Dynamics of intracellular and intercellular redox communication

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Invited Review Article - SFRRI Inaugural Alberto Boveris Award Lecture

Dynamics of intracellular and intercellular redox communication☆,☆☆

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ABSTRACT

Cell and organ metabolism is organized through various signaling mechanisms, including redox, Ca^{2+}, kinase and electrochemical pathways. Redox signaling operates at multiple levels, from interactions between individual molecules in their microenvironment to communication among subcellular organelles, single cells, organs, and the entire organism. Redox communication is a dynamic and ongoing spatiotemporal process. This article focuses on hydrogen peroxide (H_2O_2), a key second messenger that targets redox-active protein cysteine thiolates. H_2O_2 gradients across cell membranes are controlled by peroxiporins, specialized aquaporins. Redox-active endosomes, known as redoxosomes, form at the plasma membrane. Cell-to-cell redox communication involves direct contacts, such as per gap junctions that connect cells for transfer of molecules via connexons. Moreover, signaling occurs through the release of redox-active molecules and enzymes into the surrounding space, as well as through various types of extracellular vesicles (EVs) that transport these signals to nearby or distant target cells.

1. Introduction

Life processes are initiated and regulated through diverse and partially overlapping signaling pathways which depend on specific causal events. Signal transduction leads to short-term and long-term effects on the proteome, genome, and other molecular classes, such as the metabolome, metallome, lipidome, and glycome. The outcome from these signaling inputs manifests as a response pattern that ultimately influences cellular and organismal health *vs.* disease states in biology and medicine. Importantly, these effects are continuously monitored by feedback loops that track molecular fluctuations and changes in gene expression.

Biological signaling pathways operate by various modes, such as direct electrical coupling, ion signaling (notably Ca^{2+}), and post-translational modifications (PTMs) that contribute to the formation of an epiproteome (*e.g.* by phosphorylation/dephosphorylation), generation of an epigenome (*e.g.* via methylation/demethylation), and oxidation/reduction (redox) signaling. This article focuses on the role and regulation of redox communication both within cells and between cells, an active research field which has revealed fascinating new insights. For recent comprehensive reviews on the fundamentals of redox regulation and its implications to health and disease, see Refs. [1–4]. Here, the focus is primarily on H_2O_2 as a pleiotropic signaling agent in biological redox communication [5–7]. A more extensive discussion would include other small-molecule redox messengers, as well as redox potentials of the NAD^+, $NADP^+$ [8,9], and various thiol systems, all of which are enzymatically regulated by powerful dehydrogenases (see Refs. [10, 11]).

2. Redox Organization

Biological redox organisation in terms of chemistry and cell biology is guided by a set of principles, collectively termed the Redox Code [11]. Fig. 1 provides an overview of the major components of biological redox regulation, highlighting redox communication within the organizational framework (in blue). It also includes the underlying concepts (in pink), major molecular players (in green) and life processes (in yellow). This overview illustrates that communication by redox reactions is a

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☆☆ Professor Alberto Boveris has contributed outstanding research to redox biology, and he has been a congenial friend and colleague. The author expresses his heartfelt gratitude for the lifelong friendship with Alberto Boveris (see Sies, H., Fraga, C.G., Cadenas, E., Alberto Boveris (1940–2020). In Memoriam. *Free Radic. Biol. Med.* **152**, iii-v (2020) [117].

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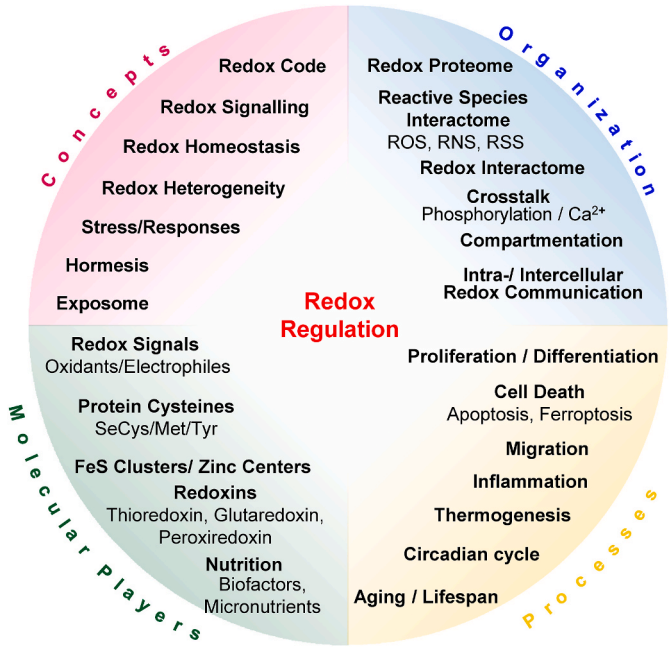

