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Frailty, Aging, and Periodontal Disease: Basic Biological Considerations

Daniel Clark, DDS, MS, PhD [Associate Researcher],
Department of Orofacial Sciences, University of California San Francisco, San Francisco, CA, USA

Eftychia Kotronia, MSc [PhD student],
Population Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, UK

Sheena E. Ramsay, BDS, MPH, FFPH, FHEA, PhD [Clinical Senior Lecturer & Hon Consultant in Public Health]
Population Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, UK

Abstract

Aging is associated with the development of disease. Periodontal disease is one of the many diseases and conditions that increase in prevalence with age. In addition to the traditional focus on individual age-related conditions, there is now a greater recognition that multi-system conditions such as frailty play an important role in the health of older populations. Frailty is a clinical condition in older adults, which increases the risk of adverse health outcomes. Both frailty and periodontal disease are common chronic conditions in older populations and share several risk factors. There is likely a bi-directional relationship between periodontal disease and frailty. Co-morbid systemic diseases, poor physical functioning, and limited ability to self-care in frail older people have been implicated to be underlying the association between frailty and periodontal disease. In addition, both frailty and periodontal disease also have strong associations with inflammatory dysregulation and other age-related pathophysiological changes that may similarly underlie their development and progression. Investigating age-related changes in immune cells that regulate inflammation may lead to a better understanding of age-related disease and could lead to therapeutic targets for the improved management of frailty and periodontal disease.

Introduction

There has been a steady increase globally in aging populations over the last few decades. The increase in life expectancy, decrease in births, and improvement of health services have contributed to an increase in older populations. In the US, according to a recent report by the U.S. Department of Health and Human Services, the population aged 65 years and older increased by 34% between 2007 and 2017[1]. Additionally, the population aged 85 years and above is projected to increase by 123% by 2040[1]. Worldwide, it is projected that by 2050, 1 in 6 people will be aged 65 years and above[2]. Areas showing the highest rate of aging are

*Corresponding Author: Daniel Clark, DDS, MS, PhD, Associate Researcher, Department of Orofacial Sciences, University of California San Francisco, San Francisco, CA, USA, Daniel.clark@gmail.com.

Eastern and South-Eastern Asia, Latin America and the Caribbean[2]. Furthermore, there are gender differences in life expectancy globally, with women living nearly 5 years longer than men[2].

Aging is also strongly associated with the development of chronic diseases and age-related health conditions, which adversely affect health and quality of life in older people[3]. It has been reported that older individuals 65 years and above have at least one chronic condition[1]. In the US, 38% had 0–1 chronic conditions, whereas 47% had 2–3 chronic conditions. Chronic conditions related to oral health also play a key role in the health of older populations. Periodontal disease is one of the most prevalent chronic diseases globally and becomes more prevalent with increasing age[4,5]. Proper oral health care is essential in older populations to maintain their quality of life, functional performance, and overall systemic health.

In addition to the traditional focus on single (or related) chronic diseases, there is now a greater recognition that multi-system conditions such as frailty, play an important role in the health of older populations. Frailty is defined as “a clinically recognizable state of increased vulnerability, resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised”[6]. Frailty is a common clinical syndrome or condition in older adults, which increases the risk of adverse health outcomes, including falls, disability, hospitalization, mortality, and long-term care[7]. Similar to chronic diseases such as periodontal disease, the prevalence of frailty increases dramatically with increasing age.

There has been much research interest over the years in exploring associations of periodontal disease with chronic diseases, particularly cardiovascular disease, type 2 diabetes, and Alzheimer’s Disease. More recently, there has also been increasing interest in understanding a similar association of periodontal disease with frailty. Rates of both frailty and periodontal disease are higher in older populations[8]. Co-morbidities, poor physical functioning and limited ability to self-care in frail older people have been implicated to be underlying the association between frailty and dental diseases such as periodontal disease. In addition, both frailty and periodontal disease also have strong associations with inflammation and other age-related pathophysiological changes that may similarly underlie their development and progression.

There are also suggestions that oral diseases, such as periodontal disease, could increase the risk of frailty. Unpacking these bi-directional associations between frailty and periodontal disease merits further research. A better understanding of these associations could lead to improved management and treatment of both frailty and of periodontal disease amongst frail older people. Moreover, understanding the mechanistic biological pathways underlying frailty and periodontal disease will enable richer insights with the potential to improve diagnostics and personalized treatment modalities for older individuals. This manuscript describes the epidemiology and risk factors of frailty and of periodontal disease, and the associations between the two chronic conditions. Additionally, the manuscript will address the molecular and cellular changes that occur with aging and how such pathophysiological

changes may contribute to both frailty and periodontal disease. The manuscript will finally draw together conclusions including implications for research and clinical care.

Epidemiology of frailty

Frailty has been described as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death"[9]. A number of assessment tools for frailty have been developed in recent years, including the Fried Frailty Phenotype and the Frailty Index. The Fried Frailty Phenotype defines frailty as a clinical syndrome which is characterized by the following criteria: (1) unintentional weight loss, (2) self-reported exhaustion, (3) weakness (grip strength), (4) slow walking speed and (5) low physical activity[10]. Having three or more of these criteria are taken to identify an individual as being frail. Alternatively, the Frailty Index, measures frailty through the accumulation of deficits over time, and it mainly represents "a proxy measure of aging and mortality"[11]. One important characteristic of the development of frailty is that there is no specific symptom that manifests first and therefore signaling the onset of frailty. However, it has been reported that the manifestation of exhaustion or weight loss can influence significantly the progression to frailty[6]. Furthermore, the manifestation of symptoms and progression of frailty differs between individuals[6]. The prevalence of frailty in older people can vary depending on the definition/instrument that was used[12]. According to a large systematic review, the prevalence of frailty in community-dwelling individuals was 10.7%, while 41.6% were reported as pre-frail[13].

