Age-associated inflammation alters the aging trajectory

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Jonathan Swift said, 'Every man desires to live long, but no man wishes to be old'. Most of us have ambivalent feelings about aging. We may want a long life, but those extra years hold less appeal if we are too ill to enjoy them. At one extreme of the aging trajectory are those who become frail, immobile and dependent in their 5th or 6th decade. At the other extreme are those who live to 100 or beyond remaining cognitively intact, active and engaged in their communities. We wonder what causes underlie this diversity in the aging process? Why do some of us age well and others poorly? The immune system plays a central role in health in our later years.

Aging is characterized by a state of chronic, low-grade systemic inflammation called age-associated inflammation, or 'inflammaging'. Levels of messenger molecules, called cytokines, increase in the tissues and circulation as we age. This increase in cytokines is observed in both healthy and unhealthy aging, but higher than average levels of these cytokines are associated with poorer health outcomes such as frailty, chronic disease and an increased rate of premature death.

What precisely is inflammation? When you get an injury, such as a cut on your hand, the wound becomes swollen, hot, red and painful. The broken skin and neighbouring tissue release what are called damage-associated molecular patterns, or DAMPs, which act like alarms for the immune system. The immune system, specifically cells of the innate immune system such as macrophages, respond to this tissue damage by releasing pro-inflammatory cytokines. These messenger molecules recruit other immune cells to the site of inflammation to help repair the damage and control any possible infection. This process continues until the wound is healed or the infection is cleared, and inflammation resolves. Both initiation and resolution of inflammation are tightly controlled and genetically regulated processes. Acute inflammation is an evolutionarily conserved process and is essential to our survival, but non-resolving chronic inflammation causes or contributes to tissue damage and chronic health conditions, such as cardiovascular disease, and autoimmune conditions, such as rheumatoid arthritis and type II diabetes.

Aging is a complex interaction of environmental and genetic factors, all of which contribute to age-associated inflammation and the mechanisms are only just beginning to be elucidated. Recent advances in the understanding of cellular senescence, immunosenescence and microbial dysbiosis have furthered our understanding of the biological mechanisms contributing to age-associated inflammation.

Cellular senescence

Senescence is a cellular response to damage or stress in which the cell cycle irreversibly arrests, halting growth and division. This can occur when a cell has acquired detrimental mutations in its DNA, or when the cell's telomeres (sequences at the end of chromosomes that prevent deterioration) become too short. Telomere shortening, as well as harmful mutations increase with age.

Senescent cells are not dead. They are still metabolically active and have a distinct phenotype called the senescence-associated secretory phenotype, or SASP. One characteristic of the SASP is the release of pro-inflammatory cytokines such interleukin (IL)-6. The accumulation of cells with this SASP is thought to fuel age-associated inflammation. Adipose tissue is especially prone to secreting inflammatory markers that result in increased systemic inflammation and activation of tissue resident innate immune cells. Fat distribution changes with age even if we maintain the same weight. Visceral fat (abdominal fat), which produces more pro-inflammatory cytokines, increases with age and this shift in fat distribution is thought to contribute to age-associated inflammation.

