

Can blocking inflammation enhance immunity during aging?



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Aging is a global burden, and the increase in life span does not increase in parallel with health span. Therefore, older adults are currently living longer with chronic diseases, increased infections, and cancer. A characteristic of aging is the presence of chronic low-grade inflammation that is characterized by elevated concentrations of IL-6, TNF- α , and C-reactive protein, which has been termed inflammaging. Previous studies have demonstrated that chronic inflammation interferes with T-cell response and macrophage function and is also detrimental for vaccine responses. This raises the question of whether therapeutic strategies that reduce inflammation may be useful for improving immunity in older adults. In this review we discuss the potential causes of inflammaging, the cellular source of the inflammatory mediators, and the mechanisms by which inflammation may inhibit immunity. Finally, we describe existing interventions that target inflammation that have been used to enhance immunity during aging. (J Allergy Clin Immunol 2020;145:1323-31.)

Key words: *Inflammaging, senescence, p38-MAP Kinase, senolytics*

Aging results in increased susceptibility to infections, reduced vaccine responses, and increased susceptibility to cancers.¹⁻³ This is due to changes in both the adaptive and innate immune system, which have been reviewed previously.^{4,5} The focus of this review was to describe how inflammation and in particular the phenomenon of *inflammaging* impact on the immune system and to discuss current therapies that are being developed to counteract the inflammatory processes that occur with aging.

INFLAMMAGING

Inflammaging, a term first proposed by Claudio Franceschi, is the state of chronic low-grade sterile inflammation that is observed with age. It is characterized by high serum concentrations of C-

Abbreviations used

CMV:	Cytomegalovirus
CRP:	C-reactive protein
DAMP:	Damage-associated molecular pattern
MAP:	Mitogen-activated protein
mTOR:	Mammalian target of rapamycin
NK:	Natural killer
PD-1:	Programmed cell death protein-1
PDL-1:	Programmed death ligand-1
SASP:	Senescence-associated secretory phenotype
TLR:	Toll-like receptor
TORC:	mTOR complex

reactive protein (CRP) and other inflammatory mediators such as IL-6, IL-8, and TNF- α .⁶ The increase in these inflammatory mediators occurs in healthy older adults in the absence of overt inflammatory disease. However, elevated circulating concentrations of IL-6, CRP, and TNF- α predict frailty in older subjects.^{7,8} Inflammaging is also associated with increased risk of mortality, in healthy and frail older adults.⁹⁻¹² In addition to elevated IL-6, CRP, and TNF- α , IL-1 β and *inflammasome*-related genes are good predictors of all-cause mortality.¹³ Conversely, lower levels of inflammatory cytokines in the peripheral blood correlate with good health outcomes, longevity, and reduced risk of death of older adults.^{9,14} It has also been shown that inflammation and inflammaging-associated cytokines are linked with poor cognitive function and elevated concentrations of plasma IL-6 and CRP are associated with cognitive decline.¹⁵⁻¹⁷

Although there is more inflammation during aging in most older adults it is not known whether it is due to the aging process itself or due to other inflammatory events such as chronic disease, viral infections, or cancer because there is increased inflammaging in older adults who have chronic diseases such as type 2 diabetes, rheumatoid arthritis, and Alzheimer disease.¹⁸ Indeed, it is known that there is a subset of older adults who do not have demonstrable evidence of inflammaging, and why these individuals do not have signs of inflammation as compared with their compatriots is currently unknown.

INFLAMMATION AND IMMUNITY

Acute inflammation is necessary to initiate an immune response against an invading pathogen. After the initial inflammatory response there is a period of resolution that occurs to prevent unnecessary tissue damage and to restore tissue *homeostasis*.¹⁹ However, there is accumulating data showing that chronic inflammation can inhibit immunity *in vivo*, as elevated inflammatory responses are detrimental for vaccine

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Terms in boldface and italics are detailed in the glossary on page 1324.

efficacy against influenza,²⁰ yellow fever,²¹ and hepatitis B. In addition, excessive inflammation, in particular TNF- α production, is linked to decreased killing and clearance of *Streptococcus pneumoniae* in macrophages in an aged mouse model of infection.²² This may occur in part by the induction of premature monocyte egress from the bone marrow by TNF- α that impairs their function. Interestingly, blockade of TNF- α restores monocyte function in old animals, showing that the effect of chronic inflammation can be reversed.²³