Frailty becomes more common with increasing age[13–16]. It has been reported that the prevalence of frailty was 4% in those 60–65 years old, 16% in individuals aged 80–84, and 26% in ≥85 year old community-dwelling populations[13]. Furthermore, women have higher rates of frailty compared to men[13]. Possible explanations are that women have lower muscle mass and strength than men[10], but also women have a higher life expectancy in comparison with men[13]. Furthermore, there are several factors, which can affect the development and progression of frailty in older people. Previous studies have reported that psychological well-being, history of depression and use of antidepressants, diabetes, arthritis, smoking, body mass index (BMI), cognitive impairment, comorbidities and hospitalizations are predictors of incident frailty in older age[16–20]. Additionally, level of mobility (walking speed), has been associated with development and progression of frailty[15]. Older individuals who reported good levels of mobility at baseline were more likely to maintain good physical function and observed no changes in their frailty status over time[15]. Also, increased levels of circulating inflammatory mediators are associated with development of frailty in older people (see Inflamm-aging section below). Frailty is also associated with a number of chronic diseases and adverse health outcomes in older people, such as cardiovascular disease, cognitive impairment, disability, falls, and mortality[21–25]. In other words, frailty could be an indicator of worsening health status and therefore is an important condition to be considered in the management of older people's health.

Epidemiology of periodontal disease in older populations

Periodontal disease is recognized as one of the most common chronic diseases[3,26]. In 2009–2010, the prevalence of periodontal disease in US adults over 30 years old was 47%[26]. Interestingly, the prevalence differed substantially between young and older individuals, with a prevalence of 24% in 30–34 year old individuals and 70% in those ≥65 years old[26]. Some differences in the prevalence of periodontal disease have also been reported by gender, whereby severe periodontal disease was more common in older men than women[5]. Smokers had higher levels of total (severe + mild/moderate) periodontal disease than non-smokers in individuals ≥65 years old[5]. Periodontal disease is of concern in older adults due to the associated root caries, tooth loss, and worsening masticatory ability, which can further effect, nutrition and speech and impact the patient's quality of life[27]. The impact of periodontal disease on the systemic health is especially concerning in older populations. Periodontal disease is associated with increased systemic inflammation, cardiovascular disease, poor nutritional status, cognitive impairment, disability and decreased physical function and other comorbidities[28–36].

Periodontal disease and its association with frailty in older populations

Research has indicated that there is an association between oral health problems and frailty in older people[8,37]. It is evident that both frailty and periodontal disease are common chronic conditions in older populations and share several risk factors (Figure 1). Both frailty and periodontal disease are associated with increased chronic systemic disease and both adversely influence quality of life by affecting food habits, physical activity, and functional independence[7,24,30,34,35]. This section summarizes results from previous studies on the associations between periodontal disease and frailty.

The relationship between frailty and oral health is likely to be bi-directional. Frail older people, particularly those living in long-term care settings have very high levels of dental diseases, including periodontal disease[8]. It is possible that frailty influences and increases the risk of oral diseases in older people. Systemic conditions, such as diabetes mellitus and arthritis are more prevalent in frail older people and are also associated with periodontal disease. These comorbidities may increase the susceptibility of frail older people to periodontal disease[8]. The presence of co-morbidities is compounded by mobility limitations in frail individuals, which may contribute to inadequate oral hygiene and decreased access to professional dental care, which could further increase the risk of periodontal disease[8].

Studies have also examined the influence of periodontal disease on the risk developing frailty. A number of studies have also focused on tooth loss, chewing difficulties, dental caries, oral pain, occlusion force, and their associations with frailty. However, fewer studies have focused on periodontal disease specifically, and they have reported mixed results. Differences in the assessment of frailty and periodontal disease may contribute to these inconsistent results. In one cross-sectional study of an aging population, individuals with remaining teeth reported better frailty status than those without any natural teeth[38] Other cross-sectional studies reported no differences in the prevalence of frailty when individuals with severe periodontal disease were compared to those with non-severe periodontal

disease[37,39–41]. However, in a longitudinal study, it was reported that severe periodontal disease at baseline, was associated with incident (development of frailty) after 3 years of follow-up[42]. Interestingly, this association remained significant even after adjusting for an interaction term between number of teeth and diabetes[42]. Another longitudinal study with 3 years of follow-up did not report any associations between periodontal disease and incidence of frailty[40]. A recent systematic review of five longitudinal studies demonstrated that oral health status was a predictor of frailty; however, the association of periodontal disease with frailty was inconsistent across the multiple studies[43].

Although frailty and periodontal disease in older populations appear to be linked, the direction of the association between the two conditions remains unclear. Nonetheless, there has been increasing awareness of the association of oral health and frailty and a growing appreciation of oral health as an important predictor of frailty[43]. Studies have highlighted that these two age-related chronic conditions may be associated through similar age-related changes to inflammatory and other biological pathways. An improved understanding of these pathophysiological changes may provide better insight into the management of periodontal disease and frailty.

Biological Considerations underlying periodontal disease and frailty

The association of frailty, aging, and periodontal disease is demonstrated by the epidemiological data as presented in the previous sections. However, a basic biological understanding of the age-related changes that contribute to frailty and periodontal disease is not fully understood. In advancing our biological understanding of aging, much work has been directed at inflammation. Of the many pathophysiological changes that occur with aging, age-related changes to the inflammatory response may be the closest pathophysiological explanation underlying both frailty and periodontal disease.

