Aging immunity

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Tipping the balance in CD4$^+$ T cells

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Signaling via T cell antigen receptors is diminished during aging. But paradoxically, CD4$^+$ T cells from older adults tend to differentiate into effector-like rather than memory cells. An altered balance between the activities of HELIOS, IL-2Rα, and STAT5 influences this decision.

Aging is associated with increased incidences of autoimmunity and decreased immune responses to infectious diseases and vaccines[1]. The public health importance of this observation is reflected each year in morbidities among the elderly population from seasonal influenza and, more recently, from SARS-CoV-2. Therefore, an area of emphasis in infectious disease and vaccine research is defining the cellular and molecular events that are dysregulated during aging. In this issue of *Nature Immunology*, Zhang et al.[2] approach this important topic by defining some of the molecular mechanisms that are affected by aging in human CD4$^+$ T cells.

Aging affects many aspects of the immune response, with both cell-extrinsic and cell-intrinsic factors influencing the activity of immune cells[1]. Perhaps the most well-known extrinsic factor affecting T cells during aging is the involution of the thymus, which causes diminished T cell numbers with age[3]. Inflammatory states associated with aging — often referred to as inflammaging — also have an extrinsic role in dysregulated T cell activity in older adults[4]. In addition, cell-intrinsic activities such as the diversity and signaling of T cell antigen receptors (TCRs) are diminished in old compared with young adults[3]. Notably, weak TCR signals are typically associated with the formation of memory T cells at the expense of differentiation to effector T cells in young adults[5,6], whereas diminished TCR signaling in older adults is associated instead with greater differentiation into aberrant short-lived effector cells[7]. These counterintuitive observations in older adults have been an enigma in the field and are preventing the rational design of methods to redress the balance between effector and memory CD4$^+$ T cells in older adults.

To start to address this conundrum, Zhang et al.[2] have characterized some of the transcriptional and epigenetic programs initiated by TCR activation in naive CD4$^+$ T cells isolated from young and old people. They first confirmed that TCR signaling was reduced in CD4$^+$ T cells from older compared with young adults; these cells also showed a propensity to initiate an effector-like program. These experiments validate the existing knowledge in the field, as well as the in vitro system of human CD4$^+$ T cells used in the study.

Zhang et al. hypothesized that reduced TCR signaling in older adults would translate into diminished chromatin accessibility at the genomic sites that open in response to TCR signals in CD4$^+$ T cells from young adults. However, this was not the case. Instead, the majority of chromatin accessibility changes in response to TCR activation occurred with similar efficiency in CD4$^+$ T cells from young and old adults; in fact, the changes actually appeared to be accelerated in older adults[2]. These data effectively uncouple chromatin accessibility from the diminished signals directly downstream of the TCR with age. These unexpected findings led the authors to explore additional cell-intrinsic activities that might contribute to the propensity of CD4$^+$ T cells to become short-lived effector-like cells in older adults.

Several lines of inquiry suggested that activation of the transcription factor STAT5 — downstream of signaling through interleukin-2 receptor alpha (IL-2Rα) — has a role in the age-associated changes in chromatin accessibility and transcription seen in CD4$^+$ T cells[2]. The first clue pointing to STAT5 was that the STAT5 motif was enriched in peaks with accelerated changes in chromatin accessibility in CD4$^+$ T cells isolated from old versus young adults. Zhang et al. then proceeded to show that CD4$^+$ T cells from older adults had increased *IL2RA* transcript and IL-2Rα protein expression, increased abundance of phosphorylated STAT5, and increased expression of STAT5-regulated transcription factors (Fig. 1). Notably, inhibition of IL-2Rα signaling or STAT5 activation in large part abrogated the propensity of CD4$^+$ T cells from old adults to initiate the short-lived effector program, restoring at least some of the characteristics more typical of cells from young adults[2]. Together, these experiments implicate enhanced IL-2Rα and STAT5 activity in age-associated programming changes in human CD4$^+$ T cells.

These findings raised questions about the mechanisms that regulate *IL2RA* expression during aging. In a series of experiments, the authors found that HELIOS — a member of the IKAROS transcription factor family — is responsible for this activity. First, experiments demonstrated that HELIOS expression was regulated during aging, with higher expression in CD4$^+$ T cells from young rather than old adults.

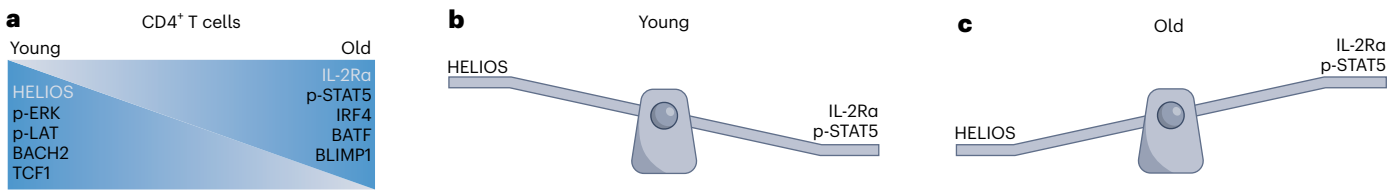

Fig. 1 | The balance between HELIOS, IL-2Rα, and STAT5 affects age-sensitive gene programming in CD4$^+$ T cells. a, Zhang et al.[2] have analyzed transcription factors and signaling pathways that are affected by aging, shown here as gradients of expression in young versus old human CD4$^+$ T cells. Gray text indicates factors with differential expression in naive CD4$^+$ T cells, and black text indicates factors that show differences after TCR activation. p-, phosphorylation. **b**,**c**, Relative balance of HELIOS and IL-2Rα expression profiles and STAT5 phosphorylation in young (**b**) and old (**c**) human CD4$^+$ T cells.

This expression pattern suggested that HELIOS, which acts as a transcriptional repressor, might directly repress *IL2RA* expression in T cells from younger adults. Second, consistent with this hypothesis, HELIOS directly associated with regulatory elements in the *IL2RA* locus and repressed the expression of this gene. Third, inhibition of HELIOS in $CD4^+$ T cells from young adults enhanced *IL2RA* expression and caused cells to initiate inflammatory potential in a synovial humanized mouse model. Collectively, the data suggest a model in which aging affects the balance between the expression of HELIOS and *IL2RA*; the activities of IL-2Rα and STAT5 in turn regulate the downstream programming potential of $CD4^+$ T cells (Fig. 1).

This intriguing new study starts to fill the gaps in our knowledge of the events that are dysregulated during aging, and suggests the complexity that would be involved in attempting to restore aspects of $CD4^+$ T cell programming in older adults. The intertwined nature of TCR and IL-2 signaling in $CD4^+$ T cell programming potential is well established[5,8], and it is interesting that both pathways are dysregulated during aging. The observation that IL-2Rα signaling is enhanced with aging, while TCR signaling is diminished, creates a unique coupling of these pathways in young and older adults. This finding suggests that the aberrant activity of $CD4^+$ T cells during aging is caused by a mixture of changes downstream of both signaling pathways, and that correcting the defects