Aging immunity may exacerbate COVID-19

By Arne N. Akbar and Derek W. Gilroy

Aging is associated with increased morbidity arising from a range of tissue dysfunctions. A common denominator of age-associated frailty is increased baseline inflammation, called inflammaging, that is present in older individuals. Recent studies have shown that the presence of excessive inflammation can inhibit immunity in both animals and humans and that this can be prevented by blocking inflammatory processes. This finding has important implications for the immunity of older individuals who are infected with pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that induce overwhelming inflammation, which can be fatal, particularly in older people. Reducing inflammation may be a therapeutic strategy for enhancing immunity in older people.

SARS-CoV-2 causes severe respiratory disease (coronavirus disease 2019, COVID-19) that mostly induces mild to moderate symptoms in younger individuals, but induces devastating morbidity and mortality in older individuals. A key hallmark of severe disease is exuberant inflammation in the respiratory tract of patients. Older healthy individuals (60 years and above) exhibit chronic low-grade sterile inflammation (not caused by a pathogen) characterized by high baseline serum concentrations of C reactive protein (CRP) and cytokines, including interleukin-6 (IL-6), and IL-8. This inflammmaging predicts frailty and earlier mortality compared with individuals of the same age group who do not exhibit increased baseline systemic inflammation (2).

Inflammaging may arise as a result of multiple mechanisms, including the accumulation of misfolded proteins, compromised gut barrier function, and obesity (2). Defective resolution of immune responses in older individuals, due to the impaired clearance of dead and dying cells from sites of immune activity, may also lead to sustained inflammation in vivo (3). Senescent cells, which no longer divide, accumulate in every organ during aging and contribute to increased baseline inflammation (4). Senescent cell populations are found within diverse lineages, including lymphocytes, and are nonproliferative as a result of telomere erosion, damaged DNA, epigenetic changes, or mitochondrial dysfunction. Senescent nonlymphoid cells secrete inflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases (MMPs). This is known as the senescence-associated secretory phenotype (SASP), and the secretion of these inflammatory molecules by any of these cell types may cause organ dysfunction during aging in humans and in animal models (4).

Inflammation is an essential component of the initiation phase of an immune response, but it is actively reduced by the clearance of dead and dying cells as well as other pro-resolution processes (3). The presence of excessive inflammation can inhibit antigen-specific immunity in vivo. This is illustrated by studies in both mice and humans showing that increased inflammation is detrimental for the efficacy of many vaccines, such as against influenza virus (5). The negative impact of inflammation on immunity during aging can be reversed in part by treatment with the mTOR (mammalian target of rapamycin) inhibitor rapamycin, which enhances influenza-specific antibody responses after influenza vaccination in treated individuals (6).

Furthermore, the short-term administration of an oral p38 mitogen-activated protein kinase (MAPK) inhibitor reduced baseline cutaneous inflammation in older people, in part by inhibiting the influx of inflammatory monocytes. This resulted in a significantly increased response to varicella zoster virus (VZV, which causes chicken pox in children and shingles in adults) recall antigen challenge (memory T cell response) in the skin in vivo (7). Therefore, reducing inflammmaging with a short-term course of mTOR or p38 MAPK inhibitors and possibly other anti-inflammatory agents (e.g., steroidal drugs such as dexamethasone) may be a strategy for immune enhancement in older people. This may be of particular relevance for older patients with COVID-19 who have severe inflammation in the respiratory tract during disease progression that may hinder antiviral immunity.

Both senescent cell numbers and baseline inflammation increase during aging, suggesting that these events are interlinked. Because senescent cells secrete proinflammatory mediators and accumulate in every organ in the body during aging, another way to enhance immunity and reduce the inflammatory burden may be to eliminate these cells. Natural mechanisms exist for clearing senescent cells from tissues. These involve the expression of “kill me signals” [e.g., natural killer (NK) cell receptor (NKR) ligands] on senescent cell populations that activate receptors on cytotoxic T lymphocytes that enable them to kill senescent nonlymphoid cells in tissues (8).

