

# Aging as an inflammatory disease and possible reversal strategies



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Acute inflammation is an essential self-limiting component of immunity to pathogens, but it can have destructive side effects on normal tissues. However, chronic inflammation may contribute to pathology after pathogen clearance by exacerbating fibrosis and scarring. This is due in part to the action of inflammatory cytokines on fibroblasts, which is necessary for wound healing after pathogen elimination. This may also occur in the absence of pathogen (known as “sterile” inflammation) due to dysregulated homeostatic processes, for example, in rheumatoid arthritis. Because some serum markers of inflammation commonly tend to be slightly higher in older adults than the usual baseline in younger adults, it has been proposed that this causes damage to normal tissues and contributes to degenerative diseases of aging. This phenomenon has been termed “Inflammaging.”<sup>1</sup> However, whether the slightly higher levels of cytokines such as IL-6 in older adults actually do cause fibrosis and tissue damage or contribute in other ways to age-associated pathologies is not proven. Possibly, increased levels of the anti-inflammatory, but profibrotic cytokine TGF- $\beta$  may be the main culprit here. Moreover, assessing biomarkers of inflammation in humans is challenging under any circumstances,<sup>2</sup> and especially in the elderly. A first conclusion to be made in attempting to answer the question of whether aging is (partly) an inflammatory disease is that we need improved means of reliably measuring markers of inflammation. How can the inflammatory state of an individual best be assessed?

Slightly raised levels of a single biomarker, usually IL-6 or C-reactive protein, in serum or plasma are often taken as surrogates of the general inflammatory state, but this is clearly unsatisfactory. Quantifying inflammatory markers in the blood under basal conditions is also likely to be less informative than changes in levels over time. This is especially true for inflammatory challenge models of which there are several in clinical use. However, these are rarely tested in older adults, for ethical and health reasons. In any case, most challenge models are poorly

standardized. Clusters of multiple parameters probably need to be assessed, and a combination thereof integrated with analysis following defined challenges. This approach would be the most informative, especially the balance between proinflammatory and anti-inflammatory factors. Clear evidence for the negative effects of “inflammaging” is required before considering interventions. But because direct experimentation is problematic in practice in older people, most studies have correlated levels of markers such as IL-6 with health status (such as frailty measures) and in the few longitudinal studies available, with mortality. Thus, the Swedish NONA study of the very old identified clusters of inflammatory parameters (high IL-6, increased neutrophils, and low albumin in the blood) associated to some extent with subsequent increased 4-year mortality rates<sup>3</sup> but without demonstrating causality and only providing quite weak associations. I think it is true to say that results of several other studies thus far have been equivocal, perhaps partly because of the difficulties in accurately measuring inflammatory status.

Nonetheless, there are still reasons to hypothesize that reducing chronic low-level inflammation, without compromising crucial acute inflammatory processes, could benefit healthspan (Fig 1). Some drugs in common use, such as cholesterol-lowering statins and the diabetes drug metformin, appear to exert anti-inflammatory effects that may result in long-term benefits; however, it will be impossible to determine whether dampening inflammation actually contributed to any such potential benefit. At least in mice, metformin does improve healthspan and lifespan,<sup>4</sup> so this may potentially be the case in humans with well-controlled diabetes as well. It therefore remains attractive to propose interventions to prevent or reverse immune dysregulation to decrease chronic inflammation and improve healthspan. In the case of statins, often used long-term by people with no overt disease, recruiting individuals matched for statin use or not might already provide some answers regarding healthspan differences. Inflammaging is at least partly attributable to dysregulated immunity, especially innate immunity.<sup>5</sup> However, the accumulation of senescent nonimmune tissue cells in older adults is likely to be responsible in large part by virtue of their “senescence-associated secretory program” (SASP), to which senescent immune cells may also make a contribution. The SASP consists of multiple chemokines and cytokines that have an overall proinflammatory effect.<sup>6</sup> Therefore, it may be more effective to eliminate senescent tissue cells or prevent their accumulation than to attempt to decrease inflammation by modulating immune cells.