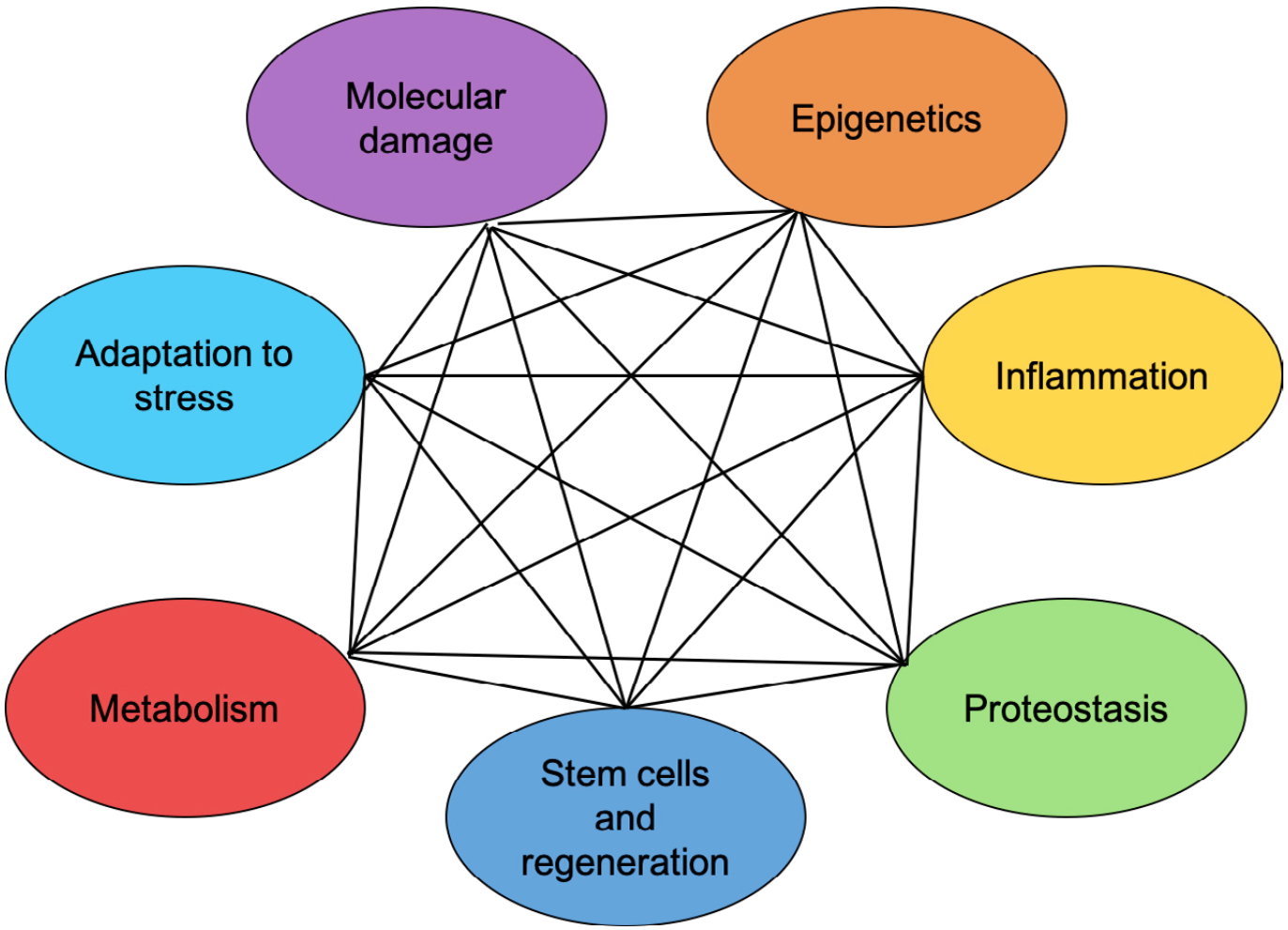

Figure 1. The seven pillars of geroscience. Age-related changes in any one physiologic system impact many others, which contribute to loss of resilience and susceptibility to age-related health conditions. This is why age-associated inflammation is a risk factor for diverse conditions that impact metabolism (e.g., type II diabetes), tissue damage (e.g., cardiovascular disease) and frailty.

Immunosenescence

As we age, adaptive immunity declines. We have fewer naive T cells to combat new infections, and a large portion of our T cells repertoire is made up of memory T cells that can only respond to one type of antigen. This overall decline in the ability to respond to novel antigens or infections with age is called immunosenescence. Early epidemiological studies have implicated cytomegalovirus (CMV) infection in accelerating immunosenescence and increasing mortality rates in old age. CMV is a widespread, often asymptomatic virus, which infects over half of adults by the age of 40. Once established, it is never fully cleared by the immune system. CMV periodically 'reactivates' and the resident memory T cell population expands to contain the virus. However, every time the virus reactivates, CMV specific memory T cells increase at the expense of other naive or memory T cells. Over time, this results in skewing the memory T cell population to favour CMV-positive T cells and the individual is less equipped to mount an adaptive immune response to a variety of novel or harmful infections. Thus, elderly individuals who are CMV positive have an adaptive immune system with reduced capabilities to respond to novel antigens. Furthermore, each reactivation of CMV and expansion of memory T cells is accompanied by the release of pro-inflammatory cytokines by these T cells, increasing the inflammatory burden. Although it is unclear whether this connection between CMV infection and premature immunosenescence applies to populations other than those included in the early epidemiologic study, there has been significant research on the link between CMV, immunosenescence and age-associated inflammation.

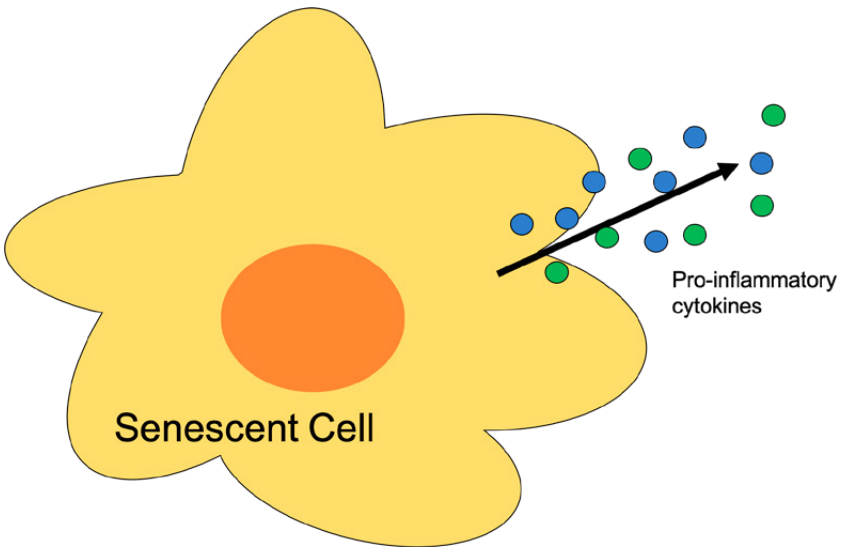

Figure 2. Senescent cells have a specific secretory phenotype that includes the release of pro-inflammatory cytokines. The accumulation of senescent cells with age contributes to inflammaging.

