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Review in Depth

Redox-based Disruption of Cellular Hormesis and Promotion of Degenerative Pathways: Perspectives on Aging Processes

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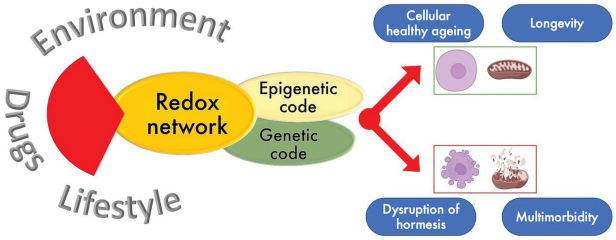
Abstract

The present work aims to link the redox and cell-centric theories of chronic processes in human biology, focusing on aging. A synthetic overview of cellular redox pathways will be integrated by the concept of hormesis, which disruption leads to several physiopathological processes. The onset of age-related diseases due to the restriction of homeodynamic capacity will be herein considered in a redox fashion. Up-to-date arguments on hormetic agents, such as geroprotectors, dietary interventions, and physical exercise are refining the presented theoretical framework, integrated by insights from extracellular vesicles, microbiota, pollutants, and timing mechanisms. The broad concepts of exposome encompass the redox-based alteration of cellular hormesis for providing meaningful perspectives on redox biogerontology.

Graphical Abstract



Keywords: Biogerontology, Exposome, Hormetic agents, Redox network, RONS

During life, the human body is exposed to various environmental phenomena and/or lifestyles (food, xenobiotics, heavy metals, drugs, alcohol, and smoke) that promote at the molecular level biochemical reactions, spontaneous errors, and progressive accumulation of molecular damage (1). Therefore, to summarize, the aging process can be viewed as the progressive multi-causal failure of the organism's maintenance, with death being the final manifestation of the breakdown in homeostasis (2).

In the 2 last decades, the hormetic concept has been related to the biology of and age-related diseases (3) and has been observed in a wide range of biological systems. It is known that redox dysregulation can be conducive to several physio-pathological outcomes, including sarcopenia and frailty (4).

In this review, we will describe the intriguing findings in the redox-signaling pathways linking hormesis to physio-pathological and aging processes. As a critical review, we have summarized and evaluated an extensive body of arguments over the topic of interest, focusing on the most recent insights and discussing the most important features and perspectives. The trough line will be the concept of cellular hormesis linked to the redox biogerontology; after a dissertation of what hormesis is, redox biology will be presented, moving then to redox biogerontology; a discussion on hormetic agents will then precede the perspectives for basic and translational research.

Hormesis

In response to several stressors, cells defend against or withstand these same stressors with adaptive responses, a phenomenon named hormesis. Between the 2 opposing parts of beneficial versus detrimental redox-based processes, the subsequent refinement of mitochondrial hormesis (mitohormesis) emerged as a slight production of reactive oxygen species (ROS) in the mitochondria that induce adaptive responses and resilience, thus promoting longevity, improving metabolism, and the immune system (5,6), as indicated in Figure 1.

The biphasic nature of dose–response (low-dose stimulation and high-dose inhibition) is pharmacologically interpreted as overcompensation reactions to disruption of cellular homeostasis by subtoxic agents, enhancing cytoprotection without pathological effects (7). Physiologically, transcription factors and redox sensors interplay to promote cytoprotection and cellular resilience in response to subthreshold exposures to several stressors.

The caloric restriction, exercise training, and intermittent fasting (the most important triggers of adaptation responses) are an example of such stressors, promoting the delay of age-associated loss of both muscle fibers, neurogenesis, cognitive and motor functions, mitochondrial biogenesis, DNA repair, and reduced inflammation and blood pressure (8,9). It is worth mentioning the concept of "xenohormesis" which refers a form of cross-species hormesis. Under stress conditions, plants or fungi synthesize some compounds (ie, salicylates, resveratrol) that stimulate hormesis responses, also in other animal species when ingested (10). Instead, one potential candidate synthetic drug might be the widely used anti-diabetic drug metformin that is thought to work by inhibiting mitochondrial function (11). For a detailed overview of possible anti-aging drugs, see below.

In this context, antioxidants may act as negative regulators apparently by preventing the hormetic response that improves health and life span. This could be another way to explain the failed results of the aforementioned trials to examine the effects of antioxidant supplementation on different age-related diseases. Moreover, this seems to be confirmed by some human studies in which exercise training is considered the stressor and where the benefits of exercise showed to be inhibited in those subjects given antioxidant supplements (12,13).

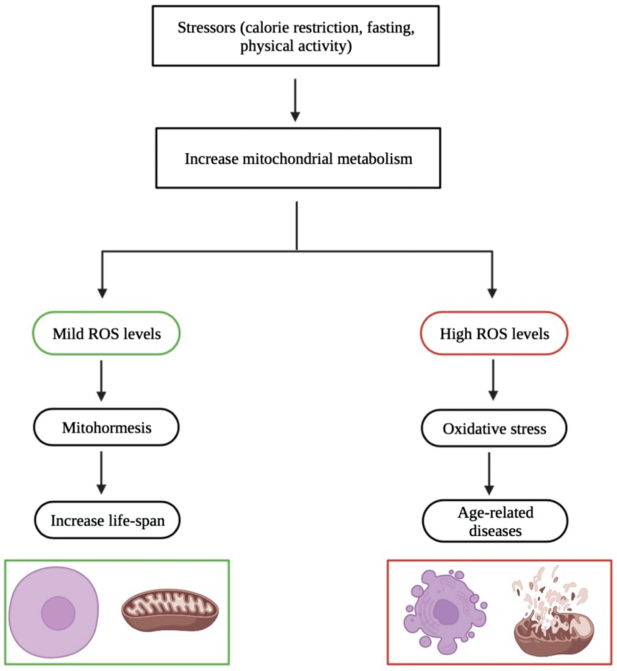


Figure 1. The detrimental and beneficial effects of ROS levels and their impact on cells and mitochondria. Image created with BioRender. ROS = reactive oxygen species. Full color version is available within the online issue.