Fig. 1. Global principles governing biological redox regulation
The major aspects of redox regulation in cells and organs are categorized into four quadrants: Organization, Concepts, Molecular Players, Processes. For details, please refer to the text in the Section titled "Redox Organization". An extensive discussion is given in a recent review [1].

fundamental aspect of practically all life processes. Once a redox signal is being generated, it can be transmitted through multiple layers of complexity, ultimately leading to a biological response. Recent advances in techniques enabled researchers to explore cellular redox biology with astounding spatiotemporal resolution [12]. It was pointed out early on that "*a fundamental principle in the organisation of living matter is that order is generated by the introduction of inhomogeneity*" [13].

The general concept of metabolic compartmentation, shown in Fig. 2, also applies to redox reactions. Intracellular compartmentation refers to the definition of a spatial compartment surrounded by permeability barriers like membranes (Fig. 2, top). This concept is further refined by several types of microheterogeneity, including compartmentation by binding, where metabolites are sequestered by specific key binding sites. This interaction influences the free thermodynamic concentration of the metabolite and helps dampen metabolic oscillations (Fig. 2, center). Further, membraneless organelles [14], formed through phase separation and molecular crowding [15] (not shown in Fig. 2), are defined as biomolecular condensates [12,16]. These structures can exist transiently or stably, leading to the formation of supramolecular assemblies such as multienzyme complexes or of redox nanodomains [17] and microdomains [18]. Intercellular compartmentation (Fig. 2, bottom) refers to cell heterogeneity, which is the result of cell differentiation and organ development. Studies of single-cell responses in cell cultures, organoids or intact organs have revealed an additional layer of heterogeneity that influence and are influenced by redox communication.

3. Intracellular redox communication: focus on H_2O_2

Reactive Oxygen Species (ROS) [6], and Reactive Electrophile Species (RES) [20] fulfill vital signaling functions under physiological conditions. A steady state level of H_2O_2 has been recognized as a normal aspect of aerobic cell metabolism [21]. Subsequent studies on the cellular production of H_2O_2 [22], its generation in mitochondria [23,24] and its presence in intact perfused liver [21,25,26] have sparked extensive research into the fundamental chemistry and hydroperoxide metabolism in mammalian systems (see Ref. [27] for early comprehensive review). Research on redox communication gained momentum about two decades ago with the introduction of genetically encoded fluorescent sensors, such as the Hyper [28] and roGFP [29] redox probes (for reviews, see Refs. [30–32]). Maintaining H_2O_2 concentration gradients between various cytological compartments presents an ongoing challenge, referred to as oxidative eustress (see Table 1) [33]. At any given moment, the local concentration of H_2O_2 in a specific compartment reflects the balance of production and removal dynamics.

The physiological production of H_2O_2 is tightly regulated by metabolic processes, including sources like NADPH oxidases (NOX) [40], the mitochondrial electron transport chain [41], and numerous oxidases (see review [6]). H_2O_2 is also enzymatically removed by various peroxidases, notably GSH peroxidases [42], by peroxiredoxins [43,44], and by catalases [45]. Moreover, diffusion plays a role in H_2O_2 clearance, with specialized proteins, such as aquaporins (peroxiporins) [46] and connexins [47], which exert gradient control across membranes. Notably, connexin hemichannels also serve communication functions at subcellular locations other than gap junctions [48]. As a result, the cellular distribution of H_2O_2 resembles a dynamic landscape, characterized by peaks of high concentration and deep troughs rather than a uniform flat pattern. This dynamic profile extends to the targets of H_2O_2, primarily redox-reactive protein cysteinyl thiolate groups that form a veritable 'proteoform landscape' [49] and act as redox switches. The functioning of such redox switches is fine-tuned by physicochemical fluctuations in their microenvironment [50].