Inflamm-aging

Inflamm-aging and Frailty

Inflamm-aging describes a chronically elevated and dysregulated inflammatory response that increases with age[44]. It is unknown if inflamm-aging results from a chronic signal that maintains and prolongs the inflammatory response or from a defect in the resolution of the inflammatory response[45]. This systemic inflammatory dysregulation is suspected to directly contribute to or result in a predisposition to the many age-related pathologies including periodontal disease and frailty[44]. Inflamm-aging is generally characterized by elevated levels of circulating inflammatory markers. Circulating levels of interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and C-reactive proteins (CRP) are elevated with increasing age, even in otherwise healthy individuals and in the absence of acute inflammatory stimulus[46,47]. Increased circulating pro-inflammatory cytokines are also associated with frailty, including interleukin-1 beta (IL-1β), interleukin-18 (IL-18), interleukin-8 (IL-8), and chemokine (C-X-C) motif ligand 10 (CXCL10)[48]. Both frailty and inflamm-aging are associated with poor health outcomes and an association with similar age-related diseases such as Alzheimer's disease, Type II diabetes, atherosclerosis, and Parkinson's disease[49]. The relationship between inflamm-aging and frailty appears strong. However, studies

have demonstrated conflicting results regarding the association of increased circulating pro-inflammatory cytokines and frailty. Longitudinal studies have demonstrated that circulating levels of CRP increase with age and higher levels were associated with adverse aging outcomes[50]. Multiple studies have similarly reported that inflammation is a good predictor of frailty but also concluded that inflammation was still increased in those who did not have a diagnosis of frailty and were in otherwise good health[51,52]. A meta-analysis was completed to better examine the association of frailty and systemic circulating pro-inflammatory cytokines. Analyzing 32 cross-sectional studies that included over 23,000 older participants, frailty was associated with significantly higher circulating levels of IL-6 and CRP compared to robust (non-frail) older adults[49]. However, they found that when they analyzed the only three longitudinal studies on the topic, levels of IL-6 and CRP were not associated with development of frailty.

Inflamm-aging and Periodontal Disease

The pathogenic processes responsible for the age-related increase in periodontal disease is not fully understood. Periodontal disease arises from a dysregulated or excessive host inflammatory response to the subgingival microbial pathogens. Therefore, it is reasonable to suggest the dysregulated inflammatory response that is characteristic of inflamm-aging may contribute to the pathogenesis of periodontal disease.

Evidence is starting to demonstrate the effect of inflamm-aging within the periodontium. Examining old and young mice, older mice demonstrate increased alveolar bone loss, and the increased bone loss was associated with higher levels of pro-inflammatory cytokine expression within the gingiva compared to young mice[53]. The increased cytokine expression included IL-1β and TNFα which are known to promote osteoclastic activity and bone loss in periodontal disease[53]. In humans, a differential inflammatory response to oral microbiota was demonstrated in an experimental gingivitis study comparing old and young subjects. All subjects were initially treated to achieve similar levels of oral health before abstaining from all oral hygiene practices for a given period of time. At the end of the study period old and young subjects had similar levels of biofilm accumulation; however, the older patients demonstrated more severe gingivitis, suggesting a more pathologic inflammatory response in the older patients[54].

The effect of inflamm-aging can be characterized locally within various tissues, which can provide insight into how the inflammatory dysregulation contributes to age-related disease. As bone loss is the clinical hallmark of periodontal disease, it would be of interest to better understand how inflamm-aging may directly affect bone. Osteoarthritis, osteoporosis, periodontal disease, and decreased regenerative capacity after injury are some of the age-related diseases and conditions that affect bone health. In osteoarthritis, the age-related increase in pro-inflammatory mediators are suspected to contribute to an increase in damage-associated molecular patterns within the synovial fluid that further drive the innate immune response[55]. The prolonged activation of the innate immune response leads to the production of metalloproteinases leading to the local destruction of tissue and the progression of osteoarthritis[55]. Osteoporosis demonstrates a multifactorial pathogenesis. However, osteoporosis is associated with systemic inflammation in postmenopausal women

as well as being associated with other systemic inflammatory conditions[56]. In osteoporosis, inflamm-aging is suspected to disrupt the homeostatic bone resorption and deposition processes resulting in a shift towards the promotion of bone resorption[57]. Fracture healing capacity is decreased with increasing age[58]. Studies have suggested the decreased healing capacity to be a result of declining skeletal stem cell function and quantity[59], while others suggest the age-related inflammatory dysregulation perturbs the proceeding anabolic and remodeling processes of fracture healing[60]. One study demonstrated how the age-related inflammatory dysregulation may be directly related to perturbed skeletal stem cell function. In a mouse model, the decreased skeletal stem cell function and quantity was attributed to the local and systemic pro-inflammatory environment, and inhibition of NF-κB activation in old mice resulted in decreased inflammation and a restoration of skeletal stem cell function and quantity[61].

Cellular and molecular changes of the aging immune response

While inflamm-aging appears to be an important driver of both frailty and periodontal disease, our understanding of what drives inflamm-aging is still limited. Investigating age-related changes in immune cells responsible for the regulation of inflammation may lead to a better understanding of the biology of aging and could lead to therapeutic targets to mitigate the effects of inflamm-aging in frailty and periodontal disease.

The following discusses the known age-related changes to the cells of the innate and adaptive immune system and other cellular and molecular changes that may contribute to the pathogenesis of frailty and periodontal disease. The following also highlights therapeutic strategies that have successfully targeted these age-related changes in human and animal studies (Table 1).

Neutrophil

Neutrophils function as the first line of defense for the innate immune system and mediate the initial host response to invading microorganisms[62]. In periodontal disease, neutrophils migrate to periodontal tissues and the gingival crevice in response to the chemotactic signals of the invading oral microorganisms[63]. Neutrophils clear microorganisms via phagocytosis; however, the production of toxic reactive oxygen species by neutrophils used to kill microorganisms contributes to the host tissue damage[63]. Therefore, proper regulation of neutrophil activity is important in the maintenance of periodontal health. Less is known about the effects of aged neutrophils specifically in the context of periodontal disease; however, age-related changes to neutrophils are well characterized in studies examining circulating neutrophils or their bone marrow progenitors.

