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Oxidative Stress, Inflammaging, and Immunosenescence: Implications for Age-Related Diseases

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ABSTRACT

Aging is accompanied by a progressive decline in physiological functions and an increased susceptibility to chronic diseases. Central to the aging process are oxidative stress, inflammaging, and immunosenescence, which collectively contribute to the pathogenesis of many age-related disorders. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, leading to cellular damage and dysfunction. Inflammaging, a chronic low-grade systemic inflammation, exacerbates tissue damage and promotes disease development. Immunosenescence, the gradual deterioration of the immune system, impairs immune surveillance and responsiveness, further increasing vulnerability to infections, cancer, and autoimmune conditions. This review provides a comprehensive overview of the mechanistic interplay between oxidative stress, inflammaging, and immunosenescence, highlighting their roles in age-related diseases such as cardiovascular disease, neurodegeneration, and metabolic syndrome. We also discuss potential therapeutic strategies aimed at mitigating these processes to promote healthy aging and improve disease outcomes.

Keywords: Oxidative stress, Inflammaging, Immunosenescence, Aging, Age-related diseases

INTRODUCTION

Aging is an intricate biological process marked by progressive deterioration in physiological functions, leading to increased vulnerability to diseases and mortality [1]. Among the multifaceted mechanisms that contribute to aging, oxidative stress, inflammaging, and immunosenescence stand out as interconnected phenomena that profoundly impact the aging process and the development of age-related diseases [2]. Oxidative stress refers to an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses, resulting in damage to essential cellular components such as DNA, proteins, and lipids [3]. This oxidative damage accumulates over time, impairing cellular function and integrity, and serves as a critical trigger for cellular senescence and inflammatory responses. Inflammaging is a term coined to describe the chronic, low-grade systemic inflammation observed in elderly individuals without overt infection [4]. This persistent inflammatory state arises due to multiple factors including the accumulation of senescent cells that secrete pro-inflammatory cytokines and chemokines (the senescence-associated secretory phenotype, or SASP), chronic activation of innate immune cells, and age-related alterations in the gut microbiota [5]. This low-grade inflammation contributes to tissue damage, fibrosis, and functional decline in various organs, fostering an environment that promotes the onset and progression of multiple chronic diseases. Immunosenescence describes the gradual decline in immune system function associated with aging, characterized by diminished adaptive immunity, altered innate immune responses, and reduced ability to respond to new antigens [6] This immunological remodeling compromises host defense against infections, decreases vaccine efficacy, and facilitates the development of cancer and autoimmune disorders [7]. Together, oxidative stress, inflammaging, and immunosenescence create a self-reinforcing cycle that accelerates aging and exacerbates age-associated pathologies [8,9]. This review will explore the mechanistic interplay of these processes, their implications in major age-related diseases such as cardiovascular disease, neurodegeneration, and metabolic syndrome, and potential therapeutic strategies aimed at mitigating their detrimental effects to promote healthy aging.

2. Oxidative Stress in Aging

Oxidative stress is a fundamental hallmark of aging, arising when the production of reactive oxygen species (ROS) surpasses the capacity of the body's antioxidant defense systems [10]. ROS are chemically reactive molecules derived primarily from mitochondrial oxidative phosphorylation, as well as enzymatic reactions involving NADPH oxidases and other cellular sources [11]. Under normal physiological conditions, ROS serve important signaling roles in cell proliferation, differentiation, and immune defense. However, with advancing age, mitochondria become less efficient and leak increased amounts of ROS, contributing to cellular damage [12]. This imbalance leads to oxidative modifications of macromolecules such as DNA, proteins, and lipids, which compromises cellular function and promotes genomic instability-a driver of cellular senescence and apoptosis [13]. The accumulation of oxidative damage is implicated in functional decline across multiple tissues, including the brain, cardiovascular system, and skeletal muscles.

Antioxidant defense mechanisms, including enzymatic antioxidants like superoxide dismutase (SOD), catalase, and glutathione peroxidase, normally mitigate ROS toxicity [14]. However, their activity diminishes with age, compounding oxidative stress. Additionally, exogenous factors such as poor diet, environmental toxins, and reduced physical activity contribute to ROS accumulation [15]. Beyond direct damage, oxidative stress activates redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB), which promotes the expression of pro-inflammatory cytokines. This links oxidative stress with inflammaging by fostering a chronic inflammatory milieu. Therapeutic strategies aimed at reducing oxidative stress or enhancing antioxidant defenses have shown promise in preclinical models to delay aging phenotypes and improve tissue function [16].