These considerations raise the important question, at least for clinical trials of interventions, as to whether it is a disease that is being treated, that is, whether aging has components of or is an inflammatory disease. This is an old question now being seriously addressed by proposing to the World Health Organization that *International Classification of Diseases* codes should be introduced to allow systematic and comprehensive disease classification and staging of senescence.<sup>7</sup> Such an approach could facilitate planned

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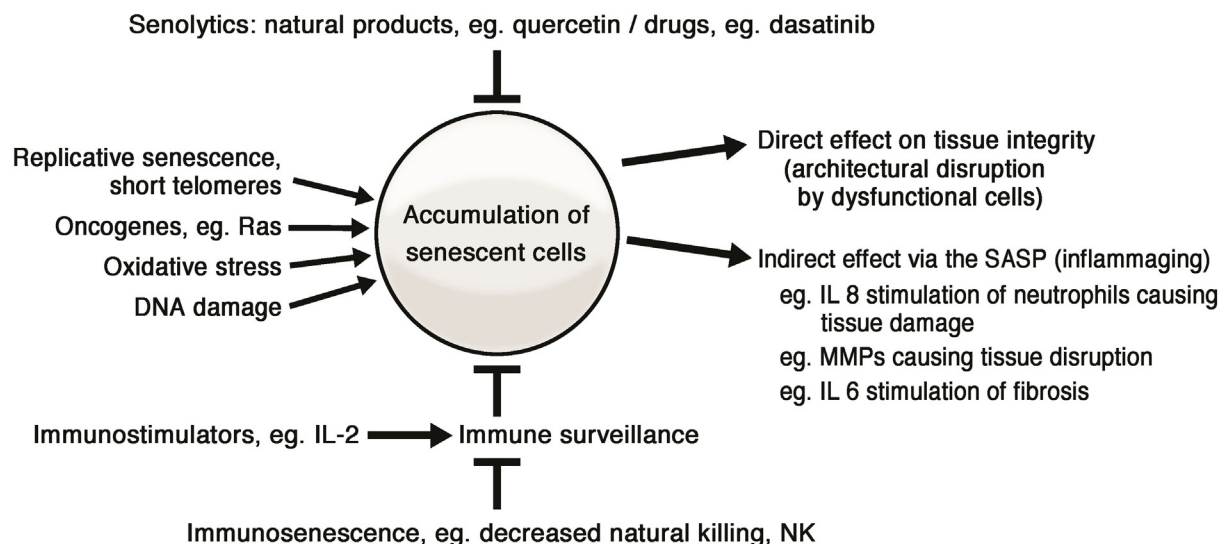
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## Hypothetical pathways for direct and indirect effects of the accumulation of senescent cells with age, and possible interventions



**FIG 1.** Hypothetical pathways for direct and indirect effects of the accumulation of senescent cells with age, and possible interventions. It is known that senescent cells accumulate with age as a result of multiple insults over time, including exposure to DNA-damaging agents, oxidative stress, oncogene activation, and many other toxic agents, or as a result of shortened telomeres after multiple divisions in the absence of telomerase (replicative senescence at the Hayflick limit). These events are viewed as tumor suppressor mechanisms, but the accumulation of such senescent cells carries a high price because they not only physically impact tissue integrity but also secrete a large range of chemokines and cytokines (the "SASP") that may damage surrounding tissue and contribute to chronic systemic inflammation. Senescent cells can be recognized and eliminated by the immune system, but this immunosurveillance may be reduced in older individuals by immunosenescence. Interventions to restore appropriate immune function would be expected to increase the capacity of the organism to eliminate senescent cells. Together with treatment with so-called senolytic agents, immune reconstitution could provide an approach to reducing systemic inflammatory mediators thought to be responsible for tissue damage caused by "inflammaging." *MMP*, Matrix metalloproteinase; *NK*, natural killer.

clinical trials of the effects of metformin, which have been stalled for several years now.<sup>8</sup> Clinical trialing of so-called senolytic agents would certainly be facilitated by recognizing the presence of excess senescent cells as a measurable parameter of a treatable disease. Removal of such cells can be beneficial in animal models,<sup>9</sup> but it is not clear whether reduced inflammation on eliminating the source of the SASP plays a major role in the outcome. This could be determined by treating the animals with senolytics and then reintroducing the SASP extrinsically. To my knowledge, this has not been done. In any event, trials of senolytic drugs in humans are only just beginning and so far are limited to serious overt disease states such as idiopathic pulmonary fibrosis<sup>10</sup> and are not being trialed in older adults without a defined disease. This again stresses the importance of the move to assign *International Classification of Diseases* codes, especially given that several senolytic agents, such as dasatinib, have been used in different approved-drug contexts at high doses for very long periods without notable negative side effects.

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