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Review Article

Cellular Senescence and Periodontal Diseases: An Overview

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Abstract

Cellular senescence refers to the progressive decline in cellular function with aging. Inflammaging keys a chronic low-grade sterile inflammatory state that arises with aging. Together, they lead to a dysfunctional immune response. Periodontitis, chronic inflammatory condition affecting the supporting tooth structures, could lead to tissue damage and tooth loss. The host's innate and adaptive host immune responses are crucial for maintaining periodontal health. Interestingly, the prevalence of periodontitis increases with age. To this end, we conducted a literature search using PubMed, Ovid and EBSCO to identify English-written articles discussing the interplay between cellular senescence and periodontal inflammation. Our research indicated that cellular senescence and inflammaging lead to an imbalanced inflammatory response within the periodontium. This imbalance exacerbates tissue damage and dysregulates the host defenses against common periodontal pathogens. Therefore, proper understanding of age-related immune dysregulation may help in developing strategies to improve geriatric patients' oral health.

Keywords: Cell senescence; Immunosenescence; Inflammaging; Periodontitis

Abbreviations: CXCL: Chemokine ligand; IL: Interleukin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; SASP: Senescence-associated secretory phenotype; TNF-α : Tumor necrosis factor-α

Introduction

Aging is an intricate physiological process that impacts organ system function. It is considered a significant risk factor for several geriatric and chronic conditions [1-3]. Aging can augment age-related bone disorders including osteoporosis, rheumatoid arthritis, and periodontitis [3]. Bone tissue is a scaffold composed of collagen, minerals, water, and non-collagenous proteins. Trabecular bone constitutes 20% of the total bone mass and cortical bone accounts for the remaining 80%. Aging causes a decline in trabecular and cortical bone masses, changes in bone tissue components, and a decline in bone's biological and mechanical characteristics. Ultimately, this increases the susceptibility to age-related bone diseases in the elderly population.

The incidence of rheumatoid arthritis increases with age, and it is recognized as a model of premature senescence [3]. In the same context, a strong association between osteoporosis, cellular senescence, and inflammaging was reported [4]. Osteoporosis is characterized by a reduction in bone minerals and damage in bone microstructure which reduces the bone's strength, and raises the risk of fractures. Osteoarthritis, a deterioration of articular cartilage that eventually leads to physical function impairment, is characterized

by an increased number of senescent chondrocytes [5]. Periodontitis is associated with chronic inflammation, alveolar bone loss and gingival recession. Interestingly, the severity and prevalence of periodontitis tends to increase with advanced age [6]. Prior studies demonstrated age-related changes in periodontium including decreased wound healing, increased senescent cell population, and increased pro-inflammatory cytokine gene expression [7]. However, the exact mechanism is not clearly elucidated. Therefore, expanding our knowledge in age-related changes in the periodontium can offer mechanistic insights and help in developing strategies to improve oral health in geriatric patients.

Aging and immune response

Several aging mechanisms, including mitochondrial dysfunction, protein imbalance, epigenetic alterations, telomere damage, unstable genomes, and cellular senescence were reported. Although each mechanism plays a role in certain aspects of the aging process, cellular senescence plays a central role in aging and inflammatory processes [3, 8]. Hayflick, et al. proposed the concept of cellular senescence in 1961. It refers to a progressive degradation in cellular function and complexity that ultimately leads to a gradual and irreversible decline in the cellular proliferative capacity [9-10]. Growth arrest, resistance to apoptosis, and a senescence-associated secretory phenotype (SASP) are hallmarks of cellular senescence and are thought to be major drivers for chronic, age-related diseases [11-12]. DNA damage can trigger cellular senescence via a prolonged DNA damage response and growth arrest [13-16]. If the damage is severe, cells may undergo apoptosis to maintain the integrity of the host genome. To maintain homeostasis, apoptotic and senescent cells are regularly removed by the immune system. However, aging decreases our immune system's ability to remove senescent and apoptotic cells. Walford RL, introduced the term immunosenescence to reflect age-related modulation of the immune system [17]. This multifactorial phenomenon impacts both innate and adaptive immunity [18]. The concept of immunosenescence and accumulation of senescent cells have been linked to various pathologies including cardiovascular diseases, age-related bone diseases, cancer, and increased susceptibility to infections.

While acute inflammation is an essential component of the natural immune response against insults, chronic inflammation can slowly lead to tissue and organ damage. Neves, et al. (2020) demonstrated that chronic inflammation is a key player in the manifestation of several age-related pathologies [19]. Francesch, et al. (2000) introduced the concept of 'inflammaging' characterized by a chronic low-grade 'sterile' inflammatory state [20]. This persistent low-grade chronic inflammation accelerates aging, which in turn exacerbates the inflammation process, creating a self-perpetuating cycle [3]. Senescent cells have been widely implicated in the promotion of inflammaging [21-22].