3. Inflammaging: Chronic Low-Grade Inflammation

Inflammaging describes the phenomenon of chronic, low-grade systemic inflammation that occurs in aging without overt infection [17]. It is characterized by increased circulating levels of pro-inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). Multiple cellular and molecular mechanisms contribute to inflammaging, making it a multifactorial process integral to the aging phenotype [18]. One key driver is the accumulation of senescent cells in various tissues. These cells adopt a senescence-associated secretory phenotype (SASP), releasing a plethora of pro-inflammatory cytokines, chemokines, growth factors, and proteases that disrupt tissue microenvironments and promote inflammation [19]. Additionally, chronic activation of innate immune cells such as macrophages and neutrophils sustains inflammation via persistent production of inflammatory mediators [20,21]. Age-associated alterations in the gut microbiota also contribute to inflammaging. Dysbiosis increases intestinal permeability, allowing translocation of microbial products such as lipopolysaccharides (LPS) into circulation, which further activates systemic inflammatory pathways [22]. Inflammaging exacerbates age-related tissue damage, impairs repair mechanisms, and contributes to the pathogenesis of multiple chronic diseases including atherosclerosis, type 2 diabetes, Alzheimer's disease, and certain cancers [23]. It also diminishes vaccine efficacy and slows wound healing. Interventions to mitigate inflammaging include lifestyle modifications such as regular exercise, dietary changes rich in anti-inflammatory nutrients, and pharmacological approaches targeting inflammatory signaling [24]. Understanding the complex biology of inflammaging is vital to developing therapies that can reduce chronic inflammation and improve healthspan.

4. Immunosenescence and Its Impact on Disease

Immunosenescence refers to the gradual deterioration of the immune system associated with aging, leading to impaired immune responses and increased susceptibility to infections, malignancies, and autoimmune diseases [25]. Both innate and adaptive immune compartments undergo significant alterations during aging, compromising immune surveillance and host defense. Adaptive immunity experiences thymic involution, resulting in decreased output of naïve T cells and accumulation of memory and senescent T cells [26]. This reduces T cell receptor diversity and limits the immune system's ability to respond to new antigens, explaining poor vaccine responses in the elderly. B cell function is also impaired, with decreased antibody production and affinity maturation. Innate immune cells, including macrophages, dendritic cells, and neutrophils, exhibit altered phenotypes with increased basal production of pro-inflammatory cytokines, reduced phagocytosis, and impaired pathogen clearance [27]. These changes contribute to the chronic inflammatory state characteristic of inflammaging. The decline in immune competence not only increases vulnerability to infectious diseases but also allows for the reactivation of latent viruses and the development of cancer [28]. Autoimmune phenomena also become more common, possibly due to reduced regulatory immune function. Efforts to reverse or delay immunosenescence include vaccination strategies tailored for older adults, immune-boosting agents, and interventions targeting metabolic and oxidative stress pathways that underlie immune aging [29]. Enhancing immune function in aging populations is crucial for reducing morbidity and mortality associated with infections and chronic diseases [30].

5. Implications for Age-Related Diseases and Therapeutic Perspectives

The interconnected processes of oxidative stress, inflammaging, and immunosenescence significantly contribute to the development and progression of a wide range of age-related diseases [31]. Cardiovascular diseases, including atherosclerosis and hypertension, are fueled by chronic oxidative and inflammatory damage to vascular endothelium [32]. Neurodegenerative diseases such as Alzheimer's and Parkinson's disease involve oxidative damage, neuroinflammation, and impaired immune surveillance in the brain [33]. Metabolic syndrome and type 2 diabetes are linked to systemic inflammation and oxidative stress impairing insulin signaling and pancreatic beta-cell function.

Given the centrality of these mechanisms, therapeutic strategies aimed at mitigating oxidative stress and inflammation, and restoring immune competence, hold promise for improving healthspan [34]. Antioxidant supplementation, including vitamins C and E, polyphenols, and novel synthetic antioxidants, aims to reduce oxidative damage, though clinical efficacy remains mixed. Senolytic drugs that selectively eliminate senescent cells are emerging as promising interventions to reduce SASP-driven inflammaging [35].

Anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), cytokine blockers, and lifestyle interventions such as caloric restriction and exercise, have shown benefits in reducing chronic inflammation [36]. Immune modulation strategies aim to enhance vaccine responses and restore immune function in the elderly.

Emerging approaches leverage advances in genomics, proteomics, and metabolomics to identify biomarkers that enable personalized interventions targeting these aging hallmarks [37]. Integrative strategies combining antioxidants, senolytics, anti-inflammatories, and immune modulators may synergize to delay or prevent age-related diseases and promote healthy longevity [38].

CONCLUSION

Oxidative stress, inflammaging, and immunosenescence are interconnected processes that collectively drive aging and contribute to the pathogenesis of numerous age-related diseases. The accumulation of oxidative damage triggers chronic low-grade inflammation, while the decline in immune function impairs host defense and tissue repair. Understanding these mechanisms offers valuable insights into aging biology and highlights potential therapeutic targets. Interventions aimed at reducing oxidative stress, modulating inflammation, and rejuvenating immune function hold promise for promoting healthy aging and mitigating disease burden. Continued research is essential to develop effective, personalized strategies that enhance longevity and quality of life.

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