effects including reduction of collagen production and matrix metalloproteinase (MMP) activity in cardiac fibroblasts"*, and inhibition of cardiac fibroblast to myofibroblast differentiation (Wang et al., 2002). *"Likewise, the role of CT-1 seems unclear as consistent with reports"* CT-1 has potent hypertrophic effects on cultured cardiomyocytes (Pennica et al., 1995; Ping et al., 2021) *"in addition to cardioprotective effects such as promoting cardiomyocyte survival"* (Sheng et al., 1997). *"In conclusion, during the process of developing cardiac hypertrophy, cytokine release is increased in response to a variety of stress stimuli, including pressure overload, injury, and mediators like AT-II. However, since IL-6 has a negative inotropic effect, its function is still unclear"* (Finkel et al., 1992), *"suggesting the possibility of detrimental impacts by IL-6 driving hypertrophy toward heart failure"* (Bazgir et al., 2023).

"According to data binding of all IL-6-type cytokines to their common receptor subunit gp130 potently activates STAT3 and to a lesser extent STAT1" (Fig. 5) (Heinrich et al., 1998; Rose-John et al., 2023). Data obtained from a study of *"transgenic mice with cardiac specific STAT3 over-expression found that STAT3 holds a key role in hypertrophic and protective signaling, respectively. STAT3 induced the expression of cardiac protective factors and guarded against decreases in the expression rates of cardiac contractile genes in the case of doxorubicin-induced cardiomyopathy"* (Kunisada et al., 2000). *"In line with this, another study that used pressure overload on ventricular-restricted gp130 receptor knockout mice found a rapid onset of dilated cardiomyopathy and induction of cardiomyocyte apoptosis. In comparison, a normal cardiac structure and function was found under basal conditions, and compensated hypertrophy was found in control mice under pressure overload"* (Hirota et al., 1999). *"These observations suggest a key role of the gp130/STAT pathway in cardiomyocytes for transmitting adaptive and protective functions in response to pressure overload and injury".* However, a study with *"transgenic mice that expressed a dominant negative mutant of gp130 (to decrease activation of this pathway) reported concomitant to a suppressed STAT3 activation a significantly smaller hypertrophic response when subjected to pressure overload"* (Uozumi et al., 2001), *"suggesting a prohypertrophic function for STAT3. Whether the effects of*

the gp130 signaling pathway are beneficial or detrimental remains unclear. Since pressure overload triggers hypertrophic responses in cardiomyocytes via GPCRs in turn activating PKC and PKD" (Fig. 5) (Dorn and Force, 2005), *"potential crosstalk of signaling pathways could be involved. Likewise, neonatal rat cardiomyocytes showed that stretch induces a transient activation in a sequential time order"* of *"PKC and […] downstream targets as"* Raf1 and MEKK as well as *"the successive components of the MAPK signaling cascade"* (Fig. 5) (Yamazaki et al., 1995b) (Bazgir et al., 2023).

"In contrast, YAP1, a downstream effector of Hippo signaling that regulates proliferation, survival, and organogenesis in mammalian cells, that can also be activated through SRC-mediated gp130 activation in cardiomyocytes" (Li et al., 2020), *"is involved in cardio-protective mechanisms against pressure overload stimulation"* of *"cardiac hypertrophy"* (Fig. 5). Activation of YAP transcriptional activity under chronic pressure overload conditions reduces the development of cardiac hypertrophy. Moreover, it reduces the effects of apoptosis and fibrosis on cardiomyocytes, which can be prerequisites for myocardial infarction (Byun et al., 2019). Under pressure overload conditions, the transcriptional activity of YAP mediates compensatory cardiac hypertrophy (Yang et al., 2015) *"to stop the progression of wall stress into myocardial infarction"*, while the effects of YAP signaling loss-of-function drives cardiomyocytes towards heart failure (Kashihara et al., 2022) (Bazgir et al., 2023).

"Concomitant hypertrophic responses via activation of PKC and MAP kinases can also be triggered by AT-II" (Fig. 5). Whereas reportedly *"cardiomyocytes under mechanical stress secrete AT-II"* (Bhullar and Dhalla, 2022; Sadoshima et al., 1993). *"Here, active PKC, with its numerous nuclear and cytosolic"* downstream *"substrates"* (Nishizuka, 1995) indicates *"the extensive crosstalk of signaling pathways in response to pressure overload. The alpha-isoform of PKC directly activates RAF1"* (Kolch et al., 1993; Luo et al., 2019), *"providing evidence for a complex link between the signaling pathways downstream of growth factor receptors in the context of cardiac hypertrophy. Others have reported that GPCR signaling can be* crosslinked *directly to Ras"* (Fig. 5) (Pudewell et al., 2021; Sadoshima and Izumo, 1996), *"and GTP-bound RAS interacts with many downstream effectors which in turn transmit the signal for activating multiple*