Among the hormetic responses, the activation of the Nrf2/ARE pathway has been interpreted as a central integrative mechanism, underlying the effect of both natural antioxidants and other hormetic agents (7). Indeed, a plethora of agents, including electrophilic stressors, dietary interventions, physical exercise, and ischemia-reperfusion, are capable of activating the Nrf (7). Within this framework, the interplay of redox reactions can be interpreted as a mechanistic link between the exogenous agents and the endogenous pathways.

Redox Signaling and Pathways

Cellular Redox Physiology

The ROS are a group of heterogeneous molecules with at least one oxygen atom and one or more unpaired electrons, deriving from molecular oxygen, which are formed by reduction-oxidation (redox) reactions or by electronic excitation. ROS are classified as radical or non-radical species. Superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) are the most representative radical and non-radical species, respectively (14).

The sources of ROS are of 2 types, endogenous and exogenous. The main endogenous enzymatic sources of $O_2^{\cdot-}$ and H_2O_2 are transmembrane NADPH oxidases (NOXs) and the mitochondrial electron transport chain. The $O_2^{\cdot-}$ produced in the extracellular compartment undergoes a rapid dismutase reaction to form H_2O_2 which can enter the cell both via diffusion or through aquaporins (15). During the mitochondrial electron transport chain, the leakage of electrons contributes highly to ROS production, which represents a hallmark event underlying different diseases (16). The involvement

of super assembled complexes in mitochondrial ROS production at a molecular level has emerged (17). In the outer mitochondrial membrane, the flavoenzyme monoamine oxidase (MAO) regulates the levels of catecholamine and serotonin through the oxidative deamination reaction associated with the production of H_2O_2 and other by-products. Both of the 2 MAO isoforms increase their expression and their ability to produce H_2O_2 with age, which acts as a relevant mediator in age-associated chronic disease (18). One of the 2 isoforms of xanthine oxidoreductase in humans, namely xanthine oxidase (XO), produces high ROS levels (both $O_2^{\cdot-}$ and H_2O_2) following different associated metabolic disorders (19). Nitric oxide synthases (NOS) generate nitric oxide (NO) by different isoforms using oxygen and L-arginine as substrates and tetrahydrobiopterin as cofactor. When this process is altered, NOS enzymes produce more ROS and less NO, thereby promoting ROS-induced damages, especially in cardiovascular disease (20). Along with ROS, the reactive nitrogen species (radical and non-radical derivatives of nitrogen), are produced by all aerobic cells, and they have a role in both aging and age-related disease (21).

On the other hand, the exogenous sources of ROS can be encompassed by the umbrella term "exposome," the whole cumulative environmental exposure, which includes molecular factors such as nutrients, drugs, toxicants, and pollutants as well as physical (ie, UV and X-ray radiation) and psychological (ie, psychosocial pressure) stressors (22). To counteract ROS, all cells have their intracellular antioxidant defenses, including mostly glutathione peroxidase, superoxide dismutase (SOD), and catalase. $O_2^{\bullet-}$ dismutase in H_2O_2 spontaneously or via SOD, while both catalase and glutathione peroxidase further scavenge H_2O_2 to H_2O and oxygen (23). Additionally, there are different kinds of minerals and vitamins taken by a diet that enhance the antioxidant defense, including vitamin E, vitamin C, flavonoids, zinc, and selenium (24).

Nonphysiological and excessive reactive oxygen and nitrogen species (RONS) production called "oxidative stress" leads to cellular damages, especially affecting proteins, lipids, and DNA. The oxidative stress is caused by "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" (25). The oxidative stress is a well-known factor involved in several pathological processes and in aging. However, oxidative stress has been questioned in its paradigm due to the aforementioned complexity of beneficial versus detrimental processes. Every cell produces physiologically RONS, due to its aerobic life and cellular resposnse to xenobiotics, pathogens, and cytokines. This phenomenon is known as "oxidative eustress" and it is necessary to regulate several important pathways, such as immune functioning, inflammation, cell survival, development, and differentiation processes (26,27).

Genetic and Epigenetic Pathways

Redox signaling affects gene expression through classical gene regulation, which relies on the activity of transcription factors, and novel gene regulation, through epigenetic regulators. Both are involved in numerous physiological processes but also implicated in various diseases. A summary of transcription factors regulated in a redox-sensitive manner is summarized in Table 1 (28–33).

The epigenetic modulation provides a flexible interface between organism and environment, which is essential for all the cell functions. The epigenetic changes mediated by ROS are due to chemical modification of cytosine residues of DNA (DNA methylation) and histone proteins associated with DNA (histone modifications), thereby regulating gene activity and expression as well as chromatin. DNA methylation is considered a gene repressive mechanism that causes gene silencing, preventing transcriptional activators' access to the target binding sites (34). Histones, which are proteins closely associated with DNA to form the chromatin structure, can be affected by epigenetic changes, due to methylation, acetylation, ubiquitination, and ADP-ribosylation, eventually underlying aging-related processes. Indeed, ROS-dependent epigenetic modifications are widely recognized as part of the genesis of several age-related diseases (35). An in-depth of redox epigenetics is summarized in Figure 2 (36–43).

