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Oxidative eustress: the physiological role of oxidants

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The perception of a pivotal role of reactive oxygen species (ROS) (Sies et al., 2022), reactive nitrogen species (RNS) and electrophiles (Parvez et al., 2018) in cell biology and physiology has gained widespread acceptance. In recent years, evidence for an important role of reactive sulfur species (RSS) has accumulated as well (Cirino et al., 2023). Oxidative stress is two-sided: whereas excessive oxidant challenge causes damage to biomolecules, the maintenance of a physiological level of oxidant challenge, termed oxidative eustress, is essential for governing life processes through redox signaling (Sies et al., 2017). As life processes utilize metabolic fuel produced by photosynthesis to support structure and function, the main net direction of redox reactions under normal metabolic conditions is towards oxidation. Thus, a constant flow of oxidants is characteristic of the physiological steady-state, i.e., maintenance of flow-equilibrium as opposed to thermodynamic equilibrium where flux is zero. Reductive stress can occur when there is deficiency of oxygen supply or upon excessive load of reductants. This has been incorporated in further development of the concept of stress (Lu et al., 2021).

A general representation of the distinction between eustress and distress is given in Figure 1. Low physiological exposure to oxidants reaches specific targets for redox signaling, supporting fundamental life processes, and the adaptive stress response systems are kept at stand-by mode. The overall cellular concentration of H_2O_2, a central redox signaling agent, is estimated at about 10 nmol L^{-1} H_2O_2, with a range between 1 and 100 nmol L^{-1} H_2O_2, depending on cell type and metabolic state. It should be mentioned that these numbers are for general orientation, because there are steep intracellular H_2O_2 gradients between the various subcellular organelles, mitochondria, peroxisomes, endoplasmic reticulum, nucleus and cytosol. When the oxidant load increases within the physiological range towards the upper threshold of approximately 100 nmol L^{-1} H_2O_2, adaptive stress response systems are activated to counteract the challenge. When the stress response capacity becomes limited, then unspecific targets of biomolecules are also affected, leading to disrupted redox signaling and pathophysiological consequences resulting from molecular damage.

Research on the roles of specific reactive species in cell biology and physiology has advanced due to novel non-invasive techniques which permit studies of subcellular processes within the intact cell and organism (see recommendations in Box 1 in Ref. (Sies et al., 2022)). The nematode, *Caenorhabditis elegans*, is a particularly suitable organism for such studies in development and aging. A striking observation was made by mild treatment of *C. elegans* embryos with paraquat, a redox-cycling agent producing mitochondrial superoxide: the mild treatment with oxidant increased lifespan (Yang and Hekimi, 2010). An augmented stress resistance and prolonged lifespan upon transient exposure to paraquat were attributed to decreased developmental histone H3 lysine4 trimethylation (H3K4me3) levels (Bazopoulou et al., 2019). H3K4me3 levels are redox-sensitive and decrease in response to oxidative stress, and transient decreases upon oxidation at a certain time window during development are sufficient to exert long-lasting effects despite the marked changes in the redox

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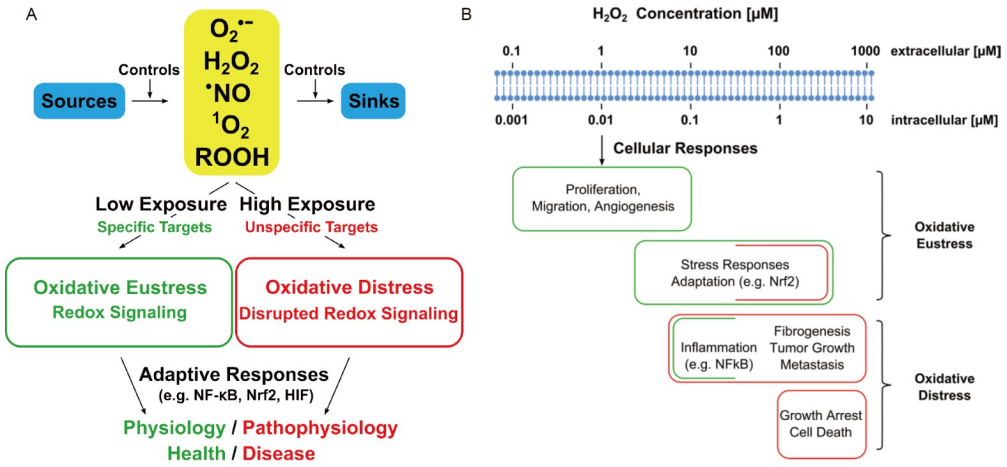

Figure 1 Oxidative stress: eustress and distress. A, Generation and removal of reactive species are enzymatically controlled. In the physiological range of concentration, specific target molecules are addressed in redox regulation (oxidative eustress). At supraphysiological concentration, there are detrimental consequences (oxidative distress) (from Sies, 2020 with copyright permission from Elsevier). B, Schematic representation of the concentration range of H_2O_2 as a signaling molecule for physiological processes (green) and stress responses up to cell damage and cell death (red). The extracellular concentration of H_2O_2 is >100-fold higher than the intracellular concentration (from Sies, 2017 (Open Access)).

environment later on during adulthood (Bazopoulou et al., 2019). These observations establish a link between early-life events, oxidant-sensitive epigenetic marks, stress-resistance and lifespan. The oxidant response follows a hormesis pattern: low exposure leads to an increase in lifespan, which reaches a maximum (eustress), before returning towards the initial lifespan at a certain point of higher oxidant exposure. Beyond this, even higher exposure then shortens lifespan (distress). The point of transition between eustress and distress has been named redox-stress signaling threshold (RST) (Meng et al., 2022). Importantly, RST is not fixed but is modifiable, e.g., it was found to be increased by starvation or by exercise, implicating effects on lifespan and healthspan through lifestyle factors (Meng et al., 2022). Thus, these observations on *C. elegans* can be viewed in a wider perspective of the role of positive oxidative stress (eustress) in aging and aging-related disease tolerance (Yan, 2014).

The molecular mechanisms which orchestrate oxidative stress responses are the focus of current ongoing research. Spatiotemporal control, specific cell-type, and the manifold internal and external cues are subject to further detailed analysis of cell proliferation, differentiation, and cell death mechanisms.

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