Elevated inflammation can also inhibit the response to cutaneous **recall antigens** *in vivo*. Older humans have decreased response to challenge with antigens such as tuberculin purified protein derivative, *candida albicans* antigens, and varicella zoster virus antigens in the skin compared with young individuals.²⁴ However, this was not due to a decrease in the number of circulating or resident **memory T cells**.^{24,25} Instead, these subjects exhibit elevated inflammatory responses induced by the injection itself, the extent of which was negatively correlated with their ability to respond to the antigen.²⁶ The temporary inhibition of systemic inflammation with an oral p38 mitogen-activated protein (MAP) (p38-MAP Kinase) kinase inhibitor enhances the response to antigen in older subjects, indicating the direct association between excessive inflammation and immune inhibition.²⁷

SOURCE OF INFLAMMATION

The exact source of elevated inflammation during aging may be due to a combination of the following mechanisms that are accentuated in older adults. These include chronic viral infection leading to immune activation, increased inflammatory mediator secretion from visceral fat, increased gut permeability resulting in leakage of bacterial components into the circulation, increase in **damage-associated molecular patterns** (DAMPs), altered immune resolution, and accumulation of senescent cells, as shown in Fig 1.

Chronic viral infections

Chronic infections, which cause a lifelong latent infection, are believed to lead to long-term activation of the immune system

over time, contributing to inflammaging. The most studied example is cytomegalovirus (CMV) infection, which induces a lifelong latent infection after the primary infection, and the virus reactivates periodically and initiates a subclinical immune response. A large proportion of T cells in seropositive older subjects are CMV-specific,^{28,29} and these cells are highly differentiated and express **senescence**-associated markers such as CD57 and KLRG1. Furthermore, these cells produce high levels of inflammatory cytokines such as IL-2, IFN- γ , and TNF- α after activation,³⁰ which may contribute to inflammaging. Individuals who are CMV seropositive and exhibit elevated CRP levels have increased all-cause mortality as compared with CMV-seropositive subjects with low CRP levels.³¹ However, the impact of CMV infection on the elevated inflammation in older subjects is controversial.³²

Increased visceral fat

Obesity, and in particular accumulation of visceral fat, is highly associated with inflammatory cytokine production.³³ Visceral fat is an inflammatory site that has an infiltration of mononuclear phagocytes, B cells, and T cells, which contribute to the production of inflammatory cytokines such as IL-6, IL-1 β , and TNF- α .³⁴ In young obese individuals, there is an alteration in their circulating leukocyte populations that resemble the cells found in older adults. There is an increase in circulating end-stage senescent-like CD4⁺ and CD8⁺ cells that secrete high levels of inflammatory cytokines after activation and decreased naive T cells.³⁵ Apart from changes in immune cells resident in fat tissue, there is an increase in visceral adiposity during aging, due in part to the age-related decrease in muscle.³⁶ This increase in visceral fat will contribute to inflammaging due to the inflammatory cytokines produced from the adipocytes themselves.³³

Gut permeability

Studies performed from aged mouse models have shown that older mice have more permeable intestines with a breakdown in cell-to-cell contacts, which leads to leakage of gut contents into

GLOSSARY

DAMAGE-ASSOCIATED MOLECULAR PATTERNS: Molecules that are released from host cells during episodes of cellular stress or cell death to induce inflammatory or cell-death signaling.

HOMEOSTASIS: The steady-state condition that exists in the absence of damage, inflammation, or infection.

INFLAMMAGING: The state of chronic low-grade inflammation that progressively increases with age in the absence of overt inflammatory disease or infection.

INFLAMMASOME: A multiprotein intracellular complex that secretes certain proinflammatory innate cytokines on activation.

MEMORY T CELLS: Long-term antigen-specific T cells that have previously encountered and responded to their cognate antigen.

MICROBIOME: The totality of the microbes and their genetic material present within a particular environment.

PATHOBIANTS: A potentially pathological organism that lives as a nonharming symbiont under normal conditions.

PATTERN RECOGNITION RECEPTOR: Receptor expressed by host cells that activate innate immune responses on detection of damage-associated molecular patterns or molecular motifs conserved within a class of microbes.

