

Advances in Geroscience: Impact on Healthspan and Chronic Disease Perspective

Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases

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Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as “inflammaging.” Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis. Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people. The session on inflammation of the Advances in Gerosciences meeting held at the National Institutes of Health/National Institute on Aging in Bethesda on October 30 and 31, 2013 was aimed at defining these important unanswered questions about inflammaging. This article reports the main outcomes of this session.

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AGING is a ubiquitous complex phenomenon that results from environmental, stochastic, genetic, and epigenetic events in different cell types and tissues and their interactions throughout life. A pervasive feature of aging tissues and most if not all age-related diseases is chronic inflammation. “Inflammaging” describes the low-grade, chronic, systemic inflammation in aging, in the absence of overt infection (“sterile” inflammation), and is a highly significant risk factor for both morbidity and mortality in the elderly people (1). There is overwhelming epidemiological evidence that a state of mild inflammation, revealed by elevated levels of inflammatory biomarkers such as C-reactive protein and interleukin-6 (IL-6), is associated and predictive of many aging phenotypes—for example, changes in body composition, energy production and utilization, metabolic homeostasis, immune senescence, and neuronal health. The etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remains largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people.

The important unanswered questions about inflammaging that have been identified and discussed in collaboration with the five panelists (Luigi Ferrucci, James L. Kirkland, Jayakrishna Ambati, Vishwa Deep, and Russell Tracy) who participated to Session 1. INFLAMMATION can be summarized as following:

HOW DO THE SOURCES OF INFLAMMATION DURING AGING AND CHRONIC DISEASE DIFFER FROM INFLAMMATORY PROCESSES IN ACUTE INSULTS/DISEASE?

Inflammation can be beneficial as an acute, transient immune response to harmful conditions such as traumatic tissue injury or an invading pathogen. This response also facilitates the repair, turnover, and adaptation of many tissues. However, acute inflammatory responses to pathogen-associated molecular patterns may be impaired during aging, leading to increased susceptibility to infection.

Chronic inflammation has many features of acute inflammation but is usually of low grade and persistent, resulting in responses that lead to tissue degeneration. There are

several possible mechanisms of chronic inflammation: (i) persistent production of reactive molecules by infiltrating leukocytes designed to kill pathogens, eventually damages the structural and cellular elements of tissues; (ii) damaged nonimmune cells and activated immune cells lead to the production of cytokines that amplify or modulate the inflammatory response and alter the phenotypes of nearby cells, often to the detriment of normal tissue function (2). Many aged tissues are probably in a chronically inflamed state, albeit without signs of infection; (iii) the interference with “anabolic signaling”; for example, IL-6 and tumor necrosis factor- α downregulate insulin, insulin-like growth factor-1, and erythropoietin signaling and protein synthesis after a meal or bout of exercise. Inflammaging most likely derives from, but is not limited to, the sources described here. These sources are not mutually exclusive, and their relative contributions require further studies.

One source of inflammaging could be the damaged macromolecules and cells (self-debris) that accumulate with age due to increased production and/or inadequate elimination. Self-debris released as a consequence of cell/organelle injury can mimic bacterial products and function as endogenous “damage”-associated molecular patterns that activate innate immunity. Damaged cellular and organelle components, free radicals from oxidative stress, metabolites such as extracellular ATP, fatty acids, urate crystals, ceramides, cardiolipin, amyloid, succinate, peroxidized lipids, advanced glycation end-products, altered *N*-glycans (3), and HMGB1 are recognized by a network of sensors (including Nlrp3 inflammasome) as “danger” signals and initiate immune reactions that are necessary for physiological repair. However, as damage accumulates, the danger responses can become chronic and hence maladaptive (4).

