Inflammaging and the Lung

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KEYWORDS

• Inflammaging • Elderly • Infection • Host defense • Macrophage • Neutrophils • Inflammation • Immunosenescence

KEY POINTS

- Age-dependent changes in immune responses cause increased morbidity and mortality in the elderly.
- Inflammaging causes immunosenescence.
- Intestinal permeability in the elderly may be responsible for inflammaging.
- The ability of alveolar macrophages to maintain pulmonary homeostasis following clearance of infection is reduced in the aged.

INTRODUCTION

With advanced age, there are changes in multiple biologic systems[1] including the immune system. Alterations in innate and adaptive immune cells in the aged have been noted.[2,3] In brief, the age-dependent effects on the innate immune response include diminished pathogen recognition, chemotaxis, and phagocytosis, and in adaptive

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immunity, declining numbers of naive T lymphocytes and reduced cytotoxicity and antibody quality and quantity.[2] Vaccine efficacy is reduced in the elderly, as are increases in autoimmunity and cancer.[2] Overall, these immune defects, referred to collectively as immunosenescence, render the host less able to withstand injury or infection relative to younger individuals.

Among the hallmarks of the aging immune system is the persistent low-grade proinflammatory state characterized by heightened basal levels of proinflammatory mediators in the blood.[4] Because of this association of advanced age and inflammation, Claudio Franceschi coined the term "inflammaging" in 2000.[4] Franceschi and coworkers[4] have reported that, even in healthy aged subjects without confirmed ailments, there is an elevated basal level of proinflammatory mediators, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α. The elevated levels of these and other proinflammatory factors in the aged can have local and systemic consequences, none of which are ultimately beneficial to the host. This rise in circulating levels of proinflammatory cytokines and other factors is thought by some to be a driving factor in the development and maintenance of immunosenescence[4,5] and contribute to chronic diseases of the lung and other organs.[6–8] In this review, the focus is on inflammaging, immunosenescence, and the lung, but it should be noted that many of the age-dependent changes are neither limited to nor likely to be caused by changes in the aging lung itself, and most of these changes are not observed unless the host is challenged by some form of stressor, such as an injury or infection.

CHANGES IN THE LUNG WITH ADVANCED AGE

A wide range of pulmonary parameters that influence lung immunity are altered with advanced age as described in **Table 1**.

INNATE IMMUNE CELLS OF THE LUNG AND CHANGES WITH ADVANCED AGE

Macrophages

The primary resident innate immune cell in the airway is the alveolar macrophage. This multifaceted cell serves as the first line of defense against invading pathogens and

Table 1
Aging of the lung

Lung Functions That Are Changed with Age	Reference
↓ Mucociliary escalator: reduced ability to clear microbes and debris from the airway	9,10
↑ Expression of proteins associated with bacteria attachment and infiltration in the pulmonary epithelial cells, including polymeric immunoglobulin receptor and platelet-activating factor receptor	11,12
↑ Expression of markers of cellular senescence	6,13
↓ Epithelial expression of antimicrobial peptides	14,15
↑ Levels of complement and surfactant proteins	15
↑ Proteostasis (and the loss of ability of cells from the aged to properly control protein abundance, proper folding, and degradation)	16,17
↑ Susceptibility to pulmonary infections	2,11,12,18–22
Dysbiosis (or the imbalance) of the pulmonary microbiome in the absence of infection and after infection	23–28

plays a critical role in lung immunologic homeostasis. Macrophages are capable of initiating and resolving an inflammatory response.[29–31] This ability to play divergent roles is caused by macrophage plasticity. Macrophages can adapt and even change phenotype in response to environmental cues, enabling them to adapt to varying conditions and perform a plethora of diverse functions.[32–35] Historically, this stimulus-induced shift in macrophage phenotype was referred to as M1 and M2 phenotypes with M1 being proinflammatory and M2 anti-inflammatory.[36,37] However, because of poor definition and inconsistencies in the cell surface markers defining these two phenotypes, a group of expert macrophage research investigators recently redefined macrophage classification terminology so that they are more narrowly classified based on the source of the macrophages and activation stimuli, and the specific group of markers associated with the particular activation phenotype.[38] Regardless of nomenclature, under resting conditions, alveolar macrophages maintain an anti-inflammatory profile to keep the pulmonary airway in check and are capable of rapidly springing into action, becoming strongly proinflammatory when alerted by the presence of foreign material (**Fig. 1**). After pathogen clearance, the ability of alveolar macrophages to promote resolution and return to an anti-inflammatory resting phenotype is equally important for maintenance of lung homeostasis.