RECALL ANTIGENS: Antigens to which an individual has developed specific memory T cells after a previous exposure.

REGULATORY T (TREG) CELLS: A subset of CD4⁺ T cells that express the transcription factor Foxp3 and suppress immune responses.

SENESCENCE: A cellular state characterized by irreversible cessation of cell division among other phenotypic changes.

SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE: A phenotype associated with senescent cells that is characterized by secretion of high levels of inflammatory cytokines, growth factors, and proteases.

SENOLYTIC: Therapeutic agents that selectively induce the death of senescent cells.

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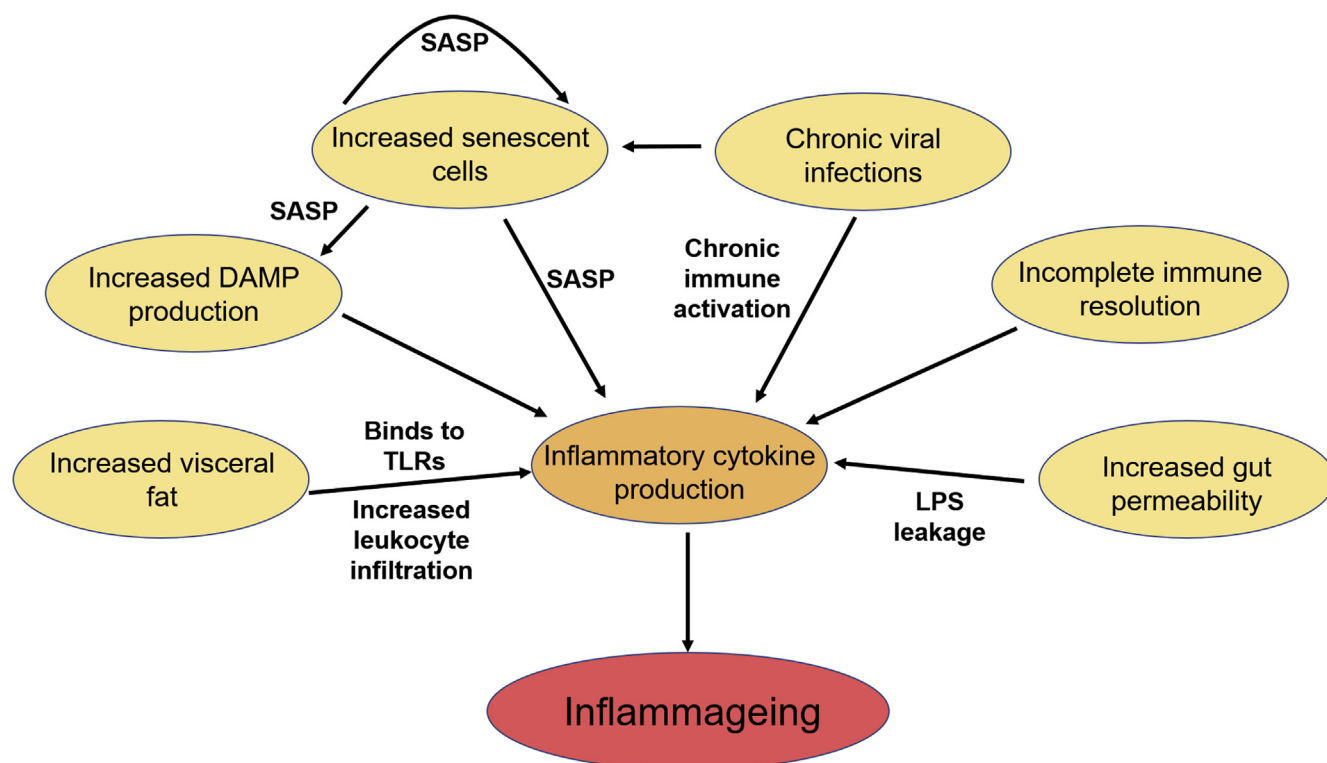


