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EDITORIAL

Redox signaling and modulation in ageing

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Abstract In spite of considerable progress that has been reached in understanding how reactive oxygen species (ROS) interact with its cellular targets, several important challenges regarding regulatory effects of redox signaling mechanisms remain to be addressed enough in aging and age-related disorders. Redox signaling is precisely regulated in different tissues and subcellular locations. It modulates the homeostatic balance of many regulatory facilities such as cell cycle, circadian rhythms, adapting the external environments, etc. The newly proposed term "adaptive redox homeostasis" describes the transient increase in ROS buffering capacity in response to amplified ROS formation rate within a physiological range. Redox-dependent second messengers are generated in subcellular locations according to a specific set of rules and regulations. Their appearance depends on cellular needs in response to variations in external and internal stimulus. The intensity and magnitude of ROS signaling determines its downstream effects. This issue includes review and research papers in the context of redox signaling mechanisms and related redox-regulatory interventions, aiming to guide for understanding the degenerative processes of biological ageing and alleviating possible prevention approaches for age-related complications.

Keywords Aging · Adaptive redox homeostasis · Redox signaling · Oxidative stress · Senotherapeutics

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This special issue of Biogerontology is the result of an open call for review and research papers in the context of redox signaling mechanisms and related redox-regulatory interventions. The main concept in understanding the degenerative processes of biological ageing and preventing age-related complications. Although considerable progress has been made in understanding how reactive oxygen species (ROS) interact with its cellular targets, several important challenges regarding regulatory effects of redox signaling mechanisms remain not to be addressed enough in aging and age-related disorders. Therefore, we invited the papers for this special issue of Biogerontology, strictly dealing with redox signaling as the main concept in understanding the degenerative processes of biological ageing and preventing age-related complications.

As a brief background, the "Free Radical Theory of Aging", which was put forward by Denham Harman in 1956, mainly based on independent observational study conducted by Rebeca Gershman and Daniel Gilbert (1954). In its main context, Harman's

theory proposed that free radicals and their reactive derivatives cause irreversible oxidative damage over time with the gradual accumulation of structural and functional problems. ROS were initially considered to be only hazardous molecules in redox metabolism but were later found to contribute to other cellular processes. The newly proposed term "adaptive redox homeostasis" describes the transient increase in ROS buffering capacity in response to amplified ROS formation rate (Atayik and Çakatay 2023a,b).

Ineffective redox adaptation and disseminated oxidative injury are the hallmarks of continuing oxidative stress. However, oxidative stress cannot be simply described as the imbalance between ROS formation and antioxidant defense capacity; it also covers impairment in redox sensing and signaling pathways. The term oxidative stress is an expression that is losing its use in modern redox biology. It is now an accepted fact ROS cannot be described as an apparent enemy or friend. Its optimum level modulates signal transduction and stress responses by acting as second messengers for redox-sensitive cascades. Redox-dependent second messengers are generated in subcellular locations according to a specific set of rules and regulations. Their appearance depends on cellular needs in response to variations in external and internal stimulus. The intensity and magnitude of ROS signaling determines its downstream effects. ROS-mediated physiological process plays a crucial role in cellular defense response. These responses are required for phagocytic activity of granulocytes and macrophages. It is a known fact that ROS also have cellular modulatory effects on redox signaling pathways, and that these pathways are in a dyshomeostatic balance with the advancing stage of aging. ROS overproduction, called oxidative stress, leads to disruption of redox signaling-mediated cellular events (Kunkemoeller and Kyriakides 2017; Lennicke and Cochemé 2021; Chaudhary et al. 2023), macromolecular damage and development of degenerative diseases such as diabetes, atherosclerosis, and aging induced proteinopathies (Çakatay 2005, 2008; Gelisgen et al. 2011; Yanar et al. 2020).

Redox sensitive proteins possess a modulatory effect for redox metabolome and related signaling events(Kunkemoeller and Kyriakides 2017; Lennicke and Cochemé 2021). The physiological level of nonradical ROS serves as primary secondary messengers to modulate physiological redox signaling pathways by interacting multiple redox-sensitive protein networks. Basics of the existence and functioning of the cellular redox code were suggested by Jones and Sies (Jones and Sies 2015). Today, "redox signaling" is now used to examine and explain all these pathways. Redox signaling can be defined as a short-lived signaling event that modulates various cellular processes in which its functional components consist of electron transfer reactions involving free radicals or related species, redox-active metal ions (e.g., iron, copper, etc.) or reductive equivalents. Long-term exposure to higher magnitude ROS-mediated signaling contributes to gradual and irreversible cellular defects including impaired proteostasis, aberrant gene expression, mitochondrial dysfunction, and deteriorated intraorganellar crosstalk while short term oxidative challenges resolved swiftly contribute to adaptive redox signaling response (Atayik and Çakatay 2023a,b). Adaptive redox signaling response appears as a result of short-term exposure of redox sensitive proteins to subtoxic levels of ROS which stimulates various redox pathways and transient generation of hormetic responses necessary to regulate redox-sensitive cellular process such as extracellular matrix synthesis and deposition (Eble and de Rezende 2014; Bagulho et al. 2015; Atayik and Çakatay 2023a,b).