Multiple factors are involved in the resolution of inflammation in the lung. These include but are not limited to (1) clearance of the pathogen or debris; (2) reduced production of neutrophil chemokines; and (3) removal of apoptotic cells, including effete neutrophils. All of these processes are orchestrated by alveolar macrophages.[39] It should be noted that the inability of macrophages to perform these functions can result in prolonged inflammation, which if left unchecked can result in damage to

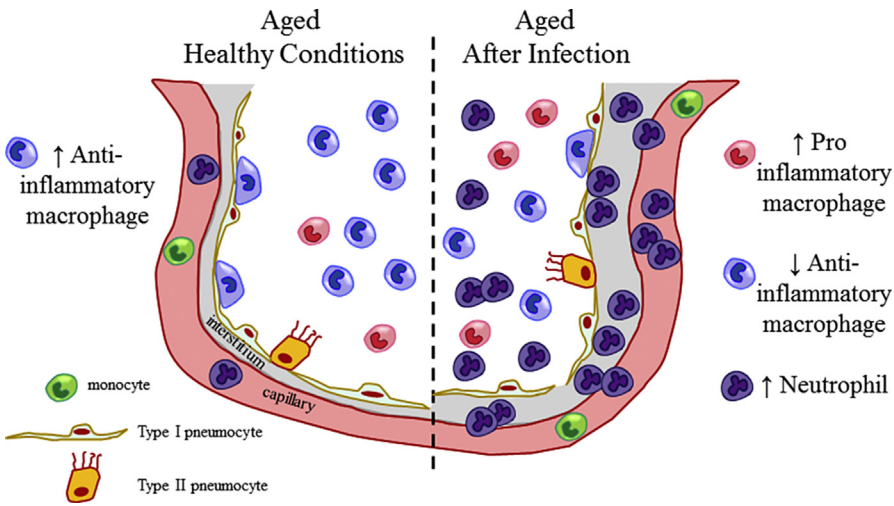

Fig. 1. Innate immune phenotype of the aged lung. Regardless of age, under healthy conditions, the major leukocyte of the distal lung is the alveolar macrophage. These multifaceted cells exist in an anti-inflammatory state to limit inflammation and maintain pulmonary homeostasis. A variety of pathogenic conditions alter alveolar macrophage function. In the young, alveolar macrophages can rapidly respond to external stimuli, such as bacteria; clear infections; and return to their anti-inflammatory state. In contrast, in the elderly, alveolar macrophages fail to mount an adequate response to infectious insult, are slow at recruiting neutrophils to help combat the respiratory pathogens, and are unable to return to their anti-inflammatory phenotype, thus leaving the lung in a compromised state.

lung tissue.[40] Central to the restoration of pulmonary homeostasis is the removal of neutrophils, which is associated with a shift in alveolar macrophages phenotype to an anti-inflammatory profile.[39]

With advanced age, it is clear that the ability of macrophages to perform their normal functions is impaired and that inflammaging plays a role in this altered response despite the lack of change in macrophage number. A comprehensive review of macrophage function and aging is available.[36] In brief, in vivo and in vitro studies conducted in humans and in various animal models suggest that many but not all of the functions of macrophages are slowed or diminished in magnitude in the aged, leaving the host unable to shift between phenotypes when needed.[2,33,36] Some of the better documented age-dependent changes in macrophage function are highlighted in **Table 2**.

Neutrophils

The neutrophil is a key innate immune cell that is often the first cell type to be recruited to sites of injury and infection. Neutrophils are capable of performing a variety of antimicrobial functions that play a critical role in removing pathogens from tissues during the early stages of lung infections. Within minutes after recognition of foreign material, macrophages become activated and initiate a cascade of events that includes the release of chemoattractant cytokines that recruit neutrophils. Working together, macrophages and neutrophils join forces to remove and destroy infectious organisms.[58,59] Neutrophil functions that are altered with advanced age are shown in **Table 3**.