FIG 1. Potential mechanisms of inflammaging. Schematic representation of the proposed causes of inflammaging observed in the old. Increased visceral fat with associated increased leukocyte infiltration; increased DAMP production that binds to TLRs; increased senescent cell production with production of SASP that also includes DAMPs; increased gut permeability and LPS leakage and subsequent TLR activation; and finally chronic viral infection that leads to chronic immune activation. The SASP secreted from the senescent cells also has the capability to drive senescence in nearby cells, increasing the number of cells overall. All these outcomes result in the production of inflammatory cytokines and the subsequent onset of inflammaging.

the bloodstream.^{22,37} This results in an increase in bacterial components such as LPS in the circulation that activate circulating mononuclear phagocytes through *pattern recognition receptor* expressed by the monocytes and results in production of inflammatory cytokines such as TNF α and IL-6.^{22,23} In addition, there are alterations in the *microbiome* of older adults that renders them distinct from younger cohorts.³⁸ Aging is associated with an increase in opportunistic proinflammatory bacteria, termed “*pathobionts*,” which are normally only observed in low numbers in young guts.³⁹ Older adults with the most evident altered gut microbiome had elevated circulating inflammatory cytokines, implying that inflammaging is linked to alteration in microbiome.⁴⁰ However, whether this dysbiosis is as a result of altered gut permeability rather than causative of increased inflammation still warrants further investigation. Evidence from an aged drosophila model has shown that microbiome dysbiosis precedes the increased gut permeability observed with age and thus microbiome dysbiosis could be a causative factor in the increase gut permeability seen with age.⁴¹

Increase in DAMPs

DAMPs are endogenous cellular components that are released at times of injury, stress, or cell death. DAMPs can consist of various cellular products including the S100 family of calcium-binding proteins, histones, genomic or mitochondrial DNA, or other secreted factors such as ATP, uric acid, or heparin sulfate.

This is not an exhaustive list, and DAMPs have been extensively reviewed previously.⁴² When DAMPs bind to their pattern recognition receptor, there is an increase in inflammatory cytokine production from the cell.

It is proposed that the processes involved in aging result in increased DAMP production, which contributes to inflammaging.⁴³ There is limited human data to support this hypothesis; however, in aged murine studies, elevated levels of high mobility group box 1 have been observed in old mice.⁴⁴ High mobility group box 1 is an alarmin family member and binds to surface Toll-like receptor (TLR)2 and TLR4, resulting in the production of inflammatory cytokines including IL-6.⁴⁵ In addition, NLRP3 inflammasome, an innate immune sensor that is activated in response to an array of DAMPs, was found to be elevated in aged mice. Removing the *NLRP3* gene from these mice resulted in a decrease in aged-related inflammation, implying DAMPs are involved in the process of inflammaging.⁴⁶

Ineffective immune resolution

After an acute inflammatory response to an infectious agent or traumatic event such as a wound healing response, there is a period of immune resolution where the tissue is restored back to its original state.¹⁹ Cells involved in resolution of inflammation include mononuclear phagocytes and stromal cells in addition to lipid mediators such as prostaglandins that are involved.¹⁹ A recent study has shown that although the onset of acute

inflammation between older and younger adults is similar, the resolution of the inflammation is impaired in the older adults.⁴⁷ Indeed, there was reduced efferocytosis and clearance of apoptotic neutrophils by the mononuclear phagocytes during the resolution phase of the inflammatory response, which led to a failure to resolve inflammation. This was due in part to reduced expression of TIM-4, a receptor that recognizes apoptotic cells, on mononuclear phagocytes.⁴⁷ This means that acute inflammatory events are not efficiently resolved in older individuals, which could contribute to inflammaging.

Senescent cell accumulation with age

Cells entering a state of senescence experience irreversible growth arrest that occurs as a result of the irreparable cell damage, for example, DNA damage, telomere erosion, or oxidative stress.⁴⁸ Senescence is a protective process that prevents the proliferation of damaged cells and is viewed as a tumor suppressor mechanism.^{49,50} However, recent evidence suggests that senescent fibroblasts may have beneficial effects and can contribute to wound healing in the skin.⁵¹ Senescent cells are characterized by the expression of CDK4/6 cyclin inhibitor p16INK4A and/or β -galactosidase; however, this is not an exhaustive list and markers of senescence have been reviewed extensively elsewhere.⁴⁸