Chemolithoautotrophic anaerobes evolved around 3.5 billion years ago as primitive life forms. They obtained all of the energy required for their own metabolism from the oxidation of inorganic substances such as hydrogen, hydrogen sulfide, and reduced metal ions. And today, there is a wide consensus that gradual accumulation of molecular oxygen in the ancient atmosphere favors the evolution of carbon-based aerobic life forms and ROS formation (Eble and de Rezende 2014). Considering the evolutionary perspective, it seems quite reasonable that aerobes have gradually adapted their newly emerged hostile habitat in order to control the harmful effects of ROS while developing new redox active second messengers to accomplish their autocrine and paracrine tasks (Laurindo 2018).

Redox signaling is precisely regulated in different tissues and subcellular locations. It modulates the homeostatic balance of many regulatory facilities such as cell cycle, circadian rhythms, adapting the external environments, etc. (Meng et al. 2021). Diffusible nonradical ROS such as hydrogen peroxide (H_2O_2) serves as signaling messengers to modulate

redox signaling related metabolic pathways by interacting multiple redox sensitive proteins (Xiang et al. 2023). Free-radical messengers that participate in ROS-related redox signaling activity are superoxide radical anion, hydrogen peroxide, hydroxyl radical, nitric oxide, and peroxynitrite. Redox signaling is accomplished by the cascade of redox-sensitive transducer proteins, which can undergo various reversible or irreversible covalent modifications upon ROS interaction including carbonylation, cysteine oxidation, methionine sulfoxidation, etc. Over the past decade, it has become more evident that tissue aging is caused by the gradual accumulation of senescent cells, which alters the physiological responses in the surrounding extracellular matrix in an autocrine and paracrine fashion through senescence-associated secretory phenotype (SASP)-related factors such as chemokines, cytokines, growth factors, and proteases (Atayik and Çakatay 2022, 2023a).

Growing experimental evidence indicates that ROS is an important mediator of several redox signaling pathways such as ROS/P53/P21 (Zhang et al. 2023), 17β-E2-mediated H_2O_2 (Xiang et al. 2023), ROS/VEGF-C/VEGFR3 (Yang et al. 2023), MAPK/NF-ķB, PI3K/Akt, Keap1/Nrf2/ARE, NOX2 (Chirumbolo et al. 2023; Wang et al. 2023; Sharma and Singh 2023; Chaudhary et al. 2023, Homolak 2023), NOX4, FoxO3a, Trx/TrxR (Atayik et al. 2022), Shh signaling pathway (Prajapati et al. 2023) and Sirt1 (Fang et al. 2023) in aging and cellular senescence.

Zhang et al. (2023) has questioned the possible effects of the SARS-COV-2 spike protein in the senescence and found that overexpression of spike protein in the infected cells decreases cell proliferation and causes the deposition of higher amounts of P53, P21, senescence-associated cytokines (e.g., IL-1β, IL-6, IL-8, ICAM, and VEGF), and ROS. Xiang et al. (2023) have assessed if 17β-estradiol possesses protective effects for vascular endothelial cell against senescence by upregulating autophagy. Their results showed that 17β-estradiol increases the estrogen receptors activity and the autophagosome formation but decreases the fusion of lysosomes with autophagic vesicles that decreases the secretion of SASP from H_2O_2. Due to their findings, 17β-estradiol can inhibit H_2O_2-induced senescence. Interestingly, L-lactate which has been incorrectly thought as a toxic remnant of anaerobic metabolism, recently data reported to be an intermittent treatment of skin fibroblasts. L-lactate inhibits the aerobic process, causes accumulation of H_2O_2, phosphorylation of AMPK and activation of the mitochondria biogenesis via PGC-1α, so activating the cellular endowment of survival genes and enzymes and finally acting as a skin protective factor. L-lactate also has shown to be involved in the signaling of neurodevelopment and immune regulation (Chirumbolo et al. 2023). Aging may lead to ROS-driven chronic inflammation, ferroptosis and muscle atrophy in skeletal muscle fibers. Lifelong exercise has beneficial consequences on detrimental effects of aforementioned events. Regulation of redox signaling pathways and Keap1/Nrf2/ARE system exhibits significant variations in different types of muscle types such as quadriceps femoris and soleus muscle (Wang et al. 2023). Sonic hedgehog signaling possesses critical importance in the development and sustaining the fundamentals of the central nervous system pathways. The initiation of the signaling cascade promotes neuroprotection and restoration during neurological pathologies. The dysregulation of sonic hedgehog signaling causes target gene suppression and eventually leading to the disruption of cell growth processes. Its aberrant signaling is responsible for several neurological complications (Prajapati et al. 2023).