The total number of neutrophils in the circulation or the neutrophil progenitor cells within the bone marrow are unchanged as a function of age[64]. However, it is not clear if age affects the neutrophil chemotaxis or the migratory response. *In vitro* studies have demonstrated the chemotactic response and the ability of neutrophils to effectively migrate to the site of infection were largely unchanged as a function of age[65,66] or slightly decreased in old age compared to young control samples[67,68]. In neutrophils from healthy older human subjects, the chemotactic response to granulocyte-colony stimulating factor (G-CSF) and

N-formyl-Met-Leu-Phe (FMLP) peptide was reduced, but the response to granulocyte macrophage-colony stimulating factor (GM-CSF) and IL-3 was largely unchanged as a function of age[64,69]. Similarly, molecules involved in the extravasation of neutrophils out of the vessel and into the tissue, such as CD15, CD11a and CD11b have been reported to be unaffected by age or slightly increased[65,70,71].

While it appears that age has less of an effect on the number of circulating neutrophils or the ability of the neutrophils to migrate to the site of infection, the antimicrobial activity of neutrophils appears to be affected by age-related changes. Bacterial phagocytosis by neutrophils has been consistently demonstrated to be decreased in samples from healthy old subjects compared to young[72,73]. Such decreases in phagocytosis have been implicated in the increased susceptibility to bacterial infections in elderly populations. Some studies have suggested that the decreased phagocytosis is a result of decreased recognition of antibodies or complement by neutrophils or from an impairment of FC-mediated phagocytosis[65,70]. Additionally, the expression of CD16 on neutrophils allows for the recognition of bacteria and induce phagocytosis, and reduced expression of CD16 in response to bacterial stimuli was demonstrated in neutrophils from elderly subjects compared to young[74]. Once phagocytized, it appears age-related changes may also result in a decreased microbial killing ability. Neutrophil microbicidal activity via production of reactive oxygen species and cytotoxic proteases has been reported to be reduced in old neutrophils compared to young[68,70,75]. However, the age-related decrease in superoxide production may be stimulus specific, as one study demonstrated decreased superoxide production in response to *Staphylococcus aureus* but normal production in response to *Escherichia coli* by old neutrophils compared to young[72].

The antimicrobial activities of aged neutrophils may be further compromised by the demonstrated age-related decrease in formation of neutrophil extracellular traps (NETs). The formation of NETs is a form of cell death in neutrophils, known as NETosis, where the nuclear and plasma membrane disintegrate and a decondensed DNA structure is released extracellularly[76]. The NET is able to physically entrap microorganisms in the extracellular space and contains antimicrobial agents, including neutrophil elastase, cathepsin G, and myeloperoxidase, to kill the microorganisms as well as eliminate their virulence factors[77]. As NET formation appears to be an important antimicrobial property of neutrophils, age-related changes affecting NET formation may results in an increase susceptibility to infection. *In vitro* studies have demonstrated weaker NET formation by neutrophils from old subjects compared to young[78–80]. In an aging mouse study, the decreased NET formation in old mice was associated with a higher dissemination of Staphylococcus aureus and a more severe infection[80]. The mechanistic defect in age-related decreased NET formation is unclear. One study has suggested that NET formation can be stimulated through activation of Toll-like receptor 2 (TLR2) and that aged neutrophils were less responsive to TLR2 ligands, resulting in a preference for apoptosis over NETosis[79].

The decreased phagocytic and microbicidal activity of aged neutrophils may be further compounded by their decreased lifespan at the site of infection. Neutrophils have a typical short life-span once recruited to the site of infection but the lifespan can be extended via survival signals that continue to propagate the inflammatory response such as GM-CSF,

GCSF, and LPS[81]. However, neutrophils from elderly subjects demonstrated decreased response to such survival signals and thus higher rates of early apoptosis[82].

In summary, age-related changes to neutrophils may contribute to the pathogenesis of periodontal disease in multiple ways. The antimicrobial properties of the neutrophil are diminished with increasing age. Decreased phagocytosis and decreased NET formation may result in increased susceptibility to the pathogenic microbiota present within the periodontium. Inadequate clearance and the continued presence of the pathogenic microbiota would result in the prolonged propagation of the inflammatory response within the periodontium. In addition, the increased apoptosis of aged neutrophils may further limit the effectiveness of microbial clearance from the periodontium. The resolution of inflammation requires adequate clearance of apoptotic neutrophils from the tissue by other phagocytes as their sustained presence will continue to propagate the inflammatory response. Thus, higher levels of apoptotic neutrophils within the periodontium may result in further inflammatory propagation and a resulting increase in collateral damage of the host tissue.

Macrophage

The macrophage is a key modulator of the innate immune system during infection, disease, or injury. Generally, macrophage phenotypes have been defined along a spectrum of proinflammatory (M1) and anti-inflammatory (M2) phenotypes that participate in distinct processes of inflammatory propagation and resolution[83,84]. Our understanding of the phenotypic diversity of macrophages is continually growing and new distinct phenotypes are regularly being characterized. Therefore, here we refer to M1 macrophages as generally a pro-inflammatory phenotype and M2 macrophage as generally an anti-inflammatory phenotype without reference to the multitude of diverse phenotypes previously identified.

During periodontal disease, M1 macrophages are presents early during the inflammatory response within the periodontium in response to the presence of subgingival bacterial pathogens. M1 macrophages mediate the host defense against bacteria and propagate the inflammatory response through production of pro-inflammatory cytokines (iNOS, TNFα, IL-1β, IL-6)[84,85]. After adequate removal of the bacterial pathogens and their associated pro-inflammatory signaling, a timely phenotypic switch away from M1 is required to prevent collateral tissue damage. The M2 macrophage phenotype acts to resolve inflammation through the production of anti-inflammatory cytokines (IL-10, Arg) and to promote healing of damaged tissues through the production of growth factors (TGFβ, VEGF)[86]. The presence of M1 and M2 type macrophages was shown to be related to increased and decreased severity of periodontal disease respectively[87,88]. A higher prevalence of M1 macrophages was associated with increased inflammatory cytokines within the gingiva of humans with periodontal disease compared to healthy controls[89]. These findings suggest that the presence of periodontal disease or the severity of disease is a function of the macrophage phenotype, and dysfunctional macrophage activity may contribute to the pathogenesis of periodontal disease.