Aging is associated with accumulation of senescent cells throughout the body and has been shown to occur in every experimental species and organ studied to date, including mouse and primate models.⁵²⁻⁵⁵ In humans, senescent stromal cells accumulate in the skin^{56,57} and kidney⁵⁸ during aging. The cell types that have been shown to be senescent in these tissues include fibroblasts, melanocytes, and endothelial cells^{51,57,59}; however, it is predicted that every cell type in the body has the potential to become senescent. Senescent stromal cells may accumulate because of long-term exposure to DNA-damaging agents such as ultra violet B and exposure to pollutants.⁴⁸ However, a recent article⁶⁰ showed that there is reduced elimination of senescent cells during aging, which would also account for their accumulation. This reduced clearance may be due in part to the expression of HLA-E by senescent fibroblasts that bind to the inhibitory receptor NKG2A expressed on natural killer (NK) and CD8⁺ T cells. Binding of HLA-E to NKG2A results in a negative signal to the NK and CD8⁺ T cells, which inhibits their cytotoxic activity and prevents killing of the senescent fibroblasts.⁵⁷ It is possible that other inhibitory receptor/ligand pairs may also be involved in this evasion strategy that enables senescent cell persistence during aging.

Senescent cells can secrete a range of inflammatory cytokines (such as IL-1 β , IL-6, and TNF- α), chemokines (such as CCL2 and IL-8), growth factors (such as fibroblast growth factor), and matrix metalloproteinase (such as metalloproteinase 1 and metalloproteinase 3). DAMPs such as high mobility group box 1 are also secreted, contributing to the inflammatory phenotype of senescent cells.⁴⁴ This secretion of proinflammatory mediators is known as the senescence-associated secretory phenotype (SASP). Multiple components of the SASP including CCL2, transforming growth factor beta, and IL-1 α have the ability to drive senescence in a paracrine manner in nearby nonsenescent cells, thus overall increasing the number of senescent cells.⁶¹ All components of SASP contribute to the local inflammatory environment and may contribute to the inflammaging phenomenon.⁶²

Although most senescence research has focused on stromal cells in tissues, there are also populations of circulating senescent-like leukocytes that accumulate during aging.⁶³ Examples of senescent-like leukocytes include terminally differentiated CD4⁺ and CD8⁺ T effector memory cells that reexpress CD45RA. These cells have low proliferative capacity and secrete inflammatory mediators such as TNF- α , IL-1 β , IL-18, and IL-6, which is similar to SASP produced by senescent stromal cells such as fibroblasts.⁶⁴⁻⁶⁶ Terminally differentiated NK cells also accumulate during aging, and these CD16^{dim}KLRG1⁺ cells have increased inflammatory cytokine production.⁶⁷ The increase in senescent-like leukocytes in older adults that secrete a raft of inflammatory mediators is proposed to contribute to the inflammaging phenomenon.

HOW DOES INFLAMMATION INHIBIT IMMUNITY?

There are direct effects that inflammation has on immunity, such as the suppressive effect of TNF- α on T-cell receptor signalling⁶⁸ and monocyte phagocytosis.²³ There are also other mechanisms by which inflammation inhibits immunity, including increasing the expression of inhibitory receptors, increasing the number and function of Foxp3⁺ *regulatory T (Treg)* cells, and increasing monocyte infiltration of the tissue.

Increase of inhibitory ligands and receptors

There is increasing evidence that inflammaging-associated cytokines can increase the expression of inhibitory ligands on immune cells. An example of this is TNF- α , which increases the expression of programmed death ligand 1 (PDL-1) on antigen-presenting cells such as mononuclear phagocytes.⁶⁹ PDL-1 binds to programmed cell death protein-1 (PD-1), which is expressed on T cells, which leads to apoptosis of the cell. The increase in PDL-1 expression is particularly relevant because increased expression of PD-1 on T cells has been shown in the skin and peripheral blood populations of these cells in older adults, which renders them more susceptible to inhibition.²⁵

Inflammation effects on Foxp3⁺ Treg cells

Treg cells are defined by the transcription factor Foxp3, and they play an important role in maintaining immune homeostasis, because in the absence of these cells, there is widespread autoimmune and inflammatory disease that leads to early death.^{70,71} There are increased number of Foxp3⁺ Treg cells in the skin of older subjects at baseline and in response to antigens that contribute to decreased cutaneous antigen-specific immune responses during aging.^{72,73} It has been proposed that the accumulation of Foxp3⁺ Treg cells in the skin of older adults may be due to inflammatory processes because Foxp3⁺ Treg cells are recruited to sites of inflammation.⁷⁴ Interestingly, inflammaging-associated cytokines such as TNF- α can increase Foxp3⁺ Treg-cell number and induce them to become more suppressive.⁷⁵ As a result, inflammaging may induce increased numbers and function of Foxp3⁺ Treg cells that can inhibit immunity.