Although senescent cells exhibit growth arrest, they maintain their metabolic viability through their SASP complex which includes secretion of a variety of proinflammatory chemokines, cytokines, growth factors, and proteases. This modulates tissue regeneration, repair, chronic inflammation, and progression of age-related dysfunction [23-25]. Deursen, et al. (2014) suggest that senescent cells utilize the SASP complex to attract immune cells and induce local inflammation [26]. In the periodontium, senescent cells can facilitate an environment that fosters inflammation which accelerates the deterioration of alveolar bone [27].

The immune system can be divided into innate immunity which includes neutrophils, monocytes and natural killer cells, and adaptive immunity which involves the B and T lymphocytes. Innate and adaptive immunity can be affected by the aging process. Neutrophils are the most common leukocytes in our body, and they confer the initial protection against invading microbes [28]. Neutrophils mediate the host immune response via several mechanisms including phagocytosis, degranulation of antimicrobial proteins, and releasing neutrophil extracellular traps (NETs) [2]. Immunosenescence can decrease the immunoprotective activity of neutrophils via impairing phagocytosis, degranulation, and decreasing the NETs [2]. In the monocyte/macrophage population, age-related decline in phagocytic capacity and dysregulation of the inflammatory cytokines were also reported.

The adaptive immune system includes a humoral immune response mediated by B-lymphocytes and antibodies as well as a cell-mediated immune response mediated by T-lymphocytes [2]. T lymphocytes are further subdivided into $CD4^+$ T-helper (Th) cells and $CD8^+$ cytotoxic T cells. Upon activation, naïve $CD4^+$ helper T-cells differentiate into different effector T cell lineage including Th1, Th17, and others; each with a unique function in orchestrating the immune response [29, 30]. Effector cytotoxic T cells induce cell death to clear intercellular pathogens. Immunosenescence downregulates the effector T-cell response through reducing the production of naïve T cells and defective T-cell signal transduction. On the other hand, senescent T cells upregulate the production of proinflammatory cytokines which contribute to immune dysregulation and inflammaging [2]. Similar age-related decline in B cell function and the associated humoral immune response were also reported [31].

Pro-inflammatory cytokines and chemokines play a central role in inflammaging and immunosenescence. With the aim of discovering immunological markers associated with aging, several studies investigated the association between pro-inflammatory mediators and aging. In a study that included 2111 participants with a mean age of 62.9 years, Lima-Silva, et al. (2024) reported a significant positive association between aging and upregulated interleukin (IL)-2, IL-4, IL-6, IL-17, tumor necrosis factor-α (TNF-α) as well as chemokine ligand-10 (CXCL10) levels [32]. CXCL10 is secreted following induction by interferon-gamma, and acts as a chemoattractant and a mediator for the inflammatory process. In agreement, Ravalet, et al. (2023) previously demonstrated the upregulation of CXCL10 level with advanced age [33]. IL-2 is a growth factor that is essential for T-lymphocyte development and maturation. IL-6, IL-17, and TNFα are proinflammatory cytokines that can mediate proinflammatory responses and play a role in inflammaging. Interestingly, Adriaensen, et al. (2015) selected IL-6 as a prognostic inflammaging biomarker that can be correlated with adverse health outcomes in elderly patients [34].

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) was upregulated in age-related chronic inflammation [35]. Tavenier, et al. (2020) proposed that elevated basal NF-κB activity in monocytes may contribute to inflammaging [36]. Moreover, NF-κB inhibition was beneficial in reducing DNA damage and delaying cellular senescence [37]. NF-κB is pivotal in activating proinflammatory pathways, resulting in altered cytokine and chemokine expressions, as well as the secretion of anti-apoptotic factors, which collectively impede the clearance of senescent cells [38]. Chien, et al. demonstrated the regulatory function of NF-κB in the SASP complex. Simply put, localized inflammation dysregulates NF-κB signaling which in turn triggers SASP. As previously discussed, the secretion of SASP recruits immune mediators to inflammation site, establishing a self-perpetuating and growing cycle of inflammatory mediator recruitment [11, 39]. Taken together, accumulating evidence has demonstrated the association between inflammatory cytokines, aging, and pathogenesis of age-related chronic inflammatory disorders [35-42].

Aging and periodontitis

Gingival and periodontal diseases are inclusive terms that encompass a wide variety of conditions affecting the tooth-supporting structures [43]. Periodontitis is a multifactorial sustained inflammatory process of the periodontium that may extend to the jaw bones. Smoking, genetics, several systemic diseases and advanced age are among risk factors contributing to its development [44]. With a prevalence of 19% among the adult population worldwide, severe periodontitis is a significant global oral health challenge [45]. In the United States, the prevalence of severe periodontitis is estimated to hover around 7.8% of the adult population [46]. Severe untreated periodontitis may damage the tooth supporting structures leading to tooth loss, aggravation of other systemic diseases and consequentially negatively impacting the quality of life.

