Nutritional modulation of cellular redox signaling in the management of age-associated disorders: NRF2 as a prime target

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Abstract: Oxidative stress caused by excessive reactive oxygen species generation is considered a major contributor to aging and several age-related disorders, including cancer, neurodegeneration, cardiovascular diseases, and diabetes. Numerous small molecules including antioxidant vitamins have exhibited preventive or therapeutic potential in preclinical studies. However, longevity studies in multiple model organisms failed to demonstrate that antioxidants prevent/delay aging processes Notably, accumulated oxidative damage does not directly correlate with aging severity. Thus, oxidative stress-induced structural damage alone is not sufficient to satisfactorily explain the age-associated functional losses. Optimal levels of reactive oxygen species act as second messengers in intracellular signal transduction and also play roles in adaptive survival responses to oxidative stress. It is now recognized that aging is influenced by cellular redox status rather than by generally accepted oxidative stress mechanisms. A new 'redox stress hypothesis' proposes that age-associated functional losses are primarily caused by a progressive pro-oxidizing shift in the redox state of the cells, which leads to the disruption of the redox-regulated signaling mechanism. Recent interest has focused on maintenance of physiological magnitude of redox signaling in aging cells. Dietary/nutritional modulation of defective redox signaling pathways in a way to restore their function will provide effective solutions to degenerative health complications of elderly. NRF2 is a key transcription factor responsible for the expression of genes involved in redox regulation. Its activity declines with age, which potentially contributes to age-related disorders. As disrupted adaptive cellular redox homeostasis is a critical hallmark of aging, precise understanding of the role will help develop a better strategy to promote healthy aging.

1. Introduction

Reactive oxygen species (ROS) are generated during normal mitochondrial metabolism and immune responses [1, 2]. Some xenobiotics and ionizing radiation can also generate ROS [1], ROS damage nucleic acids, proteins, and membrane lipids, contributing to various disorders and aging [1]. The susceptibility of cellular components to ROS depends on the local antioxidant defense capacity, which determines the redox status. Some endogenous antioxidant molecules, including reduced glutathione, thioredoxin, taurine, and α-lipoic acid, are abundant in an intracellular environment. Dietary antioxidants ascorbic acid (vitamin C) and tocopherol (vitamin E) are also involved in neutralizing ROS. If intracellular production of ROS exceeds antioxidant levels or when antioxidant defense mechanisms become defective, 'oxidative stress' can be provoked.

Oxidative stress cannot be defined solely as an imbalance between ROS production/accumulation and antioxidant defense capacity, as it also involves disruptions in cellular redox sensing and signaling pathways [2, 3]. Redox signaling represents a short-lived event mediated by ROS and/or those that respond to ROS. This involves free radical-derived electron transfer reactions, chemical or enzymatic reactions that require redox-active transition metal ions, reductive equivalents or inorganic trace elements. Notably, redox signaling is mediated by numerous redox-sensitive transducer proteins that undergo diverse covalent modifications, such as cysteine oxidation, phosphorylation, acetylation, methylation, and methionine sulfoxidation [2, 3].

It is now recognized that ROS can be both friends and foes [3, 4]. Optimal levels of ROS are pivotal in intracellular signal transduction and adaptive survival responses to oxidative stress. Physiological levels of diffusible non-radical ROS, particularly hydrogen peroxide (H_2O_2), can act as second messengers, regulating redox signaling pathways by interacting with various redox-sensitive protein networks [3, 5]. Redox signaling is essential for maintenance of the homeostatic balance of many complex regulatory networks and hence needs to be subjected to fine tuning. Disruption of this equilibrium leads to the various diseases. These findings provide a foundation for exploring redox regulation as a mechanistic basis for improving therapeutic strategies [6]. A new concept of 'adaptive redox homeostasis' has been proposed, which describes the transient increase in cellular ROS buffering capacity in response to amplified ROS formation within a physiological range [3]. According to this proposal, redox-dependent second messengers are generated in subcellular locations to rescue the cells from oxidative stress.

