Inflammaging

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Old T cells pollute with mito-litter

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The mysteries behind immune aging and its related inflammation are being unmasked. Jin et al. reveal that the defective turnover of damaged mitochondria in CD4$^+$ T cells from older individuals results in the exacerbated secretion of mitochondrial DNA, which fuels inflammaging and impairs immune responses.

People make considerable efforts to recycle their waste products to prevent environmental pollution. Similarly, cells invest a lot of energy in recycling their components — however, any defect in this process could result in them littering their surroundings with molecular 'garbage'. In this issue of *Nature Aging*, Jin and colleagues[1] demonstrate a cause–effect relationship between T cell aging and inflammaging. They find that the intracellular degradation machinery of CD4$^+$ T cells becomes faulty with age, such that nondegraded products (including damaged mitochondria and their DNA (mtDNA)) are ultimately expelled to the extracellular environment, which fuels inflammaging[1]. These results shed light on new molecular targets to ameliorate inflammaging in older people.

Inflammaging is a low-grade systemic inflammatory state that is associated with aging, and is characterized by high concentrations of proinflammatory mediators (for example, TNF and IL-6) in serum. Although inflammaging has been attributed to the accumulation of senescent cells, lifelong infections or to the loss of gut barrier integrity, a series of recent articles (reviewed in ref. 2) place T cells as active contributors of inflammaging. For example, the expansion of granzyme-K-producing CD8$^+$ T cells amplifies systemic inflammation and tissue senescence[3], and mitochondrial and lysosomal stress in CD4$^+$ and CD8$^+$ T cells results in premature inflammaging that accelerates organismal senescence and aging in mice[4,5]. In support of a role for T cells as mediators of inflammaging, Jin et al.[1] demonstrate that aged CD4$^+$ T cells with a defective autophagy system drive inflammaging through the secretion of nondegraded damage products to the extracellular medium.

Cells contain a variety of mechanisms that detect, mark and eliminate intracellular molecules and organelles that are damaged or need to be recycled to ensure homeostasis. For instance, the proteasome pathway breaks down ubiquitin-labeled proteins into small peptides and the autophagy system is responsible for the turnover of intracellular components such as mitochondria, and makes use of the endolysosomal compartment to degrade them. Injured organelles are thereby sealed into autophagosomes that require processing and fusion with lysosomes, where luminal contents are degraded in an acidic environment.

The study by Jin et al.[1] indicates that the ubiquitin–proteasome and autophagy pathways regulate each other and that both are altered in old T cells. They describe that age-associated decline in TCF1 (a transcription factor related to T cell stemness[6]) enhances the expression of the gene encoding cytokine-inducible SH2-containing protein

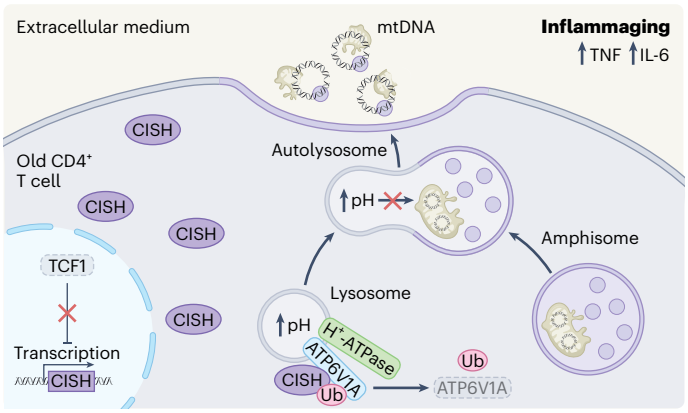

Fig. 1 | Lysosomal dysfunction in T cell aging fosters mtDNA secretion and inflammaging. The age-dependent decline in TCF1 in human CD4$^+$ T cells upregulates transcription of *CISH*, which encodes a scaffolding protein that is involved in protein ubiquitination. CISH binds to and facilitates the ubiquitin-dependent degradation of ATP6V1A (a catalytic module of the lysosomal proton (H^+) pump ATPase), leading to lysosomal dysfunction. Consequently, there is an accumulation of nondegraded cargo, including exosomes and dysfunctional mitochondria, in the endolysosomal system (that is, amphisomes); this cargo is ultimately released to the extracellular milieu, serving as source of mtDNA and correlating with inflammaging. Ub, ubiquitin.

(CISH). The study illustrates that CISH binds directly to ATP6V1A (a catalytic subunit of the lysosomal proton pump ATPase complex), which favors its ubiquitination and subsequent proteasomal degradation. Consequently, lysosomal acidification is diminished and, thus, so is its recycling function (Fig. 1). Therefore, age-related upregulation of CISH in T cells leads to lysosome dysfunction.