A second source of inflammaging might be represented by harmful products produced by the microbial constituents of the human body, such as oral or gut microbiota, which can leak into surrounding tissues and the circulation (5). Presumably, the ability of the gut to sequester these microbes and/or their products declines with age, leading to chronic low-grade inflammation. Alternatively, the gut microbiota itself might change with age so that the microbes present in the aged, but not young, gut elicit an inflammatory response. Host–pathogen balance is important in keeping other harmful agents such as Epstein–Barr virus and cytomegalovirus (CMV) inactive. Inflammatory stimuli and cytokines and the “immune risk profile” were found to be independent risk factors for survival (6) and immune risk profile resulted associated with IL-6 (7). More recently, these data were further strengthened as levels of IL-6 and soluble tumor necrosis factor- α R1 were identified as predictors of 10-year all-causes mortality (8). Quite puzzling, in CMV-infected elders, an elevated CD4:8 ratio (>5) has been found to be associated with impaired physical function (9).

Mitochondria play a major role in inflammaging and in the activation of Nlrp3 inflammasome. The Nlrp3 inflammasome is a multiprotein complex that can activate procaspase-1 in response to cellular danger resulting in the processing and secretion of the proinflammatory cytokines IL-1 β and IL-18. Most activators of the Nlrp3 inflammasome induce the generation of mitochondrial reactive oxygen species. Mitochondria as phylogenetically bacterial symbionts of early eukaryotic cells, when damaged, release mitochondrial damage-associated molecular patterns (formyl peptides and mitochondrial DNA) with evolutionarily conserved similarities to bacterial pathogen-associated molecular patterns, which are released into the circulation and are powerful activators of innate immunity (10) and Nlrp3 inflammasome. Cardiolipin, which is found only in mitochondria and bacteria, upon mitochondrial dysfunction can act as an endogenous pathogen-associated molecular pattern capable of activating the proinflammatory pathway of Nlrp3 inflammasome (11).

Third, inflammaging might be due to cellular senescence. Senescence is a cellular response to damage and stress. The senescence response prevents cancer by suppressing the proliferation of cells with a compromised genome and contributes to optimal wound healing in normal tissues. Persistent senescent cells are also thought to drive aging and age-associated pathologies through their secretory phenotype. Mechanistically, senescent cells likely fuel age-related disease because they secrete numerous proinflammatory cytokines (termed the senescence-associated secretory phenotype or SASP) that modify the tissue microenvironment and alter the function of nearby normal or transformed cells (12,13). Senescent cells accumulate with age in many tissues and are prominent at sites of many age-related pathologies. Elimination of senescent cells in prematurely aged mice prevents several age-related pathologies (14). Senescent cells accumulate to especially high levels in adipose tissue, particularly the visceral fat of obese individuals (15). Fat is another rich source of inflammatory cytokines and major changes in fat distribution and lipid composition and function may have profound clinical consequences linked to several age-related disorders (16).

Fourth, increased inflammation may derive from increasing activation of the coagulation system with age. Coagulation may be considered part of the inflammation system with many shared components and strong interactions. The increased hypercoagulable state observed with aging may account for the higher incidence of arterial and venous thrombosis in the elderly persons. For example, increased microbial translocation can result in subsequent endotoxemia, atherosclerotic plaque erosion, or loss of structural integrity around blood vessels leading to stasis.

Fifth, age-related changes to the immune system (immunosenescence) likely contribute to inflammaging.

Adaptive immunity declines with age, whereas innate immunity undergoes more subtle changes that could result in mild hyperactivity (17–19). In addition, as adaptive immunosenescence progresses, innate immunity might increase to take on the burden. These age-related changes most likely result from both lifelong exposure to pathogens and antigens, as well as intrinsic changes in immune cells and possibly genetic predisposition. A major role is likely played by persistent (and, at present impossible to eradicate) infections such as those caused by CMV and HIV, which are associated with accelerated immunosenescence and aging.

Finally, defective or inappropriate regulation of the complement pathway can lead to local inflammatory reactions in age-related macular degeneration, the leading cause of blindness in the elderly people (20). This defect is likely to apply to many other degenerative diseases.

CAN AGE-ASSOCIATED CHRONIC INFLAMMATION BE ADAPTIVE OR BENEFICIAL, OR IS IT ALWAYS PATHOGENIC?