A PARADOX: AGING CAUSES HIGHER CYTOKINE LEVELS IN VIVO, YET REDUCED PRODUCTION BY INFLAMMATORY CELLS IN VITRO

The cellular sources of the mediators responsible for inflammaging remain unknown. Interestingly, there is a disconnect between the in vivo and in vitro effects of stimulation on the inflammatory response in young adult and older subjects and in cells isolated from those subjects. From human and rodent studies in which an inflammatory stimulus, such as lipopolysaccharide, is given in vivo, it is clear that the inflammatory response is of greater magnitude and duration in older subjects relative to younger.[88–90] In contrast, in vitro stimulation of certain cell subsets, including blood monocytes, lung, or peritoneal macrophages from aged subjects, yields lower levels of cytokines relative to cells from younger individuals,[44–46,91,92] suggesting either that monocyte/macrophages are not a major source of these mediators in vivo or that there are additional factors responsible for this discrepancy. The effects of aging on monocyte/macrophage functions were comprehensively reviewed elsewhere.[36]

Table 2
Aging and macrophages

Alterations in Macrophage Function with Advanced Age	Reference
↓ Toll-like receptor expression (mRNA and protein) and downstream signaling (in most but not all studies)	23,41–46
↓ Production of proinflammatory and immunomodulatory cytokines, including tumor necrosis factor-α, IL-6, IL-1β, and CCL2 (monocyte chemoattractant protein-1) after stimulation by various agonists	44–50
↓ Telomere length	51
↑ Regulators of immune signaling, such as A20, a deubiquitinase that, in turn, inhibits toll-like receptor signaling and nuclear factor-κB activation	11,12
↓ Phagocytosis and pathogen clearance	7,49,52–57

Table 3
Aging and neutrophils

Alterations in Neutrophil Function with Advanced Age	Reference
↓ Chemotaxis	60–67
No change in chemokinesis	60
↓ Phagocytosis	62,64,68–75
↓ Production of reactive oxygen species	61,62,64,70,71,76–78
↓ Generation of neutrophil extracellular traps	79–81
↓ Production of proinflammatory cytokines and mediators, including IL-6, IL-8, myeloperoxidase, elastase, and ↑ production of anti-inflammatory cytokines, IL-10	76,82,83
No increase in lifespan following stimulation	83–87

WHAT CAUSES INFLAMMAGING?

There are multiple theories about the origin and perpetuation of inflammaging. Ones that have gained press over time include classical ideas about increased oxidative stress, DNA damage, and telomere shortening.[1,2] In brief, it is believed that with advanced age there is an increase in posttranslational modification of macromolecules including DNA, proteins, and lipids that stimulate leukocytes and other cells to secrete proinflammatory cytokines; and senescence of immune and nonimmune cells leading to an increased release of inflammatory mediators via a senescence-associated secretory phenotype.[1,2] Additionally, a complementary and newer theory about the initiation of inflammaging is emerging and gaining support in the literature. This theory revolves around changes in intestinal permeability that allows bacteria and bacterial products (eg, endotoxin and peptidoglycan) to translocate into the lymphatic system and ultimately the bloodstream where they can trigger the low systemic inflammation in the elderly.

In brief, changes in aged intestine include dysbiosis of intestinal microbiota in animal models of aging and in elderly humans,[93–96] and decreased integrity of the intestinal epithelial cell barrier in mice and humans.[97–102]

AGING, DYSBIOSIS OF INTESTINAL MICROBIOME, AND THE GUT-LIVER-LUNG AXIS

Extensive clinical and experimental evidence reveals that the intestinal barrier integrity plays a role in inflammaging that in turn alters pulmonary inflammation. The gut hypothesis states that heightened intestinal permeability, along with changes in immune function of the gut, results in increased translocation of bacteria and bacterial products.[103–105]

Like the lung, the intestine is an organ that is exposed to the outside environment with a large surface area. Although the lung and intestine provide different biologic functions, they share in common the feature of needing to maintain compartmental barriers that must remain intact to permit normal organ function to occur and to protect the host from invading pathogens. Those barriers are created by the epithelium lining the lumen of the respiratory and gastrointestinal tract. The integrity of tight junctions between adjacent epithelial cells is an essential part of these barriers. In young and the aged, this barrier is maintained in part by the complex interactions between the multiple proteins making up tight junctions, including occludins and claudins, along with multiple adaptor and scaffolding proteins. Under normal conditions, the

epithelium maintains a semipermeable barrier permitting passage of smaller molecules while preventing the movement of other materials to its underlying mucosal tissue. Regardless of the organ, breach of the epithelial barrier allows inappropriate access of microbial organisms and debris to the underlying mucosa, which can cause inflammation and tissue damage.[106–109] The integrity of this barrier is perturbed in a plethora of disease states, such as reflux esophagitis, cancer, and inflammatory bowel disease (discussed elsewhere).[108,109]