While long-term exposure to relatively large amounts of ROS can gradually cause irreversible cellular

defects including impaired proteostasis, short-term or mild oxidative challenges resolved swiftly contribute to adaptive redox signaling response. Adaptive redox signaling response induced as a consequence of short-term exposure to subtoxic levels of ROS stimulates distinct redox-sensitive cascades. This provokes hormetic responses necessary to regulate cellular homeostasis [3, 7]. Living organisms have evolved adaptive redox homeostasis mechanisms to cope with an oxidative stress and related noxious conditions. A key player in cellular adaptive stress response is the nuclear factor erythroid 2 p45-related factor (NRF2) [8]. This evolutionarily conserved and ubiquitous transcription factor has a prominent role in the transcriptional regulation of a battery of antioxidant and other cytoprotective genes, thereby maintaining intacellular redox homeostasis. NRF2 is responsible for body's defense mechanisms whereby a diverse array of toxic prooxidants and other reactive species including electrophiles and reactive nitrogen species (RNS) can be neutralized or eliminated before they damage genomic DNA or other critical cellular components [8-10]. It is noticeable that some chemoprotective and chemopreventive substances present in our daily diets are capable of activating NRF2 signaling [11,12].

2. Redox modulation of Inflammation and Immune Response

Oxidative stress and inflammation are closely interconnected and influence each other through intricate regulatory networks. They form a self-perpetuating cycle in which oxidative stress activates inflammatory pathways, while inflammation, in turn, enhances ROS generation [13]. Under normal physiological conditions, ROS-driven inflammation serves as a crucial defense mechanism, enabling the immune system to combat invading pathogens, remove cellular debris and dead cells, and facilitate tissue repair. [5]. This process is typically associated with acute inflammation, which is rapid in onset and resolves naturally once the threat is eliminated. Typically, inflamed tissues produce elevated levels of ROS and RNS that can act as critical regulators of the inflammatory process. The redox changes during immune-inflammatory responses are orchestrated by the actions of many signaling molecules such as proinflammatory (e.g., nuclear factor-κB and STAT3) and anti-inflammatory (e.g., NRF2) transcription factors [14]. ROS and RNS can regulate intracellular redox signaling through modifications of these transcription factors and their modulators at specific amino acids, particularly cysteine and lysine residues. Understanding the role of ROS/RNS on inflammation and inflammation-associated immune responses will assist in the development of relevant therapeutic strategies [15].

Redox-dependent second messengers are produced within specific subcellular compartments, and the intensity and duration of ROS signaling dictate their downstream outcomes. ROS-driven physiological processes are essential for cellular defense mechanisms, particularly in supporting the phagocytic functions of granulocytes and macrophages. The term "molecular inflammation" has been introduced to highlight the significance of underlying molecular reaction mechanisms that differ from conventional chronic or overt inflammatory responses. [16]. The immune-inflammatory response is closely linked to elevated nitro-oxidative stress. The function and survival of immune cells are regulated by redox balance, which is influenced by both intracellular and extracellular levels of ROS and RNS. These processes are strongly modulated by cellular antioxidant systems, including NRF2, glutathione, and thioredoxin pathways, all of which can become compromised under conditions of prolonged nitro-oxidative stress, such as hyperoxidation and hypernitrosylation [17]. Although NRF2 is mainly involved in cellular antioxidant defense, many studies have highlighted its ubiquitous roles in cellular cytoprotection including anti-inflammatory function [18].

3. Redox Signaling in Aging

The oxidative stress-induced damage to biomolecules has long been considered a principal mechanisms underlying aging and age-associated degenerative diseases. This hypothesis has been corroborated by the age-related increases in the rates of ROS production as a source of damage to cellular structure and function, which are postulated to be a causal factor of senescence [19]. Although aging is accelerated when the tissues that are damaged are not repaired [5], some later studies have shown that the accumulated oxidative tissue damage during aging is not necessarily proportional to degree of aging and has limited effects on the regulation of lifespan and healthspan in mammals [7, 19, 20]. Thus, oxidative stress-induced structural damage alone is insufficient to satisfactorily explain the age-associated functional losses. Boosting antioxidant defenses often fails to extend lifespan, even though it improves stress resistance [7, 19]. It remains largely elusive whether oxidative stress is the cause or result of the aging process.

Such conflicting observations led to the proposition that aging may be influenced by cellular oxido-reduction status or redox environment rather than by generally accepted oxidative stress mechanisms [20]. Since ROS play essential roles in signal transduction, gene expression, and redox regulation, their complete removal would be detrimental. The redox stress hypothesis suggests that age-related functional decline primarily results from a gradual shift toward a pro-oxidative cellular environment. This shift causes excessive oxidation of redox-sensitive protein thiols, ultimately impairing redox-regulated signaling pathways and disrupting cellular homeostasis.