In living organisms, macromolecules, cells, and tissues are continuously damaged and repaired, with the consequent continuous production of self-debris. Normal homeostatic remodeling in some organs replace up to 10%–15% of cells annually. Consequently, adaptive mechanisms may have evolved under selective pressure to optimize tissue maintenance and repair. Among these adaptive mechanisms there is inflammation (1).

Chronic inflammation generally leads to tissue degeneration but is also part of normal tissue remodeling. Perhaps this is best illustrated by the paradox of centenarians. Centenarians often have signs of systemic inflammation (e.g., high plasma levels of IL-6 and IL-8) as well as decreased antioxidant defenses and show a hypercoagulability state characterized by higher plasma level of important factors involved in the hemostasis balance. Nonetheless, these exceptional individuals avoid or delay the onset of chronic age-related diseases such as type II diabetes, cardiovascular disease, and invasive cancer, suggesting that inflammaging and hypercoagulable state are compatible with health and longevity. These paradoxes of centenarians suggests that factors other than serum or tissue levels of proinflammatory cytokines and coagulation factors might be important determinants of whether an individual's inflammatory status is adaptive or pathogenic.

One factor that can distinguish pathogenic from adaptive inflammation is the relative strength of effective anti-inflammatory responses. Anti-inflammatory responses are a critical negative regulatory component of acute inflammation. The nature and extent to which these responses occur during inflammaging is less understood. Nonetheless, anti-inflammatory responses do occur in inflammaging and they

can at least partially counteract or compensate for chronic inflammatory processes (21).

In addition, there are likely gene variants within natural populations that confer a reduced sensitivity to or capacity for inflammatory responses or heightened anti-inflammatory responses. Consequently, in some individuals, such as many centenarians, inflammaging may develop more slowly or be restricted or balanced by anti-inflammatory responses that are less prominent in the general population (21).

HOW DO LOCAL AND SYSTEMIC SOURCES OF CHRONIC INFLAMMATION CONTRIBUTE TO CHRONIC DISEASE PROCESSES?

Circulating proinflammatory molecules are strong predictors of age-related morbidity and mortality (8,22). However, it is not clear to what extent systemic factors are the important drivers of many age-related diseases in humans. In contrast, there is mounting evidence in humans that the local production of inflammatory cytokines can drive phenotypes and pathologies associated with aging. This notion is perhaps most prominently illustrated by the case of the niches surrounding malignant tumors (23). Likewise, the local (tissue) cytokine milieu is an important driver of age-related retinal vascular disease (24), and there is evidence that the SASP of damaged or senescent cells can disrupt local tissue structures and function (12,14). Thus, increased levels of inflammatory mediators in the blood may simply reflect leakage from local sources. As such, the relative importance of circulating levels of inflammatory mediators versus their levels in the surrounding tissue or microenvironment requires further investigation.

Circulating factors can also counteract aging phenotypes, at least in certain mouse tissues. Three prominent examples are the ability of a young blood supply to rejuvenate tissue repair in aged skeletal muscle (25) and the capability of young serum to rejuvenate the proliferative and differentiation capacity of human muscle stem cells (satellite cells) from old donors (26), the ability of systemic GDF11 (growth differentiation factor 11) to reverse age-related cardiac hypertrophy (27), and the ability of GnRH (gonadotropin releasing hormone) to prevent aging phenotypes in skeletal muscle, the brain, and skin (28).

The source of circulating versus local inflammatory molecules can provide insights to their relative importance. As noted, stimuli that initiate inflammaging can vary from damaged molecules to commensal flora. In addition, macroenvironmental and dietary factors (e.g., obesity) can cause or contribute to inflammaging. There is overlap in the types of inflammatory mediators that are produced by each stimulus, but little is known about whether and to what extent each has an additional unique inflammatory signature, and therefore unique physiological outcomes. Nor is it known whether stimulus-specific mediators act primarily at a distance (systemically) or locally.

