Ageing

# Blocking an inflammatory protein increases lifespan

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Mice live longer and healthier lives when a cytokine protein called IL-11 is inhibited. The findings show how researchers can move beyond broad generalizations to engage with the nuances that modulate the pace of ageing. See p.157

Viewed from a great distance, Earth appears as a pale blue dot[1]. It is only at a closer scale that interesting details emerge, such as mountains and cities. Similarly, ageing, from a distance, seems to lead to an increase in inflammatory processes, at least some of which contribute to illnesses that make old age unwelcome. To get a clear picture of how ageing and inflammation are entangled, teasing apart the specific details of this relationship will be important. On page 157, Widjaja *et al.*[2] take several steps forward in this endeavour, and, crucially, demonstrate how interventions that inhibit one node of the inflammatory nexus — the node related to the pro-inflammatory cytokine protein IL-11 — can slow the pace or extent of age-dependent changes in mice.

In normal ageing mice, Widjaja and colleagues documented increases in levels of IL-11 in the liver, muscle and white fat tissue, as well as the activation of several enzyme pathways that are linked to IL-11. Following on from these observations, the authors used several complementary approaches to evaluate the effects of modulating IL-11 signalling. These approaches included the engineered deletion of the genes that encode either a subunit of the IL-11 receptor or IL-11 itself in mice, and administration of a neutralizing antibody against IL-11 in genetically normal mice.

Compared with control mice, each mouse model with inhibited IL-11 activity exhibited signs of improved health at older ages, including better metabolic health (more lean tissue and less fat tissue), diminished production of other pro-inflammatory cytokines, less fat storage and reduced fat synthesis by the liver, and improved tolerance to glucose and responsiveness to insulin. The authors found that age-related muscle loss was decelerated and grip strength was preserved, and there was a reduction in age-dependent fibrosis (the formation of scar-like tissue).

Strikingly, mice in which *Il11* was deleted lived longer than did control mice, and administration of the anti-IL-11 antibody to genetically normal mice also extended their lifespan (Fig. 1). Because most deaths in laboratory mice are due to cancers, the lifespan results imply that IL-11 has a key role in the processes that lead to cancer at older ages in mice — and, by extension, potentially also in humans.

These discoveries raise a panoply of questions and provide some tools with which to address them. Through what cellular and

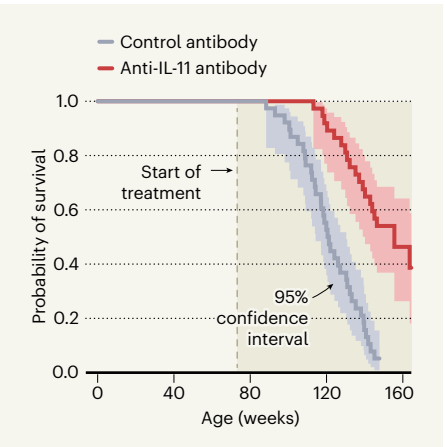


**Figure 1 | Effect on lifespan following inhibition of a pro-inflammatory protein.** Widjaja *et al.*[2] found that levels of IL-11, a cytokine involved in inflammatory signalling, increase as mice age. The authors tested the effects of blocking IL-11 activity using a neutralizing antibody. Starting from 75 weeks of age, mice were injected monthly with either an inactive control antibody or the anti-IL-11 antibody. Compared with control mice, treated mice lived longer and had fewer age-related health problems (data not shown). (Adapted from Fig. 5 of ref. 2.)

molecular interactions does an age-related increase in IL-11 promote cancer, metabolic malfunction, muscle loss and other age-dependent forms of dysfunction? What other aspects of inflammation are caused by or contribute to increases in IL-11 and IL-11-dependent pathologies at older ages? Do elevated IL-11 levels work locally in a tissue-specific way, or do they lead to systemic effects? Are there aspects of age-related disease in which the pace is unaltered in mice whose IL-11 action has been diminished? Could drugs or antibodies that inhibit IL-11 have acute or long-term benefits in humans or in mouse models of age-dependent illnesses? If so, could these approaches be used to prevent disease, or to moderate an existing illness, or both? What are the causes of age-dependent increases in IL-11 levels? Finally, do the causes of elevated IL-11 levels vary between tissues, and can such increases in IL-11 be modified therapeutically?

Researchers have developed mouse models in which ageing is delayed and lifespan is extended through single-gene mutations[3], dietary manipulations[4,5] and orally active drugs[6]. Many of these slow-ageing mice share common physiological and molecular characteristics[7], some of which — such as the increased expression of the mitochondrial protein UCP1, increases in beige fat cells in white fat tissue and alterations in the activity of the enzymes mTOR and ERK — are shown by Widjaja *et al*. to be regulated by the action of IL-11 as mice grow older.

In principle, diminished life-long IL-11 action might affect these and other related traits by changing either the levels of these characteristics throughout life or the pace at which they change with age, or both. Those traits that are altered quickly, even in young animals, by an anti-ageing intervention might be able to serve as an indicator of ageing rate[7] — that is, as instantaneous readouts of the slow-ageing state — and thus serve as useful surrogate markers for screening drugs and antibodies for possible anti-ageing effects. Widjaja and colleagues' study shows that some of the effects of diminished IL-11 action (for example, improved muscle strength) are detectable even in young mice. More information about which effects are produced quickly by IL-11 blockade will help to show the extent to which levels of IL-11 activity in early life modulate the pace of age-related change in later life.

This study also provides a model, and a spur, for moving beyond the broad, widely accepted, but non-specific, consensus that the deleterious consequences of ageing reflect 'inflammation'. Or, similarly, that they reflect the accumulation of 'senescent' cells (cells that can no longer divide) or 'epigenetic changes' as estimated by patterns of methyl-group modifications throughout the genome. It has become popular in the study of biological ageing to reify these and other vaguely defined concepts as 'hallmarks of ageing'[8]. Such pseudo-official lists of 'hallmarks' represent a kind of branding that can often block critical consideration, specification and prioritization of each hallmark lucky enough to achieve this badge of honour[9].

The designation of a broad field of enquiry as a 'hallmark' lacks sufficient cellular and molecular specificity to lead to testable hypotheses and potentially refutable claims. Are there two, ten or more varieties of senescent cell? Do they arise from different progenitors and through different influences? Do they produce disparate sets of cytokines that then exert diverse effects at local and distant age-sensitive sites? Which epigenetic changes, in which cell types, produced at which ages, lead to what age-dependent consequences? Plans to remove all senescent cells or to reverse all epigenetic changes by cellular reprogramming should be greeted with constructive scepticism rather than unbridled enthusiasm.

In the same way, the assertion that ageing is due to inflammation, coyly termed 'inflammageing'[10], should be treated not as a discovery, but as a challenge. Progress in this area might result from studies that monitor shifts in the proportions and activation levels of cell populations involved in various aspects of inflammation, such as immune cells in the spleen and lymph nodes, cytokine-producing cells in the brain, and bone-marrow stem cells. Investigating the activity of proteins such as NFκB, a transcription factor that regulates genes associated with inflammation in several cell types, might also help to advance the field. From this perspective, Widjaja and colleagues' study shows how the field of ageing research can move from a broad-brush general interest in inflammation to a more productive engagement with ways and means.

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