Communication between various subcellular organelles is facilitated by structural and functional loci known as membrane contact sites (MCTs) [51]. The intricate redox relationship between the endoplasmic reticulum, mitochondria, and peroxisomes was referred to as 'redox triangle' [52]. These organelles also establish connections with others, including lysosomes, lipid droplets [53], and the plasma membrane [54]. When H_2O_2 is generated inside peroxisomes, it can modulate the sulfenylation profiles of extraperoxisomal redox signaling proteins in the cytosol [55], highlighting the active role of peroxisomes in intracellular redox communication [56]. The plasma membrane serves as a key platform for redox communication with intracellular organelles [57,58], as well as with structures such as the cytoskeleton [59–61], and it is crucial for communication between cells [62] (see next Section below).

Interestingly, the superoxide radical anion, the product of the plasma membrane-located NADPH oxidase, is generated outside the cell and subsequently converted to H_2O_2 by extracellular superoxide dismutase (SOD3). This necessitates the transport of H_2O_2 from the extracellular space into the cell. For example, in growth factor signaling a growth factor binds to the receptor on the exterior of the cell, leading to the assembly and activation of NADPH oxidase within the cell. This process can be described as a "redox signaling slalom" across the plasma membrane (illustrated, for example, in Refs. [63,64]). H_2O_2 is transported into the cell via peroxiporins (mentioned above), with channel gating regulated by persulfidation [65]. In addition, other post-translational modifications of peroxiporins also influence their transport capacity [66].

Another pathway for importing extracellular H_2O_2 into the cell is by endocytosis, a process occurring preferentially at the lipid raft sites, such as caveolae [67]. This process leads to the formation of redox-active endosomes, known as "redoxosomes" [68], via the invagination of the plasma membrane, causing the outer leaflet of the plasma membrane to face inward towards the lumen of the redoxosome. Consequently, superoxide generated by NADPH oxidase is produced within the redoxosome and is then dismutated to H_2O_2 by SOD3. Notably, the formation of active redoxosomes was impressively demonstrated upon growth factor stimulation, using the H_2O_2 sensor Hyper fused to the EGF receptor, revealing a significant increase in H_2O_2 concentration within the redoxosome lumen following EGF addition [18]; for recent discussion of the role of redoxosomes in EGF receptor-dependent redox signaling, see [69]. Moreover, surface-enhanced Raman spectroscopy (SERS)