Redox Biology and Degenerative Diseases

As already underlined, RONS are involved in several age-related diseases, including cardiovascular, metabolic, neurodegenerative, and

Table 1. ROS-mediated Gene Regulation

Target	Reference
ROS activate the Keap1/Nrf2/ARE (Kelch-like ECH-associated protein 1/nuclear factor-E2-related factor 2/antioxidant response element) pathway, the master transcriptional activation of antioxidant response element-containing genes, including glutathione, thioredoxin, and peroxiredoxin	(28)
The NF-κB is the master regulator of inflammation pathways. ROS often stimulates the NF-κB pathway in the cytoplasm but inhibit NF-κB activity in the nucleus.	(29)
HIF-1 is a master regulator of transcriptional response of hypoxia. ROS regulation of HIF-1 can occur both under hypoxia and normoxia.	(30)
FOXO transcriptional factors maintain cellular homeostasis and control antioxidant response. Different growth factors (insulin or IGF-1) promote the activation of PI3K/Akt pathways that inhibits FOXO activation, thereby decreasing cellular antioxidant defense. ROS can modulate FOXO activity at multiple levels, including posttranslational modifications of FOXOs.	(31)
The guardian of genome p53 is induced by different stimuli, including oxidative stress. In response to low ROS levels, p53 contributes to antioxidant responses but, upon oxidative stress, p53 promotes mitochondrial impairment and apoptosis with increased of ROS production.	(32)
ROS can activate the MAPK, a pathway involved in cell survival and in several cellular processes, including proliferation, differentiation, apoptosis, and stress responses.	(33)

Notes: ECH = Enoyl-CoA-Hydratase; FOXO = Forkhead box protein O; HIF-1 = hypoxia-inducible factor-1; MAPK = mitogen-activated protein kinase; NF-κB = transcription factor nuclear factorκB; PI3K = phosphoinositide 3-kinase; ROS = reactive oxygen species.

To generate the table, "Keap1-Nrf2 and oxidative stress," "NF-κB and oxidative stress," "HIF-1 and oxidative stress," "FOXO and oxidative stress," "p53 and oxidative stress," "MAPK and oxidative stress" were searched on PubMed (only reviews).

Knowledge box – Redox epigenetics

The promoter regions of amyloid- β precursor protein (APP) and β-secretase (BACE1) represent the most target of epigenetic changes. Accordingly, several studies revealed the impact of methylation and chromatin remodelling in the pathogenesis of neurodegenerative diseases (36). E-cadherin is silenced by DNA hypermethylation and histone hypoacetylation under oxidative stress conditions, representing a common carcinogenic event (37). For a detailed understanding of epigenetic changes in cancer mediated by ROS, it recommends reading this review (38). Also sirtuins, the sensors of the metabolic and energetic state of cells and regulators of a wide range of cellular processes, can be affected by ROS; sirtuin-1, for example, can be regulated by S-glutathionylation, a redox regulatory mechanism that largely depends on the cellular redox state (39). Among their action mechanisms, sirtuin-1 regulates p53 through deacetylation, acting against ageing and age-related diseases. Moreover, sirtuin-1 regulates the ROS-dependent FOXO factors, which are responsible for cell growth, proliferation, and longevity (40).

Additionally, epigenetic changes are also mediated by the so-called non-coding RNAs (ncRNAs). About 70–90% of genetic material is transcribed into ncRNAs, including ribosomal RNAs (rRNAs), microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). The miRNAs have been shown to interfere with the generation of ROS and oxidative stress directly by targeting oxidase and antioxidant enzymes, antioxidant genes and their transcription factors, and indirectly, mainly by targeting genes involved in apoptosis, tumour–suppressor genes (e.g., p53), and interfering with pro-survival signalling pathways (e.g., Akt, IGF-1). Furthermore, miRNA expression itself can be either induced directly by ROS or modulated in response to inflammatory pathways and contribute ultimately to oxidative stress (41). Although few miRNAs, such as miR34 (42) have been directly linked to age-related diseases, several miRNA families are modulated by ROS in the development of mitochondria-mediated cell senescence implicated in several human pathologies. To date, this involvement is still little known.

Indeed, different miRNAs are involved in development of oxi-nflammation underlying age-related diseases. Notably, miR-21 and miR-146a, also called "inflammamiRs", can master NF-κB and, in turn, the release of pro-inflammatory cytokines. Additionally, the circulating levels of inflammamiRs may strongly represent biomarkers of age-related diseases (43).

Figure 2. In-depth box on main epigenetic pathways regulated by redox biology. ROS = reactive oxygen species.

cancer. For what concerns cardiovascular diseases, the main target may be Ca^{2+}-handling, negatively affected by reactive species causing myocardium damage, arrhythmia, cardiac remodeling, activation of pathways of hypertrophy, and apoptosis (21,44). Regarding the mechanisms underlying metabolic dysfunction, the dietary-related redox dysregulation can cause an unbalanced glucose uptake in various tissues, insulin resistance, and hyperglycemia, as the activation of NF-κB contributes to create a vicious circle that induces metabolic reprogramming underlying all metabolic diseases, such as diabetes and obesity (45). Regarding neurodegenerative disorders, microglia, and astrocytes are activated by several pro-inflammatory factors and, in turn, release inflammatory mediators (ie, metalloproteases, nitric oxide synthase, cyclooxygenases), thereby increasing RONS production and inflammation. This detrimental scenario leads to neuron death and neuroinflammation (46). For what concerns cancer, ROS are involved in both initiation, promotion, and progression. Indeed, ROS can induce genetic and/or genomic instability leading to the accumulation of DNA damages. ROS can also activate oncogenes (eg, RAS, c-Myc), inactivate tumor suppressor genes (eg, p53, Nrf2), and increase cell survival and cell proliferation through the modulation of several pathways (eg, MAPK, PI3K/Akt). Elevated ROS production and mitochondrial dysfunction associated with a hypoxic microenvironment and less nutrient availability promote metabolic reprogramming that ensures cancer cells adapt to these extreme conditions. Moreover, ROS can induce Wnt signaling and thus promote epithelial-mesenchymal transition, thereby supporting the dissemination of metastasis (47).