WHAT ARE THE CORE INFLAMMATORY COMPONENTS THAT CAUSE INFLAMMATORY DAMAGE ACROSS A SPECTRUM OF CHRONIC DISEASES?

Chronic inflammation entails several cytokines, molecular pathways, effector cells, and tissue responses that appear to be shared across multiple age-related diseases. Although many commonalities are described, less is known about unique inflammatory components and pathways that distinguish age-related pathologies from each other.

IL-6 is arguably the most prominent cytokine that is shared across age-related pathologies having a strong chronic inflammatory component (29). IL-6 is now a commonly used marker of inflammatory status, and a hallmark of chronic morbidity. Other inflammatory mediators that increase across multiple age-related diseases include IL-1 β and tumor necrosis factor- α . All these cytokines have pleiotropic effects, in addition to stimulating an immune reaction.

Most cytokines interact with cell surface receptors to initiate intracellular signaling cascades that ultimately activate transcription. Among the transcription factors that regulate chronic inflammation across multiple diseases and tissues there are the NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and STAT (signal transducer and activator of transcription) proteins (30). One or both of these proteins positively regulate many genes that encode proinflammatory cytokines. NF- κ B, for example, regulates the majority of genes that comprise the SASP (31). Moreover, NF- κ B has been shown to drive several aging phenotypes, particularly in the skin, spine, and brain (28,32,33). According to a number of recent articles, the activation of inflammasome is emerging as a crucial event in inflammaging and in the pathogenesis of a variety of age-related diseases such as Alzheimer's disease, atherosclerosis, macular degeneration, and degenerative arthritis, among others.

Both the intracellular signaling cascades and transcriptional pathways that regulate inflammaging are subject to numerous layers of regulation. These include regulation at the levels of transcription and translation, as well as regulation by micro-RNAs (34), posttranslational modifications, and regulated secretion (including processing by the inflammasome). Very little is known, however, about whether and to what extent these modes of regulation are shared among different age-related diseases.

ARE THERE INTERVENTIONS THAT CAN ALTER THE DYNAMICS OF INFLAMMATION AND PREVENT/LIMIT CHRONIC DISEASE?

Interventions that suppress, prevent, or alter the dynamics of chronic inflammation hold great promise for treating or preventing—simultaneously—multiple age-related pathologies. Some anti-inflammatory interventions—for example, the use of low dose aspirin or statins—are already in popular or clinical use. Further, given the evidence that obesity provides a rich reservoir of inflammatory reactions,

nutritional interventions aimed at controlling weight will likely be efficient as well. Likewise, exercise is proposed to lower morbidity by lowering chronic inflammation (35). Finally, although the extent to which the macroenvironment contributes to inflammaging is incompletely understood, improved environmental quality might be a fruitful intervention.

On the horizon, agents that eliminate senescent cells, or suppresses their SASP, hold promise for diminishing chronic inflammation caused by these cells since their clearance in a transgenic mouse model ameliorated several age-related pathologies (albeit in an accelerated aging mouse) (13). Additionally, as the signaling and transcriptional pathways that drive chronic inflammation are elucidated, new targets for interventions will be revealed. Also, if immunosenescence is a strong driver of chronic inflammation, thymic replacement or other strategies to increase adaptive immune function may be important. The extent to which these new targets are exploitable will, of course, depend on their nature, tissue specificity, and ability to identify bioactive interventions. Another promising area for intervention is the development of methods to upregulate natural anti-inflammatory responses. As noted, these responses curtail the damage inflicted by acute inflammation but could be used to limit the nature or extent of chronic inflammation. Because a robust innate inflammatory response is important and beneficial even in old age, therapies will have to balance opposing needs. Likewise, methods to maintain or restore gut integrity and/or a youthful microbiota or to limit microbial translocation (e.g., sevelamer, currently used to manage hyperphosphatemia, binds endotoxin, and limits translocation from the gut) hold promise for reducing the age-related inflammation.