Senescent cells recruit inflammatory cells via SASP

One major component of the SASP is monocyte chemoattractant chemokines such as CCL2.⁵⁷ When monocytes are

recruited into tissues and exposed to inflammatory signals, they upregulate immune resolution pathways such as CD39/CD73 and PDL-1, all of which may have a role in inhibiting immunity.^{76,77} Indeed, in patients with coronary artery disease, their mononuclear phagocytes from the periphery and atherosclerotic plaques have increased expression of PDL-1, which specifically inhibits antigen-specific T cells in a PD-1-dependent manner.⁷⁶ It has been shown that there is a negative correlation between the number of monocytes recruited to a site of inflammation and cutaneous antigen-specific immunity.²⁷

Immunoregulatory SASP components

Not all components of the SASP can be considered directly inflammatory. Indeed, transforming growth factor beta, an early component of SASP,⁷⁸ has been shown to have the potential to generate Foxp3⁺ Treg cells from CD4⁺ T effector cells.⁷⁹ Another SASP component is the lipid mediator prostaglandin E2, which is a downstream of cyclooxygenase 2.^{80,81} Prostaglandin E2 can promote a more tolerogenic environment by increasing the production of the immunoregulatory cytokine IL-10 from mononuclear phagocytes as well as increasing the number and function of Foxp3⁺ Treg cells.^{82,83} In addition, prostaglandin E2 has been shown to inhibit the antigen-specific immunity by blocking the proliferation of CD8⁺ T cells in response to viral antigens.^{84,85}

THERAPEUTIC TARGETS OF INFLAMMAGING

Because of the substantial clinical data linking inflammaging with reduced immunity, health, and increased mortality in older adults, it has become a crucial therapeutic target in older adults. The current therapies for reducing inflammation that have been proposed include the removal of senescent cells and the mammalian target of rapamycin (mTOR) and p38-MAP Kinase inhibition (Fig 2).

Senescent cells

Because senescent cells are a major contributor to the inflammaging process, they are an exciting target for reducing inflammaging. Mouse models have been developed where senescent cells can be specifically removed *in vivo*, and these studies showed that these animals have increased life span, improved fitness, and reduced fur loss.^{86,87} Indeed, removal of senescent cells even after onset of age-related disorders, such as sarcopenia and cataracts, resulted in an attenuation of disease pathology.⁸⁸ As a result of these exciting murine studies, therapies to remove senescent cells with drugs termed senolytics have been an active area of research. Assessments of senescent cell behavior *in vitro* identified that antiapoptotic/prosurvival pathways such as BCL2, p53, and CDKN1A and also phosphoinositide 3-Kinase δ signaling pathways may represent specific pathways that can be targeted for their elimination.^{89,90}

Senolytics that have been tested in aged mouse models include the combination of dasatinib and quercetin that significantly reduced vascular pathologies.⁹¹ ABT263, a specific inhibitor for BCL2 and BCL-x, was used in an aged mouse model and has resulted in a rejuvenation of hematopoietic stem cells.⁹² Inhibitors of heat shock protein 90 have prevented the onset of age-related pathologies in mice.⁹³ Although all these *senolytic* agents have

been shown to significantly reduce the senescent cells in mouse models, they have yet to be translated to humans and this is an area of intense investigation.