Microbial dysbiosis and intestinal permeability

The billions of bacteria that have coevolved on or within us, termed the microbiome, are crucial to the development of a healthy immune system. Our research group has shown that elderly mice (18 to 24 months old, equivalent to 70+ year old humans) that are germ-free (i.e., mice with no microbes living on or within them) are protected from age-associated inflammation. These data demonstrate that a microbiome can cause age-associated inflammation. Microbial dysbiosis (imbalances in the microbiome) can predispose individuals of any age to many health conditions. Microbial dysbiosis occurs with age and our research group has shown that age-associated microbial dysbiosis increases intestinal permeability. This increased intestinal permeability allows bacterial products such as muramyl dipeptide (MDP), a component of the bacterial cell wall, to enter the circulation where it is easily recognized by the immune system, resulting in an inflammatory response. Thus, intestinal permeability as a result of age-associated microbial dysbiosis contributes to systemic age-associated inflammation, or inflammaging.

Interestingly, this association between microbial dysbiosis and inflammation appears to be a two-way street. Mice that are protected from age-associated inflammation because they are genetically deficient in the pro-inflammatory cytokine tumor necrosis factor (TNF) do not undergo microbial dysbiosis or have increased intestinal permeability with age. These data indicate that age-associated inflammation and age-associated microbial dysbiosis may contribute to a vicious cycle that increases inflammaging.

The term 'inflammaging' was coined less than 20 years ago. To date, cellular senescence, chronic viral infections and age-related microbial dysbiosis have been identified as causes of age-associated inflammation; however, there are likely other factors that are yet to be discovered. Although we may not understand the definitive causes of age-associated inflammation, we know that lower levels of inflammation contribute to healthy aging. Fortunately, there is ample data telling us what we can do to reduce our age-associated inflammation; eat a healthy diet, exercise and don't smoke. Although it can be a challenge, to adhere to these guidelines, these straightforward lifestyle choices are our best bets for living long and living well. ■

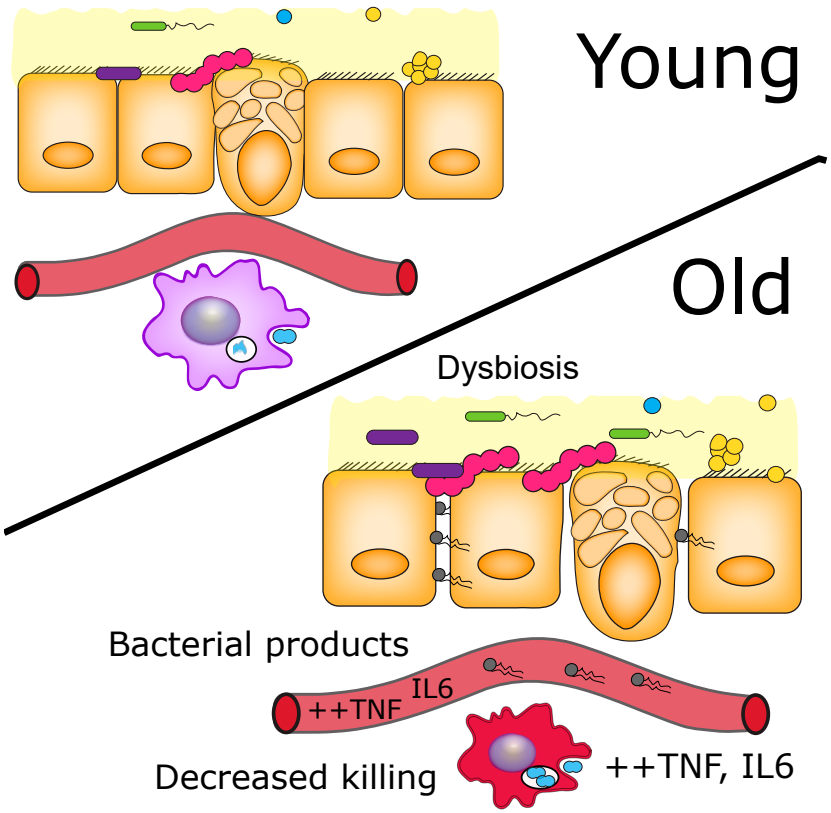

Figure 3. Age-associated microbial dysbiosis contributes to age-associated inflammation. In youth, the gut barrier is intact and does not allow bacterial products to cross. With age, the microbial communities change (dysbiosis) and become permeable to bacterial products, which enter the bloodstream. These bacterial products are recognized by the immune system and initiate an inflammatory response. Over time, exposure to inflammatory mediators impairs immune cell function and leaves us susceptible to infections. Figure from: Thevaranjan, N., Puchta, A., Schulz, C. et al. (2017) Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell, Host and Microbe 21(4), 455–466. e4.

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Further reading

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