Given the pathological roles of ROS, antioxidants were postulated to potentially play a protective role in aging and age-related diseases based on their positive impact in several studies (48). However, most clinical trials examining antioxidant supplementation failed in the prevention or treatment of various age-related diseases (49,50). Several potential reasons for these failed results have been discussed extensively, particularly for what concerns individual differences, nutritional status, and the proper dose regimen of antioxidants (51). To develop targeted therapies focusing upon oxidative signaling, it is vital to understand the balance that ROS signaling plays in both physiology and pathophysiology, as well as how the handling of this balance and the identity of the ROS may influence cellular and tissue homeostasis.

Aging

Free Radical Theory of Aging in the 2020s

The free radical theory of aging (52) is already entering the "young-old" category: since 1956, it then attracted more and more interest, with a huge area of research including and not limited to phenomenological measurements of age-associated redox disruption, treatment with dietary and pharmacological procedures, senescence, genetics, and epidemiology (53). RONS can trigger cells to acquire a senescence-associated secretory phenotype acting on various factors, which promote several acute and chronic pathological processes. Into this paradigm, oxi-inflamm-aging hypothesis postulates a loss of homeostasis due to a chronic oxidative stress that impairs regulatory systems, consequently activating the immune system to induce an inflammatory state: the vicious circle in which chronic oxidative stress and inflammation feed each other determines the pathological aging (21). The immunosenescence amplifies the oxinflammative damage, with a sequence of events that can be described as follows: (a) mitochondrial dysfunction; (b) genomic instability; (c) senescence-associated secretory phenotype; (d) higher adherence and lower migration capacity of immune cells, lower lymphoproliferative response, decreased cytotoxic activity of immune cells, and inefficient phagocytosis; (e) damage-associated molecular patterns; (f) excessive production of ROS by immune cells to destroy and remove senescent cells; and (g) vicious spiral feedback of oxi-inflammaging (54).

The core of the free radical theory of aging is argued as free radical and related oxidants disrupt cellular constituents, resulting in an accumulation of damages. However, as stated by Pomatto and Davies (55), multiple protective systems interplay and are highly regulated and modulated both within minutes and as longer-lasting (over periods of days to years), but still transitory effects. Therefore, the theory has been recently improved considering that, as age increases, impaired adaptive homeostatic capabilities, along with stress-induced structural and functional damage, occur. *Id est*, the inducibility of the adaptive response declines with age, accompanied with a sluggish cellular signaling and with the emergence of inflammaging (55).

In recent years, the theory has been directed to mitochondria, emphasizing the role of free radicals affecting mitochondrial DNA (mtDNA). Free radicals may increase transition mutations of mtDNA, and more broadly reactive species may affect mitochondrial biogenesis and/or mitochondrial turnover (56). Indeed, the lack of protection by histones makes mtDNA highly susceptible to excessive ROS formation in an aged heart, and excessive ROS production may affect mitochondrial function and apoptotic susceptibility in aged muscles (57). However, mitochondrial dynamics of fusion/fission, as well as the complex regulation for maintaining mitochondrial genome, the structural remodeling and the variety of response to countermeasure does not allow to reduce aging to redox-based mitochondrial dysfunction (58). Therefore, the old postulation that excessive ROS as waste products by mitochondria causes aging over time has been criticized, as antioxidants have largely failed to extend life span or defeat age-related disease, and actually aging encompasses mitophagy, mitochondria-to-nucleus retrograde signaling, and mitochondrial metabolism in a multifaceted system (59). Once considered only as toxic by-products of the electron transport chain, mitochondrial ROS are today considered fundamental signaling molecules, and the differential role of several ROS, as well as and the loci where ROS are produced, all account for exerting very different physiological effects (17).

Redox Biogerontology

The concept of the "redox code," as stated by Jones and Sies (60), integrates cellular organization and redox reactions which control the structure and function of cells, as the functioning of cell metabolism is governed by redox processes by fine-tuning of reaction

cascades and signaling pathways. Ultimately, redox code is based on the redox interface between an individual and its environment. The activity of the redox partners depends upon their concentrations within cellular and subcellular compartments. The redox network is constituted by kinetically controlled switches in the redox proteome and spatiotemporal sequencing in cells' life through redox sensing determines an adaptive system to respond to the environment at different scales. Diseases, and aging itself, may emerge by deviation from physiological redox steady states. Indeed, most aging processes comprise a redox component (60). Thus, the redox theory of aging emerged, postulating aging as the decline of the adaptive interface between functional genome and life-course environmental exposures (ie, exposome), not limited but strongly dependent on redox processes. In this framework, redox sensing, processing, and signaling coordinate and integrate functional networks. Redox proteome changes provide exposure memory which decreases the plasticity of genome–exposome interaction. The interconnection of redox-dependent metabolism with defense mechanisms determines the accumulation of impairments to several tissues, and all systems age (61).

The use over a life span of differentiation and environmental response systems results in decreased adaptability to further environmental stressors. The redox couples of glutathione/glutathione disulfide (GSH/GSSG) and cysteine/cystine (Cys/CySS) become oxidized with age and can be used as hallmarks of such resilience of redox networks in aging and disease. More deeply, subcellular compartments are differently affected by environmental exposure, accounting for the modularity of the redox network. As a consequence of a series of exposures and cumulative responses affecting any unit of a complex system (ie, human body), multimorbidity can be interpreted as a general consequence of morbidity because a declining organ system adds strain and impairs the adaptability of other interacting systems. In the same framework, early environmental responses can magnify adult disease risk (61).