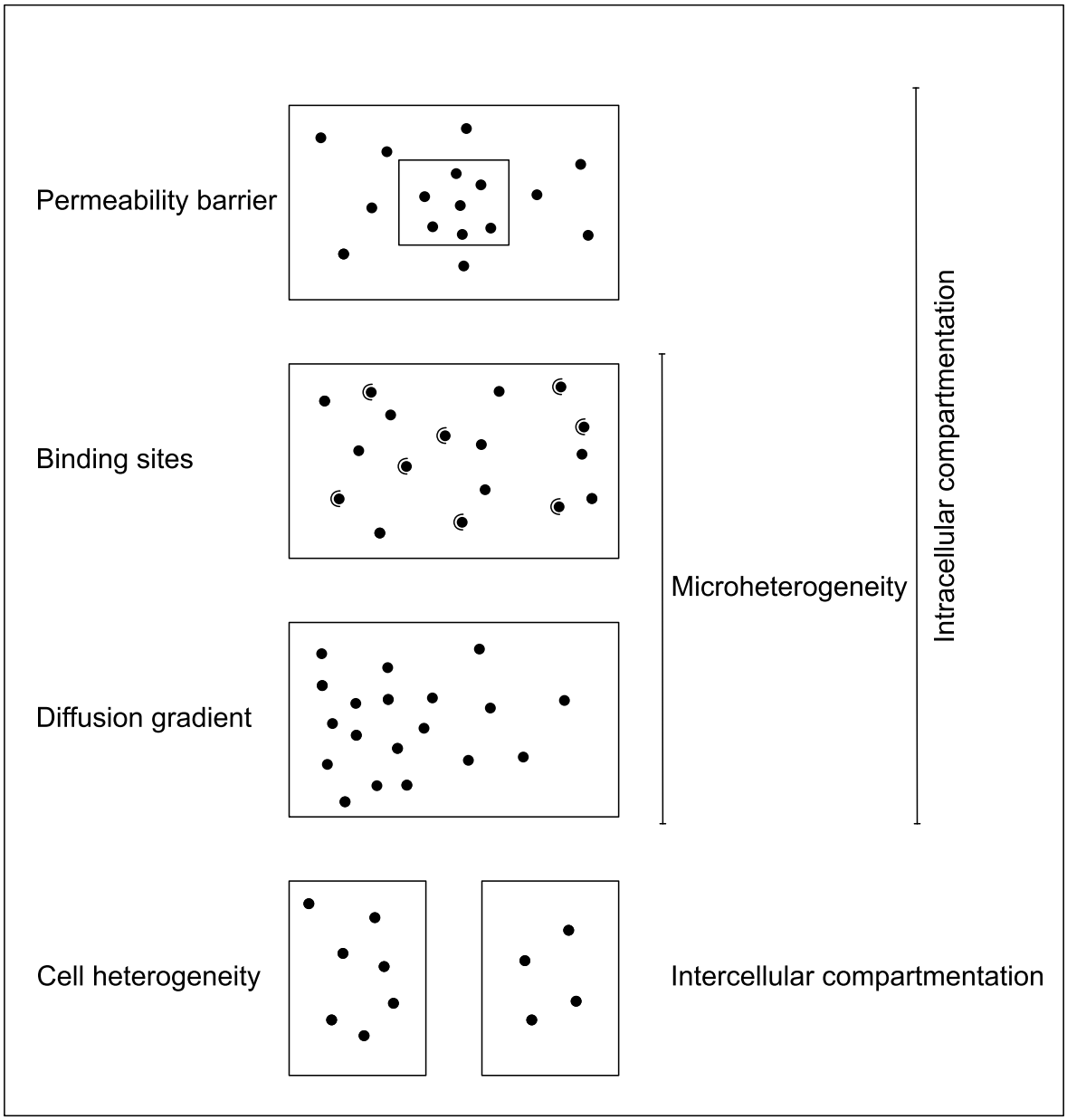

Fig. 2. Intracellular and intercellular compartmentation: Heterogeneity
Various factors contributing to the disparity between the content of a metabolite (per unit volume of cell incubation or tissue) and its thermodynamic concentration. Source: Sies, H., On metabolic compartmentation: Introductory remarks, in: *Metabolic Compartmentation* (Sies, ed.), pp.1-8, Academic Press, London (1982) [19]. *Note*: Membraneless organelles and biomolecular condensates are not depicted.

Table 1
Estimates of cellular hydrogen peroxide concentration.

	H_2O_2 (nM)	Ref.
'Overall cellular'	2–10	[27,34,35]
Cytosol	0.1–2.2	[34,36]
Mitochondrial matrix	<4	[37]
Endoplasmic reticulum	700	[38]
Peroxisome	≫ 4	M. Fransen (pers. comm.)
Nucleus	<0.1	V. Belousov (pers. comm)
Human blood plasma	1–5 μM	[39]

Data compiled from the literature. For more details, see Ref. [33].

identified considerable redox heterogeneity along the lateral dimension of the plasma membrane, with peak H_2O_2 concentrations reaching up to 12 μM, while the overall intracellular concentration was 5.1 nM [35].

The dynamics of redox communication between mitochondria and other cellular compartments has been extensively studied (for example, see Refs. [70–73]). Focusing on the role of mitochondria within intact cells, rather than isolated organelle preparations, reveals that mitochondrial redox dynamics is continuously monitored at different levels. This encompasses not only the dynamics of mitochondrial cristae [74], which have long been associated with bioenergetics [75,76], but also their involvement in spatiotemporal signaling [77,78]. In addition, cellular H_2O_2 levels exhibit diurnal fluctuations that play a role in regulation of circadian rhythms [79].