Fang et al. (2023) recently conducted a narrative review on effects of sodium-glucose cotransporter-2 inhibitor (Empagliflozin) on kidney senescence and found that Empagliflozin improves kidney senescence induced by D-galactose by upregulating Sirt1 signaling to counteract oxidative stress. Apart from inducing signaling molecules and cascades, ROS also plays a crucial role in the crosstalk between autophagy, inflammation and senescence which are the basis of the balance in homeostasis in organisms (Javali et al. 2023). Growing body of evidence suggest that aging-associated loss of regulation redox signaling events of the gastrointestinal cells causes many human pathologies such as cardiovascular diseases, cancer, diabetes, and neurodegeneration. it remains a hot topic that requires for further exploration (Homolak 2023).

Use of multivitamin supplements has become even quite popular in recent years with as many as 72% of elderly people (age > 65 years) in the US reporting supplementation (Kantor et al. 2016). As oxidative modifications in cellular macromolecules are closely related to aging and age-related diseases, antioxidant

supplements have been widely used to alleviate these undesired consequences, but their geroprotective and/or senotherapeutic efficacy is generally far from satisfactory. It is a proven fact years ago that multivitamins might act as a prooxidant, unlike many multivitamin supplementation programs that are expected to act as an antioxidant and are intended to provide amelioration in the detrimental effects of aging, even if it is relative (Kayali et al. 2007; Erdoğan et al. 2017). More specifically, Simsek et al. have systematically analyzed whether vitamin supplementation does possess beneficial effects on cardiovascular system. Their literature search was based on 87 different privileged papers, and they reach the conclusion that vitamin supplementation does not have beneficial effects on cardiovascular system (Simsek et al. 2021).

On the other hand, vitamin D deficiency is still a commonly seen health problem among elderly individuals. Multi-drug use among nursing home residents may hinder the therapeutic efficiency of Vitamin D administration (Mol et al. 2018). Vitamin D is one of the key controllers of the gene expression redox sensitive signaling proteins such as P38 MAPK, $P16^{INK4a}$, Bmi-1, and thus, senomorphic activity in bone marrow mesenchymal stem cells (Fahimeh et al. 2023).

Recent interest has focused on maintenance of physiological magnitude of redox signaling in aging cells. "5R" principle of precision redox pharmacology: "Right species, Right place, Right time, Right level, and Right target" was proposed in this sense (Meng et al. 2021). Spontaneous supplementation which is far from 5R principles may even deteriorate already impaired signaling cascades and may result in more extensive signaling interference in aging organism. Defective redox signaling pathways in which the senotherapeutic substances are used as their modulatory benefits may bring effective solutions to degenerative health problems of elderly. Elucidating mechanisms underlying adaptive redox signaling pathways could provide novel senotherapeutic targets for health life-span extension and age-related disorders (Atayik and Çakatay 2023a,b).

On the other hand, it has been reported that calorie restriction mimetics (CRMs) are a wide group of natural compounds that provide similar molecular and biochemical effects of CR, and activate autophagy. CRMs have been reported to regulate redox signaling by enhancing the antioxidant defense mechanisms through activation of the Keap1/Nrf2/ARE system, and inhibiting ROS formation through attenuation of mitochondrial dysfunction (Sharma and Singh). Moreover, CRMs also regulate other redox-sensitive signaling pathways such as the PI3K/Akt and MAPK pathways to promote neuronal cell survival. In this issue, Sharma and Singh (2023) discuss the neuroprotective effects of various CRMs at molecular and cellular levels during aging of the brain.

And lastly, excuse us to share a delight with you from Seneca's "Letters from a Stoic":

> Let us cherish and love old age; for it is full of pleasure if one knows how to use it. Fruits are most welcome when almost over; youth is most charming at its close; the last drink delights the toper, the glass which souses him and puts the finishing touch on his drunkenness. Each pleasure reserves to the end the greatest delights which it contains. Life is most delightful when it is on the downward slope, but has not yet reached the abrupt decline.

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