Age-related changes to the macrophage may perturb the phenotypic presentation and contribute to inflammatory pathologies[90]. An increase in M1-related gene expression was demonstrated in the gingiva of healthy aged non-human primate compared to young control

groups[91]. Proinflammatory cytokines secreted by M1 macrophages, such as IL-1β and TNF-α, were also found to be elevated in the gingiva of old mice compared to young[53]. However, studies evaluating cell autonomous age-related changes to macrophage function and activity have reported conflicting results. Production of pro-inflammatory cytokines by old macrophages compared to young has been reported to be increased[92], decreased[93], or not affected by age[94]. Similarly, phagocytic activity in old macrophages compared to young has been reported to be increased[95], decreased[96], or not affected by age[97]. The heterogenous literature on macrophage aging may be a function of a lack of replicability between *in vitro* and *in vivo* studies. It is important to consider that the *in vivo* microenvironment is also affected by age and certainly different than the *in vitro* cell culture environment utilized in many experiments[98]. Macrophages are of hematopoietic origin with progenitor cells that reside in the bone marrow. Age-related changes to the bone marrow microenvironment have been well characterized and include increased marrow cavity, increased vascular volume, and a shift in endothelial and mesenchymal cell population that support the hematopoietic stem cell niche[99,100]. Therefore, the aged microenvironment in which macrophages and their progenitor cells occupy may have a strong effect on cell behavior. Similarly, the *in vitro* cell culture environment may also have a strong effect on cell behavior and obscure the intrinsic age-related differences.

Intrinsic age-related changes to the macrophage are becoming more evident using unbiased, next generation sequencing methodologies that don't require exposure of isolated cells to cell culture. Macrophages isolated from a fracture callus in old mice were transcriptionally distinct from the macrophages isolated from a callus of a young mouse as measured by RNAseq[60]. The significant differentially expressed genes in old mice demonstrated increased pro-inflammatory cytokine expression and M1 markers compared to young, and such differences were associated with poor fracture healing outcomes in old mice compared to young[60]. Similar findings were demonstrated in alveolar lung macrophages from young and old mice using single cell RNAseq. Macrophages from the old mice demonstrated increased population heterogeneity with increased pro-inflammatory gene expression[101]. Other single cell RNAseq studies of the brain have demonstrated that age-related transcriptional changes are not a universal program across all cell types, and that specific cell types, including macrophages demonstrate unique aging profiles distinct from other cells within the same tissue[102].

These age-related changes appear deleterious to the normal macrophage function as evidenced by studies that have directed treatment at aged macrophages. Improved fracture healing was demonstrated in old mice by blocking the macrophage infiltration into the fracture callus[60]. In the same study, there was no effect on fracture healing in young mice with macrophage blockade. In other studies, delayed fracture or cutaneous healing was demonstrated with increasing age, but the age-related healing delay could be rescued with the transplantation of young macrophages or young macrophage progenitors into the old mice[103,104].

In summary, a full understanding of the age-related changes to macrophages and its effect on periodontal disease is lacking. However, our current understanding demonstrates age-related changes affecting cytokine secretion, phagocytosis and wound healing, all of which are

essential macrophage processes that could contribute to the pathogenesis of periodontal disease. Treatments directed at aged macrophages have demonstrated some initial support in wound healing and may justify adapting a similar strategy for the treatment of periodontal disease in elderly patients.

T Cells and the adaptive immune response

Activation of the adaptive immune response is generally characterized by the activity of T cells and B cells and their associated production of antibodies and cellular immunity[105]. Naïve lymphocytes can recognize antigens and mount a response during infection and memory lymphocytes are primed to allow for a more rapid response to previously experienced antigens. In the periodontium, low levels of T and B cells are evident during health demonstrating a diverse immunoglobulin repertoire within the crevicular fluid in response to the oral microbiota[106]. During periodontal disease, a stronger adaptive immune response is mounted and the immunoglobulin repertoire shifts towards a more homogenous response towards the pathogenic microorganisms[106].

Age-related changes to the adaptive immune response have been generally described as immune senescence and has been attributed to the increased susceptibility to infectious disease amongst the elderly. Age-related changes to T and B cells affect their activation and proliferation centrally as well as their recruitment and function locally at the site of inflammation[107]. With increased age there is an involution of the thymus, the site of naïve T cell production, resulting in an overall decline in naïve T cell numbers[108]. Similarly, decreased generation of progenitor B cells from the hematopoietic environment of the bone marrow is observed with increased age[107]. Overall, these age-related declines in naïve lymphocytes result in a decline of antigen-specific immunity and a resulting increased susceptibility to infection in the elderly[105]. The immunodeficient status associated with increased age could be expected to result in a susceptibility to subgingival microbial infection during periodontal disease.

As T cells interact with antigen presenting cells, they further differentiate into sub-populations with distinct functions. CD4+ T helper cells are considered a memory T cell and are generally characterized into two subsets based on functional characteristics. Th1 subsets produce pro-inflammatory cytokines that are cytotoxic and propagate the inflammatory response, while the Th2 subset produce largely anti-inflammatory cytokines that are involved in B cell activation and humoral immune response[109,110]. With increased age, CD4+ T helper cells appear less responsive to receptor stimulation with a resulting decrease in Th2 cell differentiation and a preference towards Th1 differentiation with the associated pro-inflammatory cytokine profile[111,112]. An increased ratio of Th1 over Th2 cells is present in the periodontium during chronic periodontitis and increased Th1 cells are associated with increased bone resorption[113].