The nucleus has significant functions in redox communication, including the role of non-coding RNAs [80], a research area not covered here. Also, the role of the mitochondrial permeability transition pore (mPTP) in redox responses and its relationship to calcium ion signaling [81] is another important topic outside the scope of this discussion. The phenomenon known as 'ROS-induced ROS release (RIRR)' [82,83],

exemplified as a sophisticated mechanism for fine-tuning redox communication, represents a biological feedback response to oxidative stress.

The orchestration of the various cellular sources of H_2O_2 production is multifactorial and cell type-specific [84–87]. Stress sensor systems, such as KEAP1, are fine-tuned to detect distinct types of stress independently [88], and the activation of transcription factors in response to H_2O_2 stress is temporally coordinated [89]. A study investigating the various H_2O_2 sources across nine different cell types found that, while mitochondrial contributions vary, in none of them mitochondria were the major contributing source of H_2O_2 [90]. Instead, NADPH oxidases emerge as significant enzymatically controlled contributors to H_2O_2 production, playing critical roles in metabolic and inflammatory signaling [91] within the larger context of reactive immunometabolites [92].

4. Intercellular redox communication: focus on H_2O_2

Redox communication between cells utilizes and expands on the tools described above for intracellular modes of communication [93,94], and it encompasses various means of cellular crosstalk [95]. As illustrated in Fig. 3, direct communication occurs between adjacent cells through gap junctions formed by connexons [47,96], as well as through the pericellular transfer of oxidant signals such as H_2O_2, which can enter neighboring cells by peroxiporins. This cell-to-cell redox communication can spread to multiple cells, creating what was referred to as a "ROS wave", a phenomenon initially observed in plants [97]. This mechanism triggers adaptive stress responses and has been conserved throughout evolution [98].

Furthermore, redox-active enzymes can be released from cells into the extracellular space to facilitate communication with other cells. For instance, thioredoxin, peroxiredoxins, and protein disulfide isomerase A1 (PDIA1) [99] have all been shown to be secreted in this manner. Notably, oxidation-sensitive proteins like PDIA1 are preferentially secreted from the endoplasmic reticulum directly into the extracellular space through a pathway that bypasses the Golgi complex [100,101].

Functional responses to changes in H_2O_2 concentration and oxidative stress [102] have been extensively studied, for example in skeletal muscle [103,104] and in many other processes in physiology and pathology [105,106].

Extracellular vesicles (EVs), which include exosomes and ectosomes (microvesicles), are produced at the plasma membrane or in the endolysosomal system. Once released from the cells, EVs can carry cargo to nearby or distant targets [107–109]. Redox-active exosomes play a crucial role in cell-to-cell signaling [110,111-113] (Fig. 3). For example, they aid in the regeneration of injured axons. When macrophage-derived exosomes containing NADPH oxidase 2 are transferred, the injured axons produce oxidants that deactivate the phosphatase PTEN, thereby enhancing the PI3K-AKT pathway, which is essential for axonal regeneration [114]. Another illustration of biological roles of EVs is their involvement in signaling to the Nrf2/HO-1 axis in stem cell biology [115].