The restriction of homeodynamic capacity leads to the onset of age-related diseases (62). As a natural consequence of free radical and redox theories of aging, several redox compounds have been suggested as geroprotectors (otherwise termed anti-aging drugs) to counteract the redox-base disruption of homeodynamic capacity. However, no simple approach has been proved to be effective in reversing aging, and a more complex and systematic paradigm needs to be promoted in order to define several interventions and their possible synergistic action for defining effective geroprotectors, which ultimately aim to increase health span, rather than life span per se (63). The database GEROPROTECTORS includes 259 life-extension experiments encompassing any intervention aimed "to increase longevity, or that reduces, delays or impedes the onset of age-related pathologies by hampering aging-related processes, repairing damage or modulating stress resistance" (http://geroprotectors.org).

Hormetic Agents, Lifestyle, and Exposome

Anti-aging Drugs

The concepts underlying geroprotectors opened a huge topic into scientific literature and industry, related to the discovery and use of anti-aging drugs. The idea was that such pharmacological agents could trigger hormetic dose–response, conferring cytoprotection against age-related degenerative processes. The physiology behind included mitochondrial metabolism and activation of "vitagenes," a group of genes encoding for stress response molecules (64). Hormesis, cellular stress response, and redox homeostasis have been highlighted in pathological processes such as neuroinflammation (65). Redox modulation of vitagenes has been reported for several compounds such as carnosic acid, resveratrol, sulforaphane, dimethyl fumarate, acetyl-L-carnitine, and carnosine (66). Other studies focused on drugs targeting autophagy and particularly on mTOR-driven aging. According to some criteria (ie, prolonging life span in model organisms, facing age-related diseases in mammals, suppressing conversion of cells from quiescence to senescence), rapamycin and other rapalogs (such as everolimus) have been ultimately defined as anti-aging drugs (67). Other promising results came from urolithin A, dPUFA, metformin, and the senolitics (68). Rapalogs and metformin, as well as aspirin and statins, affect senescence-associated secretory phenotype (69).

Most anti-aging agents involve, primarily or partially, redox pathways; however, considering aging as a necessary consequence of reactive species overproduction led to the antioxidant paradox (69). Agents targeting reactive species cannot act as primary aging-driving mechanisms, but geroprotectors may conversely act as antioxidants (70). Considering the variety of anti-aging drugs, the DrugAge database was released for supporting biogerontology research (71), and it includes 1 097 distinct drugs tested (http://genomics.senescence.info/drugs/). However, the translations of anti-aging drugs from models to preclinical and clinical effectiveness are still on their way (68). Into this background, hormetic agents (elsewhere termed "hormetins") have emerged as drugs capable of mild-stress induced hormesis and therefore promising approaches for promoting healthy aging and extending life span (72). Hormetic agents can be defined as any agents capable of improving or at least preserving cellular homeostasis in response to stressors. The following sections will focus on other agents targeting redox hormesis; particularly, nutritional factors have been studied on these terms. The other big pillar of lifestyle, that is, physical activity, will be addressed. To conclude the discussion on hormetins, extending the concept to the exposomics, a special in-depth on pollutants will be provided.

Dietary Interventions

Diet can favor healthy aging, providing a balance nutrient intake, anti-inflammatory substances, prebiotic, and metabiotic foods. Diet can provide a low content of glycation end-products, low glycaemic index and load and, as described below, supplying plants derivates well known as hormetic nutrients (eg, sulforaphane, curcumin, resveratrol), that act as potential geroprotectors on target genes such as Nf-$_{\kappa}$B, p38, and mTOR (73). The latest analyzed anti-aging strategies consider calorie restriction and antioxidants (74) that may interfere with cellular signaling pathways, influencing cellular redox state and homeostasis, and show the inverted hormetic U-shaped dose–response, producing benefits to subsequent exposure to the same compound or to other (75). Caloric restriction (CR) is the most powerful intervention to influence aging and age-related diseases (74). The assumptions about how CR affects life-span concern a delay in the development, disorder of energy metabolism (oxidative phosphorylation action with reduced ROS production), endocrine modifications (involving the IGF 1-/insulin pathway), and finally the hormesis hypothesis (76). The latter is based on complex modification of nutrient-sensing and stress-responsive cellular pathways which involve mitohormesis and the activation of factors such as AMPK, sirtuins, and Nrf2 (77,78). However, it is important to consider the entity of CR and the duration and timing of this restriction (79,80) (p3) and studies on subject with various features are needed. The

life-span extension of CR appears to be independent of the reduction in the amount of ingested food, which occurs parallelly to CR (81). Because CR has limitations, strategies that mimic their effect, such as intermittent fasting or prolonged fasting, or even protein restriction and in particular of certain amino acids such as methionine, deserve to be studied in greater depth in humans (82). Another way to mime CR concerns the natural stilbene resveratrol contained in grapes, which acts on the sirtuin system and triggers the stress response pathways (83).

However, according to the timing of doses, the dietary strategies can have a detrimental effect (84). Vitamin C is an example: In case of the supplement of very high doses, it can actually meddle with activation of endogenous defense signals favored by mild oxidant stimulations, as in case of physical activity, affecting benefits (13); vitamin E in excessive doses can also impair the physiological role of some aldehydes, such as trans-4-hydroxy-2-nonenal, generated by peroxyl radicals and involved in responses at low concentration of adaptation to oxidative stress trough Nrf2 (85). Similar to other environmental stressors, it has been even suggested that a non-pathological consumption of pro-oxidants in the diet may be beneficial for facing with further similar stressors and coping with possible pathophysiological pathways (86). Plant derivate phytochemicals such as phenolic acids, polyphenols, and flavonoids can particularly act as hormetic factors. Survival and cellular protection can be positively triggered by the interaction of polyphenol compounds with the redox and the vitagenes networks, a topic that should deserve more investigation (87). Indeed, phytochemicals can represent a pro-oxidative stimulus regulating the expression of enzymes from innate detoxification systems via the vitagenes (eg, heat shock proteins [HSPs], HSP32, HSP60 and HSP70, the Trx/TrxR system, and sirtuins) and improving the performance of mitochondrial mechanism involved in cellular respiration (72,75) by mimicking partly the CR effects. As previously mentioned, one of the most important factors regulating detoxifying pathway and providing an adaptive response to stressful conditions is the transcription factor Nrf2 (88), that binds to the AREs in the enhancer region of cytoprotective genes. One of the mechanisms associated is the expression of peroxiredoxin-6 (Prdx6) (89). There is a progressive reduction in Nrf2/ARE binding as age increases, and several agents are known to trigger this pathway. For example, it has been shown that sulporaphane restores the activity of Nrf2 and its target gene Prdx6, reinforcing the nuclear accumulation of Nrf2, thereby enhancing Nrf2/ARE binding and increasing promoter activity of Prdx6 (89).