[19]. The utilization of oxygen by aerobic organisms inevitably leads to the generation of potentially harmful ROS. When the balance between pro-oxidants and antioxidants is disrupted, cells may experience a chronic state of oxidative stress. Since oxygen is essential for life, oxidative stress becomes an unavoidable aspect of an organism's biology. This intrinsic link between oxidative stress and aerobic life can be seen as an adaptive mechanism that enables organisms to counteract and manage the potentially damaging effects of ROS. The living organisms have acquired adaptive mechanisms as part of their survival strategy that regulate and guard against oxidative stress [21]. From the evolutionary point of view, aerobes are likely to get gradually adapted to their newly emerged habitat of ROS by developing new redox active second messengers [3]. This is the core of the 'adaptive redox homeostasis' that describes the transient increase in ROS buffering capacity to survive the harmful effects of ROS-induced oxidative stress.

However, such evolutionary adaptation becomes impaired during aging because of the deterioration of endosymbiotic crosstalk [22]. Thus, adaptive redox homeostatic responses appear to be attenuated with age. ROS-mediated intracellular redox signaling pathways are often in a dyshomeostatic balance with the advancing stage of aging, and impaired adaptive redox homeostasis render elders to be more prone to age-related diseases [3]. In support of this notion, age-related loss of capabilities to regulate redox signaling events of the gastrointestinal cells was implicated in pathogenesis of many human disorders such as cardiovascular diseases, cancer, diabetes, and neurodegeneration [23]. It remains largely unresolved how the adaptive redox homeostatic mechanisms regulate the degenerative processes of biological ageing. In this context, it is interesting to note that a mild stress caused by caloric restriction has been known to increase the longevity by retarding the deleterious, aging processes. Such anti-aging effects of calorie restriction is speculated to be mediated through modulation of the intracellular redox environment in a way to upregulate the stress-responsive genes; these include those encode the anti-oxidative enzymes and other cytoprotective proteins [24]. This activation often involves hormetic stress responses, where low-level stresses induce beneficial cellular adaptations. In essence, caloric restriction's impact on stress-responsive genes, particularly those involved in antioxidant defense, is a key aspect of its potential health benefits and its ability to promote longevity and protect against age-related diseases.

Since the early postulations that oxidative damage could be a major causal factor of senescence and age-related diseases, dietary antioxidant supplements have been widely recommended to prevent or alleviate these undesired complications. However, their geroprotective and/or senotherapeutic efficacy is generally far from satisfactory. This is partly due to requirement of ROS-signaling for cellular homeostasis, and increasing ROS can activate cellular stress pathways to protect tissues from degeneration, thereby promoting healthy aging [6, 7]. Antioxidant administration may dampen body's intrinsic stress defense capability which is stimulated, for instance, by mild ROS generated during the exercise. Precise elucidation of adaptive redox homeostatic signaling pathways could provide promising senotherapeutic targets for healthy life-span extension and age-related disorders [3]. NRF2 is key lynchpin of the adaptive stress-response pathway that plays a crucial role as a master transcriptional regulator of many antioxidant enzymes and other cytoprotective proteins [8-10]. Age-related decreases in this stress responsive transcription factor have been associated with diminished antioxidant defense and increased ROS in elderly [25]. Dysregulation of the NRF2 pathway can be a prominent cause of selective susceptibility to oxidative and inflammatory tissue damage which can accelerate aging. The importance of mechanisms targeting NRF2 to suppress oxidative stress and inflammation provide the new preventive or therapeutic strategies in the management of age-related disorders [19,21,22].

4. Conclusion

Future research should focus on exploring the therapeutic potential of NRF2 modulation in aging and age-related disorders. Identifying novel natural compounds and nutraceuticals that can selectively activate NRF2 without disrupting redox balance could open new avenues for senotherapeutic interventions. Additionally, further studies are needed to clarify the hormetic role of ROS and how mild oxidative stress can be harnessed to promote healthy aging. Integrating personalized nutrition strategies and investigating dietary interventions that optimize NRF2 signaling may provide translational insights for preventing or delaying the onset of age-associated diseases. The oxidative stress and damage which increases as an organism age has been postulated to be responsible for senescence. However, the idea that aging is influenced by the intracellular redox status or environment rather than simply by oxidative stress, suggests a more nuanced understanding of the aging process. While oxidative stress, the imbalance between ROS and antioxidants, is a well-established factor, research is now exploring how the overall redox environment within cells might play a more dominant role in aging. This includes considering how shifts in the balance between reduced and oxidized molecules within the cell affect cellular function and contribute to age-related decline. Dietary/nutritional modulation of defective redox signaling pathways in a way to restore their function will provide effective solutions to degenerative health complications of elderly.

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