Thus, although there are promising interventions in current use, many other opportunities for novel and more efficacious interventions are foreseeable.

CONCLUSIONS AND TAKE HOME MESSAGE

"Inflammaging" describes the low-grade chronic inflammation in aging and is a highly significant risk factor for both morbidity and mortality in the elderly people, but it can be prevented and cured (36).

Acute, transient inflammation can be beneficial as a basic immune response to harmful conditions such as traumatic tissue injury or an invading pathogen; chronic inflammation is usually of low grade and persistent, resulting in responses that lead to tissue damage/degeneration.

Inflammaging Stimuli

The major identified sources of inflammaging are: (i) endogenous host-derived cell debris (damage-associated molecular patterns, i.e., damaged organelles, cells, and macromolecules) that accumulate with age as a consequence of both increased production and impaired elimination; (ii) senescent cells and their SASP; (iii) immunosenescence

that can be accelerated and aggravated by persistent infections such as CMV, HIV, and Epstein–Barr virus; (iv) harmful products (pathogen-associated molecular patterns) and metabolites having local and systemic effects produced by the gut and other microbiota (oral) that undergo profound changes with age; and (v) the coagulation system and its increasing activation with aging.

Inflammaging and Anti-inflammaging

Centenarians are inflamed and have markers of a hypercoagulable state but do not suffer most of the detrimental effects of inflammaging and thus they can be assumed as a good model to identify factors that can neutralize or protect from high serum or tissue levels of proinflammatory cytokines and that decide whether an individual's inflammatory status is adaptive or pathogenic (inflammaging vs anti-inflammaging) (21).

In addition, genetic predisposition can play a role in inflammaging, and from this point of view, the genome of centenarians might confer a global reduced sensitivity to or capacity for inflammatory responses or heightened anti-inflammatory responses (21).

Aging, Inflammaging, and the Role of the Systemic Macroevironment

Circulating proinflammatory molecules are strong predictors of age-related morbidity and mortality; it is not clear to what extent systemic factors are the important drivers of many age-related diseases in humans. The source of circulating versus local inflammatory molecules can provide insights to their relative importance.

Circulating molecules (mostly to be identified), including miRNA, can maintain and propagate inflammaging and, to some extent, the aging phenotype itself. Circulating factors can also counteract aging phenotypes, at least in certain mouse tissues.

Major Pathways Involved in and Responsible for Inflammaging

The large variety of the stimuli fuelling inflammaging apparently converge on few basic mechanisms and pathways such as activation of NF- κ B and Nlrp3 inflammasome, responsible for the production of inflammatory molecules. It is also clear that reactive oxygen species production following mitochondrial dysfunction, DNA damage and DNA damage response and cell senescence are major players in this scenario (37). Both the intracellular signaling cascades and transcriptional pathways that regulate inflammaging are subject to numerous layers of regulation. Very little is known, however, about whether and to what extent these modes of regulation are shared among different organs and cell types as well as among age-related diseases.

Preventive and Therapeutic Strategies

On the horizon, agents that eliminate senescent cells, or suppress their SASP, hold promise for diminishing chronic inflammation caused by these cells (38). In a mouse model, reduction in the Nlrp3 inflammasome-dependent proinflammatory cascade attenuated age-related degenerative changes across multiple organs (39). Additionally, as the signaling and transcriptional pathways that drive chronic inflammation are elucidated, new targets for interventions will be revealed. Also, if immunosenescence is a strong driver of chronic inflammation, thymic replacement or other strategies, for example, local and/or systemic neutralization of proinflammatory cytokines such as IL-6, effective vaccine against CMV and HIV, may be important to increase adaptive immune function and to reduce the erosion of the immune system. Finally, healthy lifestyle, that is, age-appropriate physical exercise and elderly tailored diet, including pro- and prebiotics (and in the next future ad hoc fecal microbiota transplantation), can contribute to reduce inflammaging and age-related pathologies. These last strategies are totally doable and should be pursued at population level.

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