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How inflammaging diminishes adaptive immunity

Chambers et al. show that senescent skin cells in older adults provoke monocyte-dependent local inflammation in response to injury, which hampers T cell recall responses to viruses. Importantly, they further show that this phenomenon can be blocked pharmacologically to boost adaptive immunity.

Herbert Kasler and Eric Verdin

The last 150 years have seen a progressive and consistent increase of life expectancy at a rate of two years per decade, and a concomitant proportional growth of the elderly population. By 2050, the world's population aged 60 years and older is expected to total 2 billion, up from 900 million in 2015 (ref. [1]).

However, this remarkable increase in lifespan does not coincide with a commensurate increase in healthspan: that is, the period of life free from serious chronic diseases and disability. In fact, aging is associated with increased prevalence of a number of chronic conditions, coined the 'chronic diseases of aging', for which aging is the major risk factor[2]. These include among others: atherosclerosis (leading to stroke and myocardial infarction), neurodegenerative diseases (Parkinson's and Alzheimer's), type 2 diabetes mellitus, osteoarthritis, macular degeneration and glaucoma, hearing loss and many forms of cancer[2]. Importantly, aging is also associated with deep alterations in the innate and adaptive immune systems. In this issue of *Nature Aging*[3], elegant work by Chambers et al. identifies the main proximate cause of attenuated T cell responses in aged individuals as a proinflammatory population of innate monocytes, recruited from the blood by CCL2, which is secreted by senescent cells in the aged skin. These data provide significant, technically tractable approaches to enhancing adaptive immunity in aged humans.

Aging leads to a decline in adaptive immune responses with thymic atrophy, a reduction in the number of peripheral blood naïve cells and a relative increase in the frequency of memory cells. These alterations lead to increased vulnerability to infectious diseases, reactivation of latent viral infections such as the herpesvirus varicella-zoster virus (VZV; also known as chickenpox), diminished responses to vaccination and decreased cancer immunosurveillance. Aging is also associated with a chronic state of innate immune activation, called 'inflammaging',

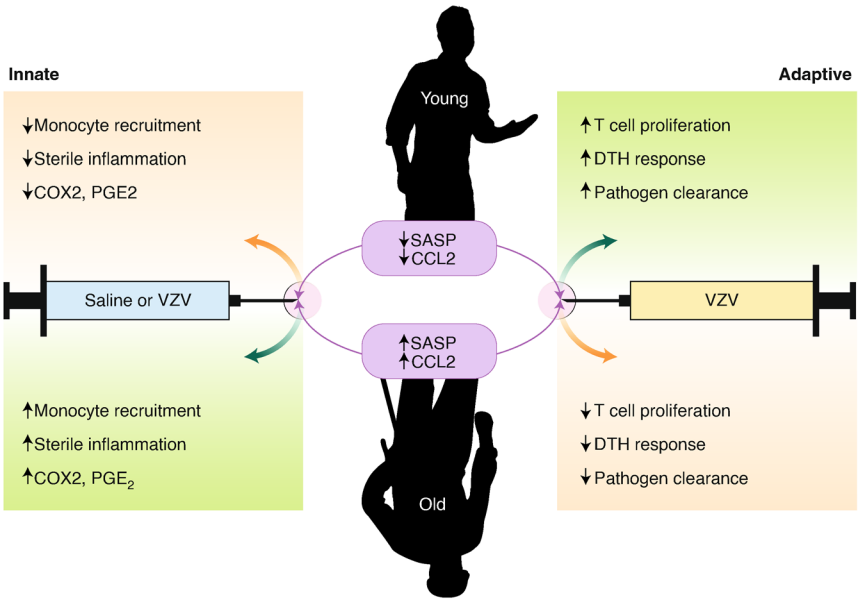

Fig. 1 | How senescence links inflammaging to impaired adaptive immunity. Innate and adaptive immune responses show opposing changes in the skin of young versus older adults. In aged individuals, the production of CCL2 in the skin by senescent cells as part of the SASP attracts monocytes from the bloodstream. These monocytes produce cyclooxygenases and prostaglandins, which inhibit the ability of T cells in the skin to respond to a challenge with the VZV vaccine. PGE_2, prostaglandin E_2; DTH, delayed-type hypersensitivity.

which contributes to the pathogenesis of the chronic immune diseases of aging[4]. The relevance of these observations has recently been highlighted by the fact that older individuals disproportionately suffer worse outcomes after COVID-19 not only because of their inability to mount an efficient adaptive immune response, but also due to their exaggerated innate response ('cytokine storm')[5]. This increased burden of disease associated with aging contributes to a significant degradation of life quality in older individuals. It also imposes a significant economic burden on aging individuals and their families and is expected to impose stark challenges to all countries in the near future to ensure that their health and social systems are able to sustain increasing healthcare costs.