A further subset of Th1 cells that has been implicated in periodontal disease is Th17 cells, named after their characteristic production of the pro-inflammatory cytokine IL-17[114]. Th17 cell expansion and IL-17 expression are pathogenic mediators in periodontal disease[115,116]. There are multiple cellular sources of IL-17 within the gingiva; however, during periodontal disease Th17 cells represent 80% of the IL-17+ cells[115]. Inhibition

of Th17 cell differentiation was shown to decrease periodontal disease severity[115]. Interestingly, Th17 cells demonstrate increased homeostatic expansion within the gingiva of old mice and humans compared to young controls[117]. Similar increased Th17 expansion was demonstrated in the circulating blood samples of healthy old human subjects compared to young controls[118]. Increased Th17 cells expansion was also noted in other age related disease, including corneal epithelial disease where treatment directed at reducing Th17 cell numbers decreased disease severity in aged mouse models[119]. However, it is unknown what drives this age-related expansion of Th17 cells. Th17 cell expansion is stimulated by IL-6 and IL-23 signaling[114]. There are multiple cellular sources of IL-6 and IL-23 and macrophages demonstrating the M1-like phenotype secrete both cytokines. The previous section described a shift towards an M1 macrophage phenotype with increasing age. Such age-related changes in the macrophage may drive downstream cellular effectors of the immune response, such as Th17 cells, and further contribute to age-associated inflammatory dysregulation.

In summary, aging affects the adaptive immune response, in part, by reducing the T and B cell naïve repertoire during microbial infection. In addition, aging is characterized by a shift in the T cell phenotypes towards the pro-inflammatory TH1 and TH17 subpopulations, which demonstrate a cytokine profile that promotes bone resorption and contribute to the pathogenesis of periodontal disease.

Cellular Senescence

Cellular senescence defines an exit from the normal cell cycle where the cell is no longer able to replicate but remains resistant to apoptosis[120]. Cellular senescence can be initiated when a cell reaches the end of its replicative capacity or upon exposure to various stressors[120,121]. The process of cellular senescence appears to be a normal protective measure to prevent malignancies by stopping the proliferation of damaged or premalignant cells[122]. However, senescent cells accumulate within tissue with increasing age and such accumulation is suspected to drive age-related pathologies[123,124]. It is not clear if the age-related increased accumulation of senescent cells is a result of more cells becoming senescent with increasing age or dysfunctional clearance of senescent cells with increasing age, or both[125].

The detrimental impact of senescent cells within tissue appears to be a result of its characteristic pro-inflammatory phenotype known as the senescent-associated secretory phenotype (SASP)[126]. The SASP is characterized by the secretion of numerous pro-inflammatory cytokines, chemokines, and other proteins and molecules. The role of the SASP appears to be to maintain the cell cycle arrest in an autocrine manner as well as to induce senescence in neighboring cells in a further effort to prevent malignancy[127]. However, the accumulation and continued production of SASP compounds is detrimental to the surrounding tissues and cells resulting in impaired tissue function and the development of a chronic inflammatory environment[128]. For this reason, cellular senescence is suspected to be a primary diver of inflamm-aging[129]. As inflamm-aging is associated with age-related diseases, senescent cell accumulation has also been associated with a wide variety of chronic inflammatory conditions that increase in prevalence with age. In human and animal studies,

accumulation of senescent cells has been associated with macular degeneration[130], chronic obstruction pulmonary disease[131], dementia[132], Parkinson disease[133], osteoarthritis[134], and atherosclerosis[135].

Less is understood about the contribution of cellular senescence to the pathogenesis of periodontal disease. The SASP is a source of pro-inflammatory cytokines within the tissue and includes pro-inflammatory cytokines (IL-6, IL-1β, TNFα) that are also implicated in periodontal disease[126,136]. Senescent cells have also been identified within the periodontium. Cellular senescent markers were demonstrated in osteocytes isolated from mouse alveolar bone[137]. In addition, LPS was shown to to induce senescence of alveolar osteocytes *in vitro*, suggesting a role of bacteria in contributing to senescent cell accumulation within the periodontium[137]. Periodontal derived ligament stem cells (PDLSCs) isolated from older adults were shown to have higher levels of senescent cell markers compared to cells isolated from younger subjects[138]. The older PDLSCs were also shown to be less osteoinductive[138]. Similarly, another study demonstrated that induction of senescence in human periodontal ligament fibroblasts results in decreased osteoblastic differentiation potential *in vitro*[139]. Bone outside of the oral cavity has also been shown to be affected by cellular senescence. Osteoprogenitor cells, osteoblasts, and osteocytes from the bone marrow of old mice had higher levels of senescent markers compared to cells in young mice[140]. These findings suggest that senescent cell could accumulate within the periodontium with increasing age and contribute to the pathogenesis of periodontal disease by serving as a source of pro-inflammatory cytokines and limiting the regenerative capacity of the soft and hard tissues of the periodontium.

Senescent cell accumulation within young subjects has been associated with chronic disease. Chronic inflammatory conditions such as obesity[141], atherosclerosis[142], and chronic kidney disease[143] have all demonstrated increased senescent cell accumulation within the affected tissues and organs regardless of age. It is not known if senescent cells accumulate within the periodontium during periodontal disease. If so, periodontal disease at any age could result in the accumulation of senescent cells within the periodontium, which would further increase the susceptibility to periodontal disease in the future. In this manner, treatment of periodontal disease may be best directed at removing the bacterial etiologic agents as well as removing the senescent cells that have accumulated within the tissue.