Curcumin, which at nontoxic concentrations is a potent inducer of OH-1, as well as epigallocatechin-3-gallate in green tea and the superseded resveratrol might be considered in this argument (88(p),(90,91). Oxidative metabolites of carotenoids can also regulate the pathway Nrf2/ARE (91). Flavonoids and curcuminoids analogues can support a biphasic protective activity, by scavenging oxidants directly and inducing cytoprotective enzymes through Michael reactions (92). Phytocompounds can act either at the level Nrf2/KEAP1 complex or at the kinase level, as phosphatidylinositol-3-kinase (PI3K), extracellular signal-regulated protein kinase, protein kinase C, and c-jun N-termina kinase (90). It is interesting to observe how the phytocompounds can modulate and reset any alterations of the antioxidant pathway through epigenetic processes (93). However, it is difficult to achieve in vivo intracellular concentration that has proven effective in vitro studies with oral administration. Despite some compounds are well absorbed at the level of enterocytes (94), not every compound is able to take action at a systemic level. The reducing action of some compounds realistically is expressed at the level of the gastrointestinal tract, and the compound hardly came to target tissues (75); the action of some compounds could rather have a prebiotic effect on gut microbiota (95). In this sense, some compounds may have indirectly a neuro-hormetic role related to the strong bidirectional connection between central nervous system and gut microbiota, encompassing the alterations responsible for low-grade chronic inflammatory in older adults (96). The metabolism of these compounds from microbiota would explain the low bio-availability/ high bio-activity paradox of phytocompounds and the interindividual differences (97). These substances introduced as supplements do not always give desired effects, but it depends also in part on the pharmacokinetic properties according to which nutritional supplements have low bioavailability (98,99), and they can potentially interact with drugs (98). It is worth mentioning that no dietary agent is likely to act by one mechanism alone without influencing other targets of a signaling network (93). The study on which impact nutrients have as separated and incorporated as part of specific dietetic models is an essential prerogative to integrate into biogerontology, leading the way of nutri-gerontology, with the aim to reducing the risk of diseases age and promote longevity (100).

Kinesiological Interventions

It is widely recognized that physical activity (PA) has a positive effect on health-related outcomes in all age groups, especially in older adults, playing a fundamental role in primary and secondary prevention of more than 25 chronic diseases, such as neurodegenerative, cardiovascular, cancer, and on premature mortality (101,102). Moreover, PA has been acknowledged as one of the only factors able to decrease the physiological loss of muscle mass and function through upregulation in mitochondrial plasticity and redox-regulated responses in older adults (103). In particular, PA can increase catalase, SOD, glutathione reductase, and glutathione peroxidase levels, which are involved in the repair systems against oxidative stress, and transcriptional factors that regulate redox systems in skeletal muscle and plasma (104,105).

Concerning the type of PA, moderate physical exercise can produce cell adaptation to oxidative stress via induction and expression of antioxidant enzymes through up-regulation of NF-kB and other protective systems, such as HSP, resulting in an inhibitor of the inflammatory mediators (106). Regular aerobic training can activate the body's antioxidant system, upregulate endogenous antioxidant factors, and strengthen the activity of antioxidant enzymes (107). Resistance training can impact mitochondrial function and reactive species (108). Combined training (endurance + resistance) can induce protective effects against DNA damage in lymphocytes, that could be related to the increase in antioxidant capacity (109). All in all, the relation between PA and redox biology in older adults is controversial and depends on the type, duration, and intensity of exercise (110). Training specificity insights should lead to planning and recommendations of physical exercise, providing roads of interest for facing sarcopenia and frailty in the older adults (111). Redox and inflammatory mediators vary as a function of frequency, intensity, time, and type of exercise and novel studies should evaluate how those mediators affect the secretion of myokines and organokines in response to exercise (112). Surely, more studies are needed in order to understand the best type of exercise able to improve the redox-based adaptive system. However, from a clinical point of view, it seems clear that PA should be applied as a therapeutic and preventative tool to counteract age-related disease due to its role in contrasting the redox homeodynamic impairment associated with aging.

In particular, physical exercise can extend the peak of the hormesis curve, that is, it can extend or stretch the levels of reactive

species associated with better physical functions. In this vein, moderate exercise, despite inactivity or overtraining, has been suggested to optimize the hormetic response (113). Indeed, recalling the bell-shaped curve that defines the response of biological systems to stressors, Radak and colleagues (114) suggested that this hormesis curve (with physical function on Y-axis and levels of ROS on X-axis) can be interestingly evoked by PA. They argued that moderate levels of oxidative damage are fundamental for the maintenance and viability of cells and that the curve has 2 endpoints on physical inactivity and overtraining.