Both arms of the adaptive immune system, the T and B cell responses, are required for effective immunization and acquired resistance to disease, but both arms decline with increasing age. This phenomenon goes hand-in-hand with the general increase in severity of various viral and bacterial infections in older individuals, making them especially vulnerable, even if they have been vaccinated — an observation with modern relevance as we are currently facing the COVID-19 pandemic and contemplating the vaccination of millions of older individuals. The prevailing model of why this occurs has long been centered on T cells, which undergo both an age-dependent decline in the diversity of the naïve repertoire and a progressive accumulation of less-effective memory

T cells specific to previously encountered pathogens, particularly those that cause chronic infections like herpesviruses. The combination of these two T-cell-intrinsic phenomena is clearly important in age-dependent immune decline and makes a very tidy conceptual package, but this is not necessarily the whole story.

Prior work from the Akbar group showed that VZV-specific CD4$^+$ T cells are functional in the skin of both younger and older individuals[6]. However, the VZV-specific CD4$^+$ T cells in older individuals express more of inhibitory receptor PD1 and are accompanied by more FOXP3$^+$ regulatory T cells that likely engage PD1. Vukmanovic-Stejic et al. later established that in older study volunteers, the tissue injury from injection itself caused a markedly greater recruitment of innate immune cells to the site than in younger individuals, creating a more proinflammatory cytokine environment[7]. Somewhat counterintuitively, the increased inflammation they observed in older individuals correlated with weaker rather than stronger memory T cell responses after immunization with antigens from VZV. Importantly, they also found that pretreatment of the older volunteers with an inhibitor of the inflammation-associated p38 mitogen-activated protein kinase (MAPK) reduced the recruitment of these apparently maladaptive innate immune cells to the site of injury and also enhanced their VZV-specific T cell responses.

Chambers et al. now expand significantly on that model by identifying several key cellular and molecular players involved in the cutaneous recall antigen challenge[3], a test often used as a measure of effective immunity. They further tie this maladaptive innate immune response to the well-studied, age-dependent phenomenon of cellular senescence. Using a combination of approaches, they identify the main proximate cause of attenuated T cell responses in aged individuals as a proinflammatory population of innate monocytes, recruited from the blood, that upregulate cyclooxygenases and secrete T-cell-suppressing prostaglandins. Microscopy- and flow cytometry-based experiments showed a greater accumulation of these cells in old versus young skin in one arm that was injected with saline or air, which was inversely correlated with the strength of the same volunteers' T cell responses to VZV antigens that were injected into the other arm (Fig. 1). Chambers et al. show that prostaglandin E2 inhibits CD4$^+$ T cell and resident memory T cell proliferation in vitro, and this prostaglandin is also known to promote *FOXP3* expression and regulatory T cell activity[8,9].

Importantly, they also showed that one of the main mechanisms recruiting those harmful innate immune cells to the site of injection in older individuals is elevated levels of CCL2, an immune-cell-attracting chemokine that is recognized by the receptor CCR2 on the proinflammatory monocytes. CCL2 is produced by senescent tissue fibroblasts, which are much more abundant in aged individuals. Secretion of CCL2 is part of the well-characterized, largely proinflammatory senescence-associated secretory phenotype (SASP), which has been implicated in many of the deleterious effects of chronological age, including tissue loss (sarcopenia), increased cancer incidence and a constellation of degenerative changes in different organ systems that falls under the rubric of 'inflammaging'[4]. The relationship between the accumulation of senescent cells and various deleterious inflammatory responses has given rise to efforts in both academia and industry to develop so-called senolytics: that is, compounds that selectively kill senescent cells and thus mitigate their harmful effects[10]. The study featured here speaks to an obvious new application for such compounds, perhaps even applied locally, and also identifies the CCL2–CCR2 axis as a specific pathway that may be targeted to boost the efficacy of immunization in older people.

Pertinent to the current COVID-19 pandemic, these results confirm previous observations that monocytes can suppress immune responses. Since COVID-19 outcomes significantly worsen as a function of age, it is likely that monocytes found infiltrating the lungs of patients infected with SARS-CoV-2 inhibit the adaptive arm of the immune system and the function of virus-specific T cells[5].

The observations reported in this paper also support the idea that suppression of the innate immune response by cyclooxygenase 2 (COX2) or MAPK inhibitors may boost immunity in older patients and possibly those infected with SARS-CoV-2. Recent experiments have explored the potential benefit of rapalogs (mTOR inhibitors) for the same purpose[11]. Future work in this direction will likely provide new therapeutic opportunities to improve immunity in older individuals. ❐

Herbert Kasler and Eric Verdin ✉
Buck Institute for Research on Aging, Novato, CA, USA.
✉*e-mail: everdin@buckinstitute.org*

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Competing interests

The authors declare no competing interests.