The role of senescent cells in aging has further been supported by studies demonstrating that the clearance of senescent cells can ameliorate age-related pathologies. The initial studies utilized genetically engineered mouse models that allowed for inducible elimination of senescent cells and demonstrated that removal of senescent cells throughout the lifetime of the animal resulted in the delay of age-related disease and extension of lifespan[144]. More recent efforts have been focused on the development of senolytic drugs that attempt to induce apoptosis in senescent cells as a means of limiting their accumulation within tissue. Many studies have further demonstrated the benefit of the removal of senescent cells in multiple disease and tissue-specific contexts. In animal models, the removal of senescent cells was show to prevent age-related bone loss[145], prevent hepatic steatosis[146], and improve cognitive declines in an Alzheimer's model[147]. In human trials, Dasatinib and Quercetin have been used in combination as a senolytic treatment. In the first human

trial, patients with idiopathic pulmonary fibrosis, a condition characterized by high levels of senescence cells within lung tissue, received treatment with the senolytic combination and demonstrated improvement in their physical function[148]. In another human trial, a cohort of diabetic kidney disease patients also received the Dasatinib and Quercetin senolytic treatment and demonstrated a decreased quantity of senescent cells in multiple different tissues[149]. Other senolytic agents have been characterized and tested and there is much interest in understanding the potential benefits of senolytic therapy to treat the myriad of age-related disease. Questions remain about proper administration of senolytic agents as to whether they should be administered throughout the lifetime to prevent senescent cell accumulation, or if administration is best focused as a treatment of chronic inflammatory conditions.

In summary, senescent cells have been shown to accumulate within the periodontium. The associated SASP produces cytokines known to contribute to the pathogenesis of periodontal disease, and senolytic drugs have demonstrated success as a treatment for age-related inflammatory pathologies. Therefore, treatment directed at the removal of senescent cells within the periodontium may be a justified therapeutic approach to managing periodontal disease.

mTOR and aging

To better understand aging, much effort has been placed in trying to identify a more singular process or mediator of aging that similarly changes throughout the organism. For example, epigenetic changes, cellular senescence, telomere shortening, and mitochondrial dysfunction have all been show to increase with age across multiple cell types and organisms and contribute to age-related pathologies[150]. Additionally, mammalian target of rapamycin (mTOR) is a protein kinase that has received much attention for its potential role in modulating aging. mTOR consists of an extensive and wide-ranging signaling network involved in protein production, autophagy, and metabolism across all eukaryotic cells[151].

It appears the activation of the mTOR pathway stimulates multiple cellular and molecular activities that contribute to aging. For one, activation of mTOR promotes translation and protein production, and an accumulation of misfolded and altered proteins are characteristic of aging[152]. Decreased mTOR activity is suspected to decrease the cellular burden of the altered proteins and their harmful metabolic by-products and result in improved cellular function[152]. Additionally, mTOR activity promotes the production of transcription factors that regulate pro-inflammatory cytokine synthesis[152]. Increased pro-inflammatory cytokine expression is a hallmark of aging as described in the previous sections. An additional hallmark of aging is the accumulation of senescent cells within tissue. Senescent cells demonstrate hyperactivity of the mTOR pathway, which likely contributes to the pathologic increase of pro-inflammatory cytokine production[153]. Finally, autophagy is inversely regulated by mTOR activity, where increased mTOR activity resulted in decreased autophagy. Autophagy is an essential cellular process to recycle and remove degenerated or damaged organelles, and the accumulation of these organelles within the cell can result in mitochondrial damage and cellular dysfunction. Increased mTOR activity results

in decreased autophagy and likely contributes the cellular dysfunction associated with aging[150].

The strongest implication of mTOR activity in the aging process is the broad base of evidence that demonstrates that the inhibition of mTOR activity can increase both lifespan and health span[154]. Genetic depletion of mTOR was shown to extend lifespan in flies and mammals[155,156]. Additionally, treatment with rapamycin, a pharmacologic that inhibits mTOR activity, demonstrates similar improvements in lifespan and health span[157,158]. Interestingly, there are a few studies that have examined the effect of rapamycin treatment on periodontal disease in aged animal models. It had previously been shown that old mice demonstrate increased alveolar bone loss and an associated increased local pro-inflammatory cytokine expression compared to young mice[53]. In one study, mice were treated with rapamycin for their entire adult life and periodontal disease was then evaluated when the mice reached old age (35 months). Mice treated with rapamycin demonstrated significantly increased alveolar bone compared to the age-matched controls[159]. In another study, old mice (20 month) were treated with a course of rapamycin for only 8 weeks. The short course of treatment resulted in significantly increased alveolar bone compared to age-matched controls, which was also associated with a local decrease of NF-κB pro-inflammatory signaling within the periodontium[160]. Interestingly, the same study showed that the short course of rapamycin treatment resulted in new bone formation, as the treated groups had significantly more alveolar bone compared to pre-treatment levels for the same animal (as measured by *in vivo* micro-CT)[160]. In summary, these results suggest that targeting mTOR may be a future treatment strategy for periodontal disease in older patient populations. In addition, the findings further implicate periodontal disease as an age-related disease by showing that targeting a dysregulated pathway central to the aging process (mTOR) improves periodontal health.

Conclusions

The association of aging, frailty, and periodontal disease is supported by the epidemiological and basic cellular and molecular research presented here (Figure 1). With a rapidly aging population globally, there is a pressing need to address the challenges of periodontal disease and frailty in older populations. Evidence suggests a bi-directional relationship between frailty and periodontal disease, which remains to be fully understood. Nonetheless, there is a need for improved prevention and management of periodontal disease, particularly in frail older people. Our current understanding provides strong support that the pathophysiological changes that occur with aging contribute to periodontal disease and could explain, in part, the increased prevalence of periodontal disease in frail older populations. An appreciation for the age-related changes that contribute to periodontal disease will lead to expanded translational work developing novel approaches to diagnosis and treatment of periodontal disease. Multiple cellular and molecular targets have been implicated as pathophysiological changes that occur with aging and periodontal disease (Table 1). Animal models have demonstrated proof of principle that treatment directed at the altered physiology of aging can be therapeutically beneficial, and recent clinical trials have shown this approach to be successful in humans. Directing treatment at the specific physiological changes that occur with age could be an important step towards delivering personalized healthcare.