Jin et al.[1] reveal that the age-associated blockade of autophagy flux in human CD4$^+$ T cells expands the entire endolysosomal compartment, including the accumulation of multivesicular bodies that contain exosomes, autophagosomes, amphisomes and autolysosomes. However, the luminal contents of these bodies are not degraded, which fosters the intracellular accumulation of damaged components. Bektas et al. previously reported that CD4$^+$ T cells from older individuals exhibited an increased number of dysfunctional mitochondria in the autophagic compartment, reflecting a defect in mitochondrial recycling[7]. Accordingly, Jin and colleagues observe that, during aging, autophagy-impaired human CD4$^+$ T cells accumulate amphisomes that are charged with damaged mitochondria (Fig. 1), depicting a molecular mechanism by which lysosomal function is corrupted during T cell aging.

Then, how is this molecular garbage managed when the recycling machinery does not work properly? Jin et at. describe that aged CD4$^+$ T cells secrete amphisome-derived exosomes together with damaged mitochondrion components, increasing the concentration of extracellular mtDNA (Fig. 1). These findings fit with previously published data

from these authors that show that lysosomal dysfunction in CD4$^+$ T cells from older individuals prompted the secretion of granzyme-B-enriched exosomes with highly cytotoxic properties to neighboring cells[8]. In addition, circulating levels of mtDNA in humans increase with age in parallel with the concentration of proinflammatory cytokines[9] and, notably, Jin and colleagues[1] correlate the levels of T-cell-derived mtDNA with parameters of inflammaging. Adoptively transferring antigen-specific CD4$^+$ T cells to young, immunized mice increases serum levels of mtDNA along with concentrations of TNF and IL-6, which is prevented by silencing *CISH* in donor T cells.

Mechanistically, it is known that mtDNA is sensed as a damage-associated molecular pattern through the endosomal TLR9 or via the cytosolic cGAS–STING and NLRP3–inflammasome pathways, all of which converge on the activation of a proinflammatory program[10]. Whether mtDNA derived from old CD4$^+$ T cells is secreted naked or associated with exosomes or other types of vesicles (such as mitochondria-derived vesicles)[11] in this scenario requires further investigation. CD4$^+$ T cells can transfer mtDNA via exosomes to nearby immune cells, activating their intracellular cGAS–STING pathway[12]. mtDNA from damaged mitochondria could thereby be shuttled from old CD4$^+$ T cells to the extracellular medium and reach other bystander cells, firing the aforementioned inflammatory signaling cascades. However, it is still an open question how secreted mtDNA from aged T cells is sensed by surrounding cells to provoke inflammaging. Importantly, extracellular release of other mitochondria-derived damage-associated molecular patterns (such as cardiolipin, *N*-formyl peptides, ATP or TFAM) could also act as an immunomodulatory cue in the development of inflammaging[10].

Inflammaging underlies also defective immune responses of older people, who have a higher susceptibility to infectious and oncological diseases as well as a poor vaccination efficacy. Targeting CISH-induced lysosomal dysfunction in CD4$^+$ T cells not only attenuates premature inflammaging, but also improves antibody responses in young recipient mice subjected to a viral and noninfectious challenge. In particular, immunized mice that receive CISH-deficient CD4$^+$ T cells display an increased number of T follicular cells, which tailor T-cell-dependent antibody responses and, accordingly, an increased production of antigen-specific antibodies. Recent findings have uncovered that knocking out CISH enhances T cell antitumor activity and the susceptibility of tumors to PD-1 blockade; this is the foundation of a current human clinical trial that is testing adoptive T cell therapy for the treatment of patients with gastrointestinal cancer (NCT04426669)[13]. The results of Jin et al. suggest that *CISH* silencing could mitigate complications that derive from adoptive T cell therapy, such as inflammatory cytokine release syndrome (which is an important challenge in cancer immunotherapy). Therefore, their study could have important clinical implications for approaches that aim to boost T cell immunity while keeping inflammation at bay.

This timely piece of work reinforces the idea that old T cells with defective mitochondria have an active role in inflammaging. The defective disposal of dysfunctional mitochondria through autophagy in CD4$^+$ T cells from older individuals results in the extracellular secretion of mtDNA, fueling chronic inflammation. This research not only supports a growing body of evidence that shows an age-dependent decline in the CD4$^+$ T cell autophagy system[7,8,14], but also highlights its relevance in mitochondrial quality control and provides mechanistic insights into how old T cells accumulate dysfunctional mitochondria. Mimicking the age-related mitochondrial decline in T cells results in lysosome dysfunction and alterations in the autophagic flux[4,5]. The intimate bidirectional crosstalk between the endolysosomal system and mitochondria could thereby be exploited to rejuvenate the T cell compartment, as well as to delay inflammaging to foster healthier aging.

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Competing interests

The authors declare no competing interests.

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