signaling pathways" (Nakhaei-Rad et al., 2023; Nauth et al., 2023), *"potentially promoting hypertrophic responses in cardiomyocytes"*. Concomitant, *"others reported that the C terminus of the AT 1 receptor associates with JAK2 upon binding of the ligand, resulting in JAK2/STAT3 pathway activation"* (Ali et al., 2000; Ali et al., 1997; Marrero et al., 1995; Seta et al., 2002), *"indicating another example of the crosstalk"* interaction *"of signaling pathways in response to hypertrophy-associated stress signals. These lines of evidence indicate that the discrepancy of data regarding the gp130 signaling pathway may be due to the extensive crosstalk between intracellular signaling pathways"* (Fig. 5). *"Taken together, there are contradictory reports regarding the individual effects of IL-6, LIF, CT-1 and their signaling via the gp130 pathway in cardiac hypertrophy, thus further investigation is necessary for elucidating the exact mechanisms"* (Bazgir et al., 2023).

Calcineurin/NFAT in cardiac hypertrophy. *"Calcineurin as a Ca^{2+}-dependent serine/threonine protein-phosphatase has been found to exhibit central pro-hypertrophic functions in the myocardium"* (Fig. 5) (Lunde et al., 2022; Luo et al., 2021; Molkentin et al., 1998). *"Calcineurin contains two subunits: the 57-61-kDa catalytic subunit (CnA) and the 19-kDa regulatory subunit (CnB). Activation of this dimeric protein occurs through direct binding of the Ca^{2+}-saturated adaptor protein calmodulin"* (Chaklader and Rothermel, 2021; Wilkins and Molkentin, 2004). *"The mammalian heart only expresses CnAα, CnAβ, and CnB1, although there are three genes including CnAa, ß, and y encoding for CnA, and two genes (CnB1 and B2) encode for CnB. Calcineurin becomes activated in response to increased Ca^{2+} levels, which enables binding to transcription factors of the nuclear factor of activated T cells (NFAT) family"* (Fig. 5) (Chaklader and Rothermel, 2021; Wilkins and Molkentin, 2004) (Bazgir et al., 2023).
"Pro-hypertrophic gene expression is activated upon binding, and through dephosphorylation of conserved serine residues at the N terminus of NFAT by calcineurin, resulting in NFAT translocating into the nucleus" (Fig. 5) (Wilkins and Molkentin, 2004). *"Here, NFAT regulates expression of cardiac genes via association with GATA4 and myocyte enhancer factor 2 (MEF2), which are also transcription factors"* (Frey and Olson, 2003; Han et al., 2022; Wilkins et al.,

2002). *"Noteworthy, several studies indicate that NFAT transcription factors act as primary calcineurin effectors in the heart, as they have been identified as necessary and sufficient mediators promoting cardiac hypertrophy"* (Lunde et al., 2022; Molkentin et al., 1998; Wilkins et al., 2002). *"Moreover, cardiomyocytes contain structural proteins located in the repetitive Z-disc that have been found to regulate calcineurin in addition to the activation via increased Ca^{2+}"* (Frey et al., 2004a; Frey et al., 2000b; Heineke et al., 2005; Li et al., 2004; Riaz et al., 2022). *"GPCR stimulation with hypertrophic agonists, including AT-II and PE on cultured neonatal rat cardiomyocytes indicated an increase in calcineurin enzymatic activity"* (Table 4), *"which was induced by increased calcineurin Aß (CnAβ) mRNA and protein, compared to CnAα or CnAγ"* (Taigen et al., 2000; Zhou et al., 2022). Consistent, others found that *"human hypertrophied and failing hearts"* (Fig. 7) *"also exhibit increased calcineurin activity"* (Haq et al., 2000), *"as well as in ventricular muscle with exposure to AT-II, ET-1, and Urotensin II in human failing heart"* (Li et al., 2005). According, others found that *"hypertrophied hearts in rodents subjected to aortic banding displayed upregulated calcineurin activity"* (De Windt et al., 2001; Lim et al., 2000; Saito et al., 2003; Shimoyama et al., 1999; Zou et al., 2001). Above all, *"profound cardiac hypertrophy with rapid progression to dilated cardiomyopathy, extensive fibrosis, congestive heart failure, and sudden death"* (Fig. 7) *"were observed in active calcineurin expressing transgenic mice"* (Molkentin et al., 1998) (Bazgir et al., 2023).

"Upregulated NFAT activity has been observed upon both physiological stimuli (exercise training, growth hormone-IGF1 infusion) and pathological stimuli (pressure overload, myocardial infarction) (Table 1)" (Wilkins et al., 2004). *"In contrast, the hypertrophic response to pressure overload and GPCR agonists was impaired in a model of transgenic mice exhibiting a targeted inactivation of calcineurin Aβ"* (Bueno et al., 2002) *"and in transgenic mice expressing a dominant negative form of calcineurin A"* (Zou et al., 2001). Above all, *"cardiac hypertrophy was prevented in a model using pharmacological inhibition of calcineurin A activity on transgenic mice with constitutively active calcineurin A"* (Chaklader and Rothermel, 2021; Molkentin et al., 1998) (Bazgir et al., 2023).