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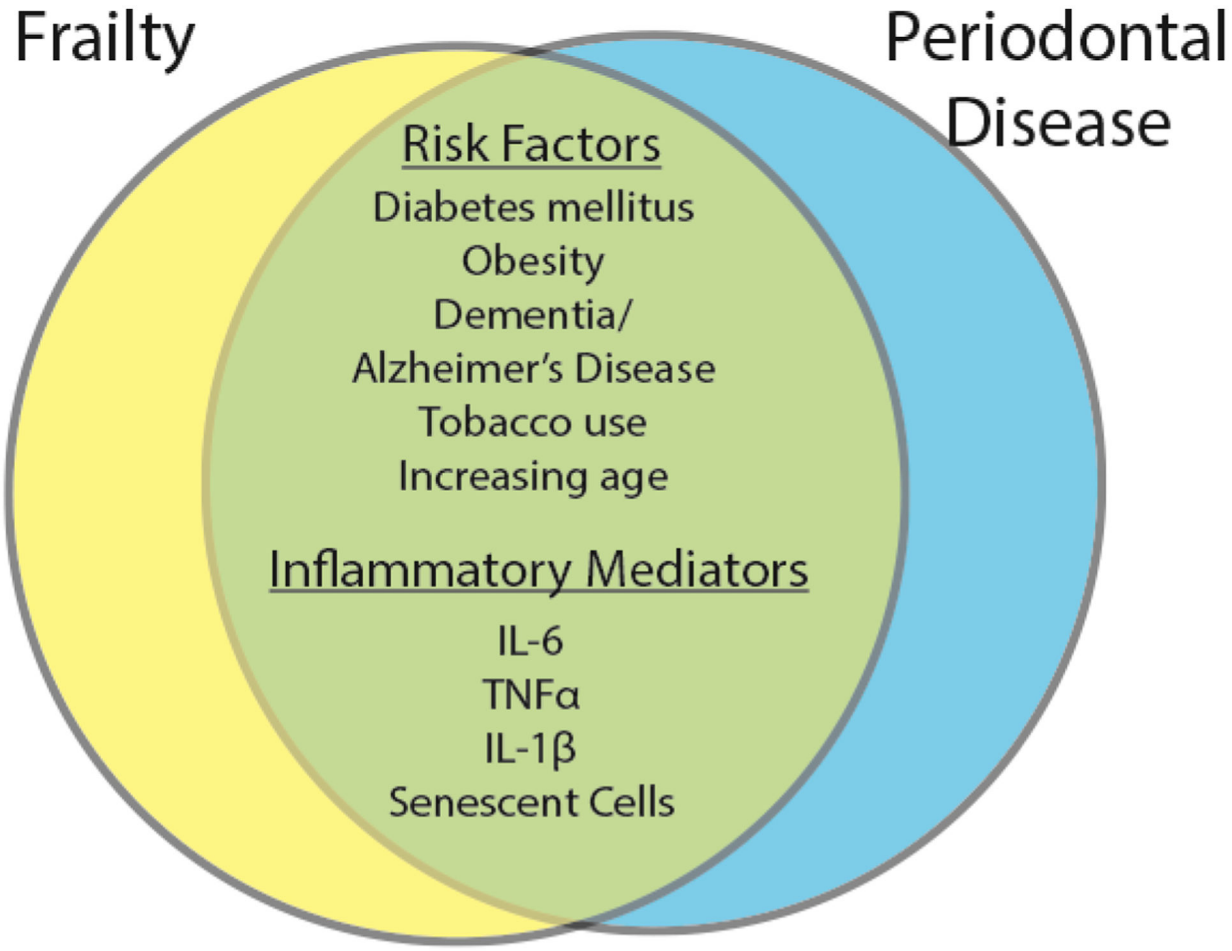

Figure 1:
Shared features of periodontal disease and frailty. Many of the risk factors and comorbid diseases are similarly associated with frailty and periodontal disease. Similarly, systemic and local inflammatory mediators are shared across the two conditions[48,49,53,136,137]

Table 1:

Therapeutic targeting of age-related changes: Studies reporting a therapeutic benefit by targeting cellular and physiological age-related changes using animal models and human trials.

Target	Disease/Condition	Method	Outcome
Aged infiltrating macrophages (Mouse model)	Fracture healing[60]	Pharmacologic inhibition of M-CSF	Improved fracture healing in old animals resulting from the inhibition of macrophage infiltration
Aged Macrophages (Mouse model)	Cutaneous Healing[103]	Transplant of young macrophages into old mice	Acceleration in healing of experimental cutaneous wounds with application of young macrophages in old mice.
Th17 Cells (Mouse model)	Periodontal Disease[115]	Pharmacologic inhibition of Th17 cell differentiation	Reduced periodontal disease severity in mice resulting from the reduction of Th17 cell differentiation.
Th17 Cells (Mouse model)	Corneal epithelial disease[119]	Antibody treatment	Decreased Th17 cell quantity with antibody treatment resulted in decreased disease severity.
Senescent Cells (Mouse models)	Osteoporosis[145] Liver disease[146] Alzheimer's disease[147]	Senolytics	Reduction of senescent cells within tissue resulted in decreased disease severity
Senescent Cells (Human trials)	Idiopathic pulmonary fibrosis[148] Diabetic kidney disease[149]	Senolytics (Dasatinib + Quercetin)	Decreased disease severity[148], and decreased quantity of senescent cells in adipose tissue[149]
mTOR (Mouse models)	Periodontal Disease[159,160]	Pharmacologic inhibition of mTOR (Rapamycin)	Decreased disease severity with lifetime of rapamycin administration[159]. Increased alveolar bone formation with short course of rapamycin in old mice[160].