One mechanism of altering the epithelial status quo is mediated by the enzyme myosin light chain kinase (MLCK), the long 210-kDa form that remains inactive in the cytoplasm of epithelial (and endothelial) cells. When activated, MLCK phosphorylates myosin regulatory light-chain (MLC) at serine 19, allowing it to interact with actin. The interaction between actin and MLC causes cytoskeletal sliding, which disrupts tight junctions and creates a gap in the epithelial barrier,[110,111] thus permitting the uncontrolled flow of fluid, bacteria, bacterial products, and other materials across the epithelial lining.[112,113] Of interest to research on the elderly, the same set of proinflammatory mediators that are elevated in the circulation of the aged and serve as hallmarks of inflammaging, namely IL-1β, IL-6, and tumor necrosis factor-α, can trigger the activation of MLCK. Additionally, in the lung, when MLCK is activated in the capillary lining endothelial cells, it results in paracellular permeability, which can lead to pulmonary edema.[110] One of the consequences of the leakiness of the intestinal epithelium is the translocation of bacteria from the intestinal lumen to the underlying mucosal tissue and to regional lymph nodes. Subsequently, these products can traffic to the liver where they can stimulate production of proinflammatory cytokines (Fig. 2). If not appropriately contained by the aging immune system, the dissemination of

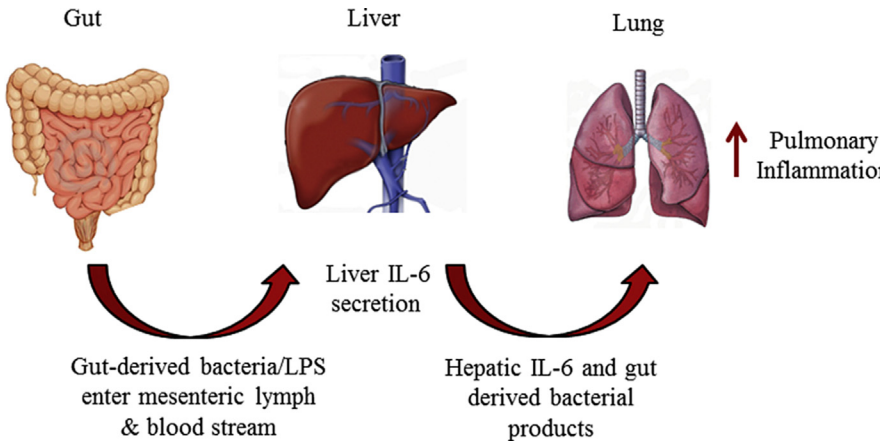

Fig. 2. The gut-liver-lung axis. Under healthy conditions, the epithelial cells lining the intestine maintain tight junctions preventing luminal contents from invading the underlying mucosal tissues. In the aged, it is thought that epithelial cell tight junctions loosen, possibly in response to the presence of the proinflammatory cytokines associated with inflammaging. This loosening of junctional complexes and subsequent increase in paracellular permeability allows gut-derived bacteria, bacterial products, and endotoxins to enter the mesenteric lymph and the bloodstream. Bacteria and their products then trigger Kupffer cells and other cells in the liver to produce and secrete proinflammatory cytokines, including IL-6. Hepatic-derived IL-6, along with the gut-derived bacteria products in the circulation, promotes baseline lung inflammation, which can then be further exacerbated in the aged after injury or infection. LPS, lipopolysaccharide.

bacteria and/or release of bacteria and bacterial products, such as endotoxins, throughout the body can occur, leading to prolonged and exacerbated inflammation in all organs, which likely contributes to increased morbidity and mortality in the aged. Hence, the intestine and its microbial contents can play a critical role in inducing or exacerbating complications in various patient populations[111,114] and in the aged.[101,102,115–117]

SUMMARY AND FUTURE DIRECTIONS

Factors or treatments that reduce inflammaging are of interest to basic and clinical researchers because they may be able to dampen the prolonged and heightened inflammation seen in the elderly after attempting to combat an infection. Thoughts about the design of therapeutic interventions to reduce inflammaging can be directed either at cells themselves or the proinflammatory environment in which they reside. Animal studies involving adoptive transfer of subsets of leukocytes are in progress, as are numerous clinical and basic research studies investigating antioxidant and anti-inflammatory agents to attenuate the overexuberant inflammatory response in the aged. Some believe that taking the indirect approach of reducing intestinal inflammation or restoring the intestinal microbiota may have benefit, but this is not without controversy.[118–120] It would be of interest to determine if patients receiving anti-inflammatory therapies for other conditions have restored intestinal barrier function and if this, in turn, improves systemic responses to the injury or infection in the aged population. Further exploration of these direct and indirect avenues of therapeutic manipulation may be of benefit to the overall health of the aged and with that will likely improve overall lung health of the elderly.

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