Taken together, these lines of evidence *"indicate that calcineurin/NFAT plays a major role in the conversion of pathogenic stimuli into pathological cardiac*

remodeling, suggesting it is a key target in the setup of clinical prevention of cardiac hypertrophy" (Fig. 7). *"But data seems contradictory, as a study reported accentuated hypertrophy, impaired histopathology as well as risk for early death when applying calcineurin inhibitors"* (Fatkin et al., 2000). *"Thus, further investigation is necessary to clarify if calcineurin/NFAT could be considered as a key target"* (Bazgir et al., 2023).

ANP/BNP in cardiac hypertrophy. Studies on both human and animal models have reported that the development of pathological cardiac hypertrophy is frequently associated with an increase in mRNA expression of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) (Iemitsu et al., 2001; Sangaralingham et al., 2023; Takahashi et al., 1992), as well as elevated *"plasma levels of ANP and BNP with the severity of heart failure"*. However, under critical conditions, the secretion of BNP exceeds that of ANP, mainly occurring in the ventricles and atria, respectively. But, ANP is also secreted in the ventricles, as heart failure worsens. Thus, *"the ventricles are crucial locations for both BNP and ANP"* (Yoshimura et al., 2001). In the clinical diagnosis and management of heart failure, both ANP and BNP, as well as their more stable cleavage products, NT-proANP and NT-proBNP, respectively, are efficient biomarkers (Fig. 7) (Dunn et al., 2017; Engle and Watson, 2016) (Bazgir et al., 2023).

ANP and BNP not only exert physiological effects such as regulating sodium reabsorption, maintaining water balance, and inhibiting the renin-angiotensin-aldosterone (RAA) system, collectively responding to cardiac pressure and volume dynamics and suppressing heart failure (de Bold et al., 1981; Wong et al., 2017). They also activate the cGMP-dependent PKG (Fig. 5), which in turn stimulates the Ca2+/calmodulin-dependent endothelial nitric oxide (NO) synthase to increase NO production. The latter helps to relax the vascular smooth muscle cells and lower systemic blood pressure (Elesgaray et al., 2008; Gorbe et al., 2010; Wong et al., 2017) (Bazgir et al., 2023).

Together, ANP/BNP and NO have been described to counteract the effects of NE on the size expansion of cardiomyocytes, supposably via the cardioprotective axis mediated by cGMP-PKG, which results in the reduction of NE-stimulated Ca^{2+} influx (Calderone et al., 1998; Gorbe et al., 2010) (Bazgir et al., 2023).

In addition, *"ANP and BNP expression is […] regulated by pro-hypertrophic transcriptional activation of NFAT"*. However, they also act *"as negative regulators of hypertrophy"* through *"PKG-mediated inhibition of calcineurin".* This inhibition helps to limit the nuclear translocation of NFAT (Fig. 5) (Fiedler et al., 2002; Li et al., 2017; Takimoto et al., 2005) (Bazgir et al., 2023).

8. Concluding remarks and future directions

"The microenvironment involved in the development of cardiac hypertrophy involves cardiomyocytes and non-myocardial cells, and the accompanying release of numerous pro-hypertrophic, pro-fibrotic, and pro-inflammatory mediators facilitating reciprocal interactions" (Bazgir et al., 2023).

"Cardiac fibroblasts are the main players in the development of fibrosis, nevertheless, endothelial cells that can undergo EndMT toward a myofibroblast-like phenotype are closely involved as well. Resident and infiltrating immune cells (mast cells, macrophages, neutrophils) enhance these processes while simultaneously contributing to tissue inflammation. Thus, considering all these mechanisms in the hypertrophic microenvironment", it appears that *"tailoring an efficient treatment regimen"* is *"extremely complex",* requiring multidirectional approaches and sophisticated strategies, in which all signaling components are integrated (Bazgir et al., 2023).

"Since it is not feasible to discuss every cellular and molecular process involved in the development of different types of cardiac hypertrophy", this study "*aimed to outline the main drivers of the hypertrophic microenvironment and the respective signaling pathways being affected. A necessary future approach will be the identification of the precise involvement of different cell types, cellular mediators released by them, and the respective activation of second messengers. This will allow us to evaluate the known and thus far unrecognized molecular signaling axes during disease development. Given the high prevalence of heart disease in the Western world, an important future effort should be to translate the knowledge gained into new pharmacological targets that help to delay or even stop the remodeling process and the severe consequences that patients experience after diagnosis of a diastolic or systolic dysfunction"* (Bazgir et al., 2023).

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