Pollution and OxInflammation

To provide a comprehensive overview of exposome inducing redox homeodynamic impairments, along with drugs and lifestyle factors, air pollutants definitely cannot be overlooked. Adverse health effects of polluted air (consisting of gaseous components and heterogeneous solid and liquid particles suspended) represent a crucial burden of current times and diseased people and older adults are sensitive subpopulations. Accounting for the multifaceted nature of exposome, particulate matter exposure can limit health gains from physical activity (115). In the same vein, particulate matter exposure can also affect the gut microbiome, resulting possibly in a complex adverse outcome on the gut-skin-brain axis (116). Therefore, hormetic agents, physiological pathways, and pollutants are intriguingly interconnected. In this topic, oxinflammation, as the outcome of the cross-talk between redox stress and inflammation, emerges considerably to promote and aggravate the adverse health effects of pollutants (116). Among the molecular pathways mentioned before, the sensor-response system of Nrf2 can protect from immunotoxicity due to environmental pollutants (117). This intracellular redox-sensitive target, responding to oxidative challenges as a thiol-based apparatus, is central for adaptive homeostasis mechanisms based on redox signaling, and it is subject to agedependent decline (14).

Perspectives

In recent years, extracellular vesicles (EVs) biology has pervaded massively biomolecular sciences. Redox biology was no exception to this flood. Briefly, the EVs are plasmatic membrane-coated nanoparticles actively released by virtually all cell types that permit contact-free substance exchange between cells and act as signaling vesicles in autocrine, endocrine, juxtracrine, paracrine, or distal modes of communication. It has been shown that EVs are involved in various biological processes, including viral infection, immune responses, mammalian development, and reproduction (118). An excess of ROS can affect the cell signaling network and EVs biology, as redox modifications can alter both the number and cargo of EVs released by cells (119). The analysis of EVs cargo from several body fluids, along with tissue-specific proteins, could serve as new indicators of the origin and the redox status of the releasing cells. This could be used for the discovery of new biomarkers for redox-related diseases (119). Although hormesis has not yet been a key topic in EVs research, interestingly, EVs release can potentially act as a cellular healing mechanism mediated by the disposal of harmful molecules (120). Indeed, the cargo of oxidized lipids and proteins can mediate detrimental effects on target cells. On the other hand, the cargo can also include antioxidants that modulate the response in target cells protecting them. Therefore, antioxidants can be horizontally transferred across cells via EVs. To complete the picture, EVs can autonomously produce ROS. All in all, the release and the biochemical features of EVs are considerably affected by the redox status of originating cells, depending on the cell type and on a subclass of EVs analyzed (121).

Another hot topic across biomedical science in the last decades is represented by microbiome research. As nutrition has been largely discussed above, it is worth mentioning (Figure 3) an original link between nutrition, microbiome, and a well-known redox pathway (NO biology), enough that the relative pathophysiological perspective would deserve future attention (122–127).

Several chemical, biological, and physical external factors trigger physiological responses through redox cascades. Most functions are interlocked with internal cycles, which constitute the timing system of human bodies. Since the internal clock pathways are inherently linked with hormesis and are redox dependant, the pathophysiological perspective would deserve future attention, as summarized in Figure 4 (128–130).

The Hormesis-fashioned Medical Perspectives

Low doses of damaging agents can protect cells against the damage of subsequent exposure to higher doses of damaging agents: Therefore, the dose–response characteristics of preconditioning leading to a protective effect are a manifestation of hormesis (2). Redox homeodynamics disruption and inflammatory response interact to affect degenerative and survival mechanisms within cells, as schematized in Figure 5. The general model of hormetic agents affecting hormesys by redox code across lifespan is presented in Figure 6.

Advancing the U-shaped dose–response framework in toxicology, developing therapeutic strategies based on preconditioning has therefore emerged as a frontier area of research. Having 2 possible contrasting properties is what defines Janus-faced agents. As hereinto mentioned, redox agents can be thought in terms of Janus-faced molecules, with crucial implication for the understanding of physiological and pathological processes. For example, it has been suggested that tumor microenvironment (TME) lies on Janus-faced characteristics of the redox axis: cancer cells expressing increased levels of antioxidants that protect them to the elevated reactive cells as typical in TME; instead, non-cancer cells into the same TME are not able to avoid the fatal oxidative damage (131). Among reactive species, NO has been described to have Janus-faced properties with important implication for the nervous system in the cytoprotective versus cytotoxic balance (132), and susceptibility to nitrosative stress varies between cells, with neurons being particularly vulnerable (133).

Nutraceuticals can represent easily implemented tools to deal with the purposes of redox network and hormesis leading to health and longevity. Accumulating evidence into this field includes, for example, mushrooms-led modulation of inflammation and neurohormesis

Perspective box – Nitric oxide, microbiome and disease

As mentioned, bacteria affect redox homeodynamics in humans. It is possible by modifying molecules of food/beverages in the digestive tract and using several molecules (such as glucose) to produce antioxidants for the host. Among its several functions, microbiota is capable of producing NO both chemically, biologically, and via enzymatic pathways. Recently, it has been highlighted the role of oral bacteria in regulating NO homeostasis. In particular, entero salivary commensal bacteria can use exogenous and endogenous nitrate and reduce it into nitrite. Microbial diversity and oral diseases both affect the nitrate-nitrite-NO pathway (122). Dietary nitrate supplementation (e.g. with beetroot juice), promoting the ecosystemic shift in nitrate-sensitive oral microbiome and increasing NO bioavailability, may be a therapeutic target in ageing, hallmarked by microbiome dysfunction and reduced NO production (123). Mediating the effect of dietary nitrate on blood pressure and boosting oral and plasmatic NO3 bioavailability, the interspecies synergies of nitrate/nitrite-reducing bacteria are protective on cardiometabolic health, as opposed to periodontal pathogenic bacteria (122). The complex interactions within the oral bacterial community are affected by dietary nitrate interventions and link microbiome and diet to NO-mediated functional outcomes. These effects are of particular interest for maintaining cardiovascular and cognitive health in the older adults (123).