Another potential therapeutic area is to unleash the activity of the individuals' own immune system against senescent cells. Because there are strategies that enable the evasion of senescent cells from immune surveillance, preventing this inhibitory axis would facilitate the recognition and removal of senescent cells in older adults. Because the expression of the inhibitory receptor HLA-E by the senescent fibroblasts binds to its cognate ligand, NKG2A expressed on NK and CD8⁺ T cells, and provides a negative signal to the leukocytes that prevents killing and clearance of senescent cells,⁵⁷ strategies that block the interaction between HLA-E and NKG2A would enable the NK and CD8⁺ T cells to recognize the senescent cells and to enhance senescent cell clearance *in vivo*. An anti-NKG2A mAb, monalizumab, has been developed as a check point inhibitor, and has been shown to enhance antitumor immunity via preventing the negative signaling through NKG2A, and thus enabling the NK and CD8⁺ T cells to kill tumor cells that also express HLA-E.^{94,95} It is possible that monalizumab could be used as a senolytic agent to facilitate removal of senescent cells from older adults using their own NK cells and CD8⁺ T cells; however, this requires further investigation. However, it will be important to assess the capability of older adults' NK cells to kill senescent fibroblasts, because NK cells from older adults have reduced killing capacity.⁹⁶

The mammalian target of rapamycin

mTOR is composed of 2 distinct protein complexes—mTOR complex (TORC)1 and TORC2—that are involved with numerous cellular processes including inflammation. mTOR is involved in many inflammatory processes; in particular, mTOR signaling is downstream of a number of innate immune cell receptors such as TLRs including TLR4, cytokine receptors such as IL-15, and lipid receptors such as prostaglandin receptors, all of which can increase inflammatory mediator production from cells.⁹⁷ In addition, mTOR has been shown to be a regulator of the SASP in senescent cells via promoting IL-1 α production.⁹⁸ mTOR inhibition, via rapamycin, has been shown to increase life expectancy.⁹⁹ However, more recently it has been used to improve vaccine responses in older adults *in vivo*.¹⁰⁰ Mannick et al¹⁰⁰ treated older subjects with a specific TORC1 inhibitor called RAD001 before influenza vaccination. They found that there was an enhanced response to vaccination as determined by circulating antibody titers. This improvement in vaccine response was proposed to be due to reduced expression of the inhibitory receptor PD-1 on circulating CD4⁺ and CD8⁺ T cells.¹⁰⁰ A subsequent study by the same group demonstrated that TORC1 inhibitor treatment before vaccination also significantly reduced influenza infections in older subjects.¹⁰¹ However, it is not clear whether rapamycin is acting directly on the inflammation in these subjects or some other process to enhance vaccine efficacy.

p38 MAP Kinase

p38 MAP Kinase has been shown to be a major signaling molecule upstream of SASP production from senescent fibroblasts and from CD8⁺ T effector memory cells that reexpress