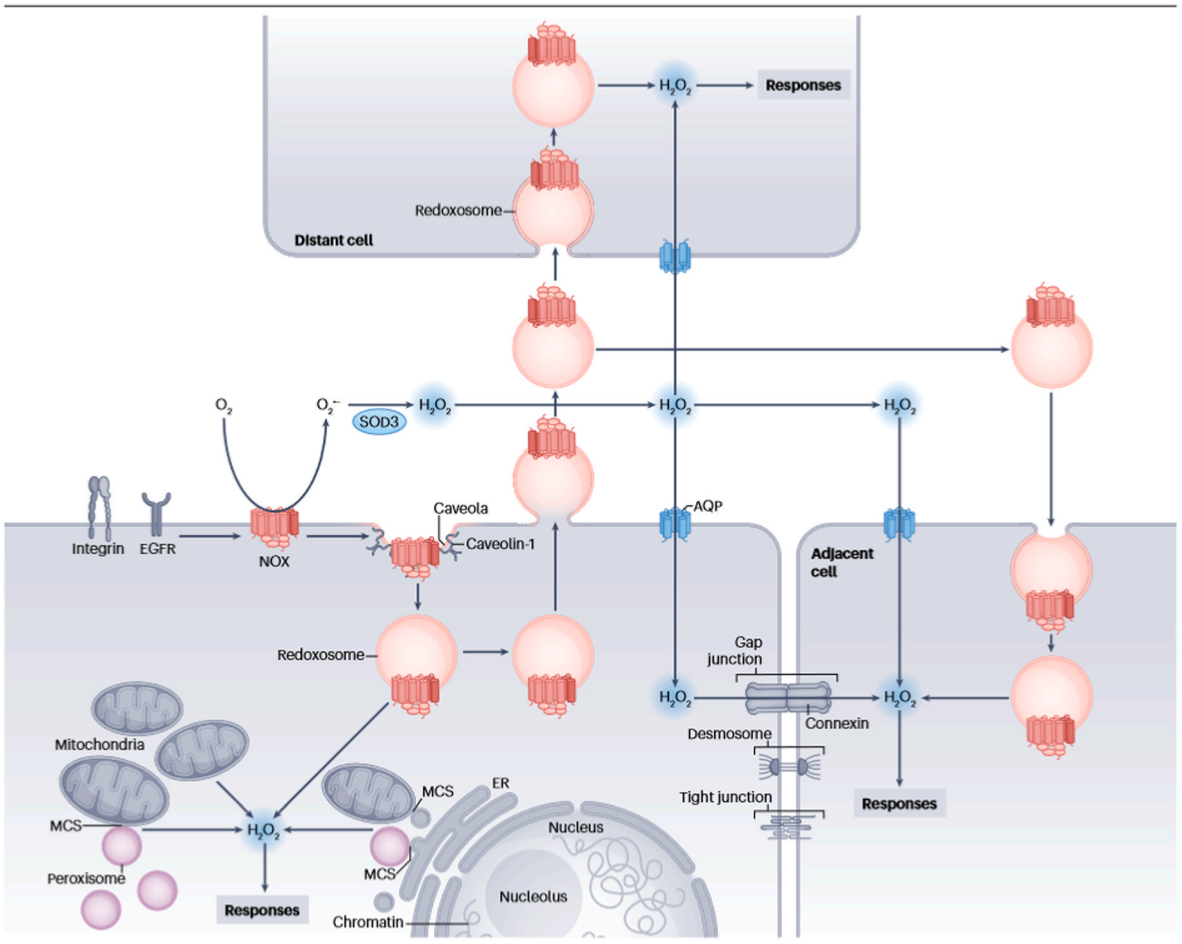

Fig. 3. Schematic overview of redox communication in and between cells.
This simplified scheme focuses on H_2O_2 as a major cellular signaling oxidant. For details, see text. *Source*: Sies, H., Mailloux, R.J., and Jakob, U., Fundamentals of redox regulation in biology, *Nat. Rev. Mol. Cell. Biol.* **25**, 701–719 (2024) [1].

5. Concluding remarks

Dynamic communication within cells and tissues via various signaling routes is an essential feature of living systems. The scope of redox communication spans over ten orders of magnitude, encompassing timescales from the nanosecond interactions between individual molecules to the entire lifespan of an organism. Research on intracellular organelles, including membraneless organelles, has revealed fascinating insights into the continuous monitoring and control of metabolic homeostasis.

The diverse pathways of redox communication between cells, especially in the context of extracellular vesicles (EVs), represent a rich area for further investigation. As indicated in the Introduction, redox communication encompasses many classes of redox-active molecules, but here the focus is restricted to H_2O_2 as a prototypical example. The crosstalk between the different types of signaling modes becomes increasingly amenable to exploration by systems biology and network analysis. Advances in methodologies to study individual molecules noninvasively within their natural microenvironment *in vivo* open perspectives that seemed far-fetched a few decades ago [116].

Declaration of interest

I declare that there is no competing interest.

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