The NO-microbiome processes are not limited to the oral cavity, as oral and gut microbiota are interconnected. This connection is both indirect - through metabolic pathways - and direct - through hematogenous and enterial bacterial transfer (124). The nitrate-nitrite-NO pathway acts across the oral-gut axis and participates in intracellular redox pathways thereby accounting for host-microbiota metabolic interactions (125). The probiotic bacterial-induced generation of reactive species stimulates intracellular signalling, determining a redox-based cross-talk between microbe and host physiology (126). Redox biology have also be suggested to play a key role in linking microbiota to both hormesis and oncogenesis, as bacteria can improve or impair the homeostatic properties of the environment (127).

Figure 3. In-depth box on nitrate-nitrite-NO pathway, oral-gut axis, and microbiota.

Perspective box – Circadian clock regulation

The system of clock-controlled genes and cooperative loops, along with endocrine and nervous networks, that harmonize peripheral oscillators and assist homeostasis, decline with age. Daily rhythms of NO and antioxidant systems are negatively altered during ageing (128). As a reduction of homeodynamic space or buffering capacity that limits the possibility to survive and stay healthy (129), ageing may be highlighted by a detrimental impairment of timing systems, with diminished and desynchronized molecular interaction limiting hormesis. Various hormetic agents such as dietary restrictions, polyphenols (e.g., resveratrol and curcumin), short-term hypoxia, and factors inducing over-expression of heat shock proteins can positively support circadian timing system via sirtuins. Therefore, sirtuins may be the key factor underpinning the interlinked systems of timing and hormesis (128). Over last years, the role of sirtuins has emerged in modulating antioxidant and redox signaling, with a plethora of mechanisms in both mitochondria, cytoplasm and nucleus. All in all, sirtuins play a fundamental role in maintaining redox homeostasis at a cellular level with both distinct and synergistic mechanisms (130), and sirtuins should be considered in the complex network linking hormesis, redox biology, and ageing.

Figure 4. In-depth box on clock-controlled genes and redox homeostasis.

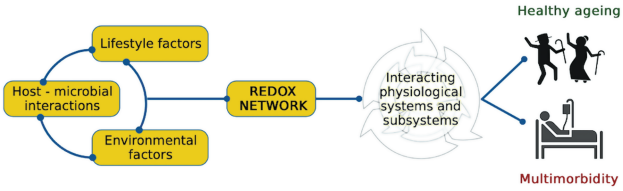


Figure 5. Theoretical paradigm of redox biogerontology based on individual/environment interactions. Image created with BioRender. Credits: Pixabay. Full color version is available within the online issue.

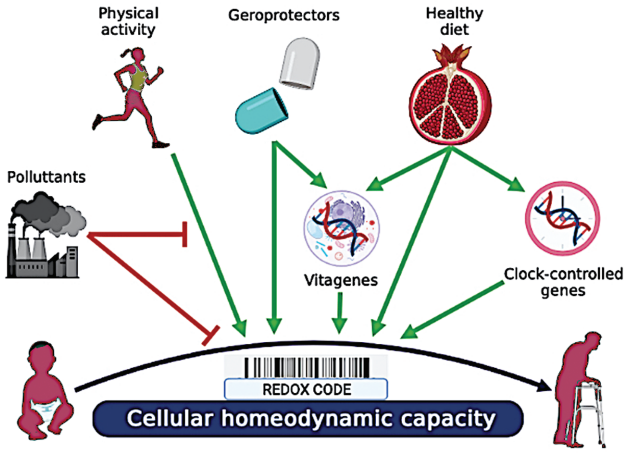


Figure 6. The framework of hormetic agents and exposome affecting aging through redox network. Image created with BioRender. Full color version is available within the online issue.

(134), and several neurohormetic phytochemicals, such as sulforaphan, through triggering adaptive stress signaling pathways in cells possibly improve brain health (135). Myrosinase is the enzyme responsible for cutting glucoraphanin (abundant in crucifer vegetables) into glucose and sulforaphane. Although myrosinase is not found in humans, it is also detected in many strains of bacteria that are commonly found in humans' lower gut, that ultimately allow the sulforaphane absorption from natural fonts (136). The polyphenols hydroxytyrosol and oleuropein aglycone can increase survival and prevent neurodegeneration (137); in addition to aging-related neurodegenerative diseases, hydroxytyrosol treatment has been proposed to combat aging itself (138). Natural substances such as curcumin may be used for medical purposes as potent activators of Nrf2, modulating levels of neurotransmitters and protecting nervous system cells against inflammation (139). However, nutraceuticals studied in animal models are often at a supra-physiological dose and not achievable in humans without risk of toxicity, as well as adequate trials for defined populations are needed to improve the field (87). Exploiting and developing hormetic dose–response strategies based on Nrf activation should enable to prevent and combat disease, as well as support healthy aging and longevity (7). The deep understanding of Nrf2 and its crosstalk with other transcription factors as a hormetic mediator may nurture the development of effective therapeutic agents (7).

Conclusion

Hormesis can comprehensively unify several arguments related to aging processes, including dose–response mechanisms, redox networks, inflammaging, and oxinflammation (140). Therefore, anti-aging strategies should target this evolutionary concept to foster healthy aging and longevity. Anti-aging drugs have emerged as a storm in the last decade, targeting vitagenes, cell senescence, autophagy, inflammation, and redox systems. Notwithstanding the promising evidence of hormesis-fashioned medical interventions, yet the translational path of clinical trials in humans has not been solidly traversed. However, the combination of anti-aging drugs with lifestyle interventions may maximize geroprotector effects (67).

Modulating environmental factors and controlling stress–response processes may represent an advanced and refined perspective for redox medicine (14). In this framework, a deep comprehension of redox biogerontology and hormetic pathways is needed to clarify the underlying mechanisms, improve benefits, and minimize detrimental effects of any intervention. In the same vein, defining robust biomarkers of aging could take the biogerontological research to the next level.

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Conflict of Interest

None declared.

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