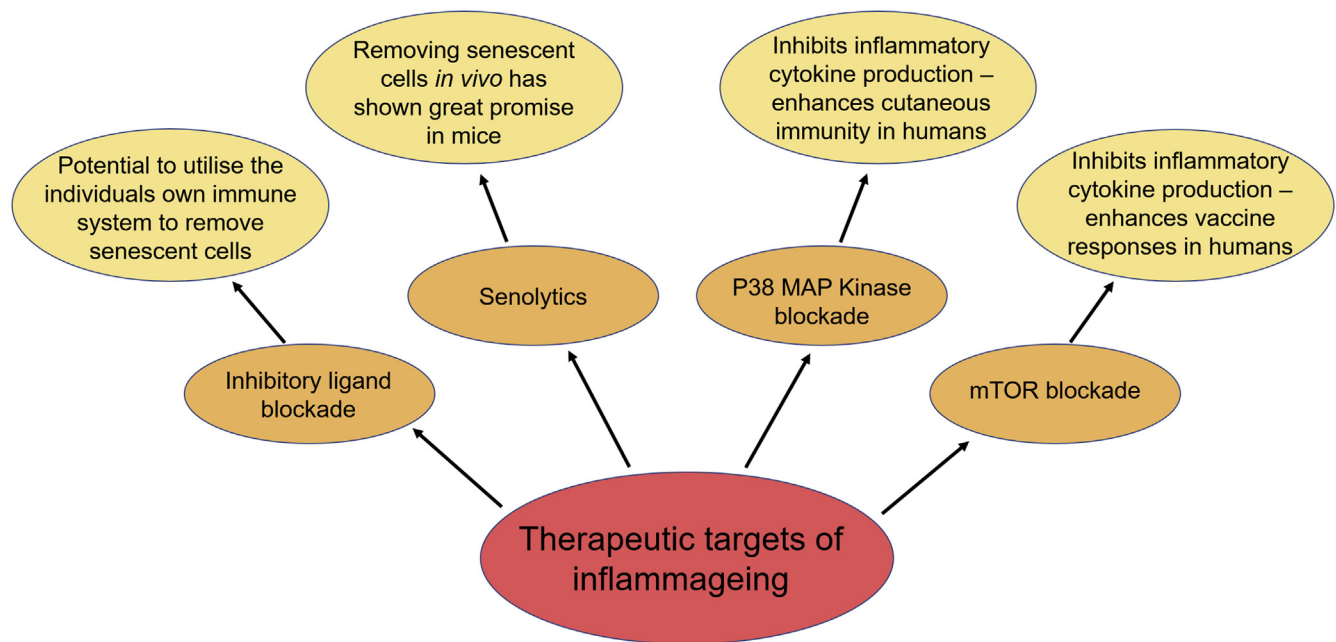


FIG 2. Schematic representation of the current therapeutic targets of inflammaging. In humans, the 2 main targets to date have been the use of mTOR blockade to enhance vaccine responses and p38 MAP Kinase blockade to enhance antigen-specific cutaneous immunity. In mouse models, senolytics have been shown to be a very promising target and are as yet untried in humans. The most untested approach is the use of inhibitory ligand blockade to enhance senescent cell clearance via the hosts' own immune system.

CD45 cells.¹⁰²⁻¹⁰⁴ It was shown that a nonspecific inflammatory response occurs after mild tissue injury after saline injection in the skin of older but not young adults and that this was associated with p38 MAP Kinase signaling.²⁷ The older subjects also have increased numbers of senescent cells in the skin compared with younger individuals. The observed inflammatory response was reminiscent of inflammaging and correlated negatively with their response to recall antigen challenge (varicella zoster virus antigens) in the skin.²⁷ To test directly whether the inflammation observed was responsible for decreasing the immune response, old subjects were pretreated with an oral p38 MAP Kinase inhibitor (losmapimod) for 4 days before injection of the antigen.¹⁰⁵ It was found that blocking p38 *in vivo* significantly increased cutaneous immunity, which was associated with an increase in T-cell recruitment to the site of antigen challenge.²⁷ Therefore, in addition to senescent cell elimination as a strategy to reduce inflammation, the inflammatory response itself can be manipulated in older individuals with benefit to immunity. It remains to be determined whether the inhibition of inflammation may also alleviate other facets of frailty during aging. However, although short-term inhibition would be acceptable, longer-term inhibition, especially with p38 MAP Kinase inhibitors, is associated with hepatotoxicity.¹⁰⁶

FUTURE PERSPECTIVES

Inflammaging is caused by a combination of age-related defects including increased DAMP production, increased gut permeability, increased visceral fat, chronic infections, and increase in senescent cell numbers. Senescent cells contribute to inflammaging because of their SASP production, which includes a wide range of inflammatory cytokines and DAMPs.

Therefore, strategies to remove the senescent cells from the body are a promising therapeutic target. There has been extensive research in mouse models to show that removal of senescent cells from an old mouse renders the mouse young again. However, what the long-term implications are for removing senescent structural cells, such as fibroblasts, from tissues when they make up a major proportion of the tissue structure needs further investigation. An exciting potential drug candidate to targeting inflammaging is metformin, which activates the AMP-activated protein kinase signaling pathway, and thus blocking inflammatory cytokine signaling has been successfully used as a long-term therapy in older adults as a first-line therapy for type 2 diabetes. It has been shown to improve cardiovascular health in these individuals.¹⁰⁷ However, strategies that target inflammatory signaling pathways using rapamycin and metformin have been used with some success, but the effect of longer-term inhibition and potential side effects are not clear at present.

Current therapies that have been developed use a short-term inhibition of inflammation to boost immunity without side effects in older individuals and may be of benefit as an adjunct to vaccination and/or antitumor therapy. A combination of approaches including 1 or more of senolytic drug, checkpoint inhibitors (anti-NKG2A), and anti-inflammatory agents may be required for optimal blocking of inflammaging to reduce frailty and enhance immunity in older adults.

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