The ability of T and NK cells to eliminate senescent cells raises the question of why nonlymphoid senescent cells accumulate during aging. One possibility is that the general multifactorial age-associated decline in immunity also extends to surveillance of senescent tissue cells in different organs. Alternatively, senescent cells may display evasion strategies that enable them to escape from immune clearance. These mechanisms include the shedding of decoy receptors that interfere with the ability of cytotoxic T cells to recognize them (9) and also the expression of inhibitory “don’t kill me” signals (such as human leukocyte antigen E (HLA-E), a ligand for the inhibitory NKR, NKG2A) on their cell surface (8). The removal of senescent (p16INK4A-expressing) cells in transgenic mice by inducing activation of thymidine kinase can reverse age-associated organ dysfunction. The negative impact of senescent cells in aging has prompted the development of therapies to remove senescent cells with drugs called senolytics that are currently being tested in mice and humans (10).

Blocking inflammation directly or eliminating the cells that produce inflammatory mediators can improve health and immunity. The inflammatory nature of senescent cells in various tissues may inhibit immune responses of older individuals, and this must be factored in when considering the cause of hyperinflammatory responses during some SARS-CoV-2 infections. Because senescent cells increase in the lungs during aging (11), they are very likely to be present in the lungs of older COVID-19 patients and may participate in the initiation of an inflammatory cascade. Although the secretion of proinflammatory mediators by adipose tissue may contribute to inflammmaging, it is not yet known.
whether senescent cells within the adipose tissue or the adipocytes themselves produce these mediators. This is relevant in the context of COVID-19 because obesity is a comorbidity for severe disease.

A key unknown issue is the relationship between high baseline inflammation and the hyperinflammation that occurs in older COVID-19 patients with severe disease. One hypothesis is that preexisting inflammatory cells, including senescent populations and adipocytes, create the inflamming phenotype that amplifies subsequent inflammatory events. This would involve the recruitment of other inflammatory cells. For example, during an immune response, monocytes are recruited from the circulation into the skin of old individuals (22), and this may also occur in the lungs of COVID-19 patients with severe disease. Nevertheless, high amounts of inflammation alone do not explain the devastating tissue destruction that is observed in the lungs of COVID-19 patients with severe disease, and it may be that age-associated changes in T cells have a role in the immunopathology.

T lymphocytes that are highly differentiated and exhibit senescence-like characteristics accumulate in older individuals. These cells lose the capacity to proliferate after activation and express multiple markers of senescence, including DNA damage associated proteins [e.g., phosphorylated histone H2AX (γH2AX)] and cyclin-dependent kinase inhibitors (e.g., p16INK4a), but are highly efficient cytotoxic cells (13). However, these aged T cells express NKRs and can kill different cell types that express NKR ligands (13). Inflammation has been shown to increase the expression of NKR ligands by different cell types, including senescent nonlymphoid cells (14). Therefore, aged T cells that infiltrate the lungs of COVID-19 patients may not function well in an antigen-specific manner because of the inflammation present but also because they acquire NK cell activity and do not recognize specific antigens. NK cells are lymphocytes that do not require prior sensitization with antigens to mediate cytotoxic responses to infected and/or malignant cells. The inflammation in the lungs of COVID-19 patients, possibly resulting in part from the infiltration of inflammatory monocytes, would induce the expression of NKR ligands by nonlymphoid cells (14), and these may be targeted and killed by infiltrating T cells (see the figure). This would contribute to the reported collateral tissue damage in the respiratory tract of COVID-19 patients. There is an urgent need for immunohistological data from the lungs of these patients to address this possibility.

The propensity to mount inflammatory responses in tissues and changes in the behavior of different leukocyte populations have to be considered when addressing the immune responses of older individuals during infection. The baseline inflammation may not be detrimental in itself; instead, it may initiate an inflammatory cascade that amplifies the excessive inflammation that occurs in response to pathogens. In addition to senescent cells, other inflammatory cell types, such as adipocytes, may also trigger inflammation. Inflammaging has many implications for COVID-19 patients: The accumulation of senescent cells in the respiratory tract of older patients may be involved in the initiation of an inflammatory cascade that could inhibit T cell responses to virally infected cells that are present. Another consequence of the inflammation is the induction of NKR ligand expression by cells in the lung (14) that would make them susceptible to killing by infiltrating T cells that express NKRs. The search for an effective vaccine for COVID-19 should also consider the decreased vaccination efficacy in older individuals that may be associated with inflamaging (15). Therefore, the effective treatment of COVID-19 patients may require a combination of anti-inflammatory and antiviral regimes to complement vaccination against the virus.

REFERENCES AND NOTES


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Aged immune responses to SARS-CoV-2 infection

Highly differentiated T cells in older individuals may induce damage in SARS-CoV-2–infected lungs, as hypothesized in the diagram.
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