Periodontitis is characterized by a dysregulated immune response towards dysbiotic bacteria leading to gingival detachment, deepening of the subgingival crevice, degradation of the periodontal ligament, and loss of the alveolar bone [47, 48]. Disease progression occurs upon the dysregulation of the immuno-inflammatory response towards bacterial challenge, resulting in uncontrolled host reactions involving both innate and adaptive immunity. Moreover, breakdown products from host tissues facilitate the growth and persistence of dysbiotic microbiota which further generates a self-perpetuating pathogenic cycle. Due to its direct proximity to teeth, the subgingival crevice serves as the primary locus for harboring complex bacterial species [49]. Neutrophils, macrophages, T-lymphocytes and other immune cells contribute to the defense mechanism against periodontal pathogens and their dysregulation contribute to the development of periodontitis. Following successful combat against infection, the pro-inflammatory process is downregulated, and immune cells exit the infection site and re-enter the vascular system (a phenomenon known as reverse migration). This process not only contributes to the proper resolution of infection but also prevents localized damage to periodontal tissue [50].

For instance, dysfunction of neutrophil reverse migration can amplify the inflammatory response and contribute to the development of periodontitis. In addition, the declining function of neutrophils with aging leads to lower antimicrobial activity and negatively impacts the wound healing process [2, 51]. In the same context, altered Th17 cells and regulatory T-cell ratio with aging leads to altered cytokine expression and imbalanced pre-inflammatory/anti-inflammatory immune response [52]. Cytokines are fundamental mediators to maintain the intricate balance between homeostasis and inflammation. Positioned at barrier sites, like the subgingival crevice, they orchestrate sophisticated communication between connective tissue cells, immune cells, and other accessory cell populations [53, 54]. For instance, IL-8 is a potent chemoattractant that facilitates the extravasation of neutrophils into the subgingival crevice, and beta-2 integrins play pivotal roles in the immunological processes including leukocyte trafficking, phagocytosis, ROS production, and T-cell activation [55, 56]. On the other hand, accumulating evidence demonstrated the role of several cytokine families in the pro-inflammatory process activation, stimulation of the bone-resorbing osteoclasts, and the progression of periodontitis [57]. Polymorphisms in genes encoding IL-1A, IL-1B, IL-6, and IL-10 are significantly associated with an increased risk for periodontitis. In addition, the amplification of the inflammatory cascade mediated by Th17, IL-17 and related cytokines lead to excessive recruitment of neutrophils, which orchestrate immunopathological processes that eventually lead to bone loss [58].

The prevalence and severity of periodontitis increases with advanced age [6]. Senescent cells present with a gradual decline in functionality and can release pro-inflammatory cytokines that contribute to tissue damage. For instance, the periodontal ligament stem cells present with declining proliferative and osteogenic-differentiation capacity with age [35]. Increased SASP levels including but not limited to TNF-α, interferon-gamma (INF-γ), IL-1, IL-6, and IL-8 were detected in the gingival crevicular fluid. These pro-inflammatory cytokines contribute to dysregulated immune response, tissue damage and enhance alveolar bone loss in periodontitis. Loss of alveolar bone occurs due to an imbalance between bone formation and resorption. Yamashita, et al. demonstrated that NF-κB can significantly enhance osteoclast differentiation and maturation downstream of receptor activator of NF-κB ligand (RANKL) [59]. Similarly, TNF-α plays a crucial role in osteoclastogenesis and periodontal tissue destruction. Jain, et al. demonstrated a positive correlation between increased serum levels of TNF-α and periodontitis [60]. Taken together, the increased secretion of pro-inflammatory associated with aging will contribute to inflammaging in the periodontium and enhance the osteoclasts activity leading to imbalanced bone remodeling and subsequent bone loss. In addition, the ongoing inflammatory process in the periodontium will upregulate the secretion of IL-6 which will consequently activate osteoclastic activity and promote alveolar bone loss [3]. Therefore, in addition to its prognostic value in inflammaging, IL-6 plays an important role in the development of periodontal diseases as well as other immune disorders [34, 61, 62].

Conclusion

Aging, dysbiotic microbiota, and multiple environmental factors including tobacco smoking can all increase oxidative DNA

damage, thereby accelerating the accumulation of senescent cells and SASP. At the same time, the aged immune system becomes less efficient in removing senescent and apoptotic cells. This can plausibly contribute to the development of age-related chronic diseases. It is however unclear whether the rise in senescent cells with age is due to a greater number of cells becoming senescent or an impaired clearance of senescent cells due to immunosenescence, or a combination of both [26]. Nevertheless, in response to heightened senescent cell population, Zhou, et al. elucidated that aging is also associated with increased immune cell populations [63]. Immune cells proliferation enhances the expression of proinflammatory mediators, potentially accelerating the progression of age-related diseases. This altered immune response will contribute to an aggravated state of low-grade chronic inflammation or inflammaging which may exacerbate periodontal health and contribute to the development of severe periodontitis.

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Conflict of Interest

The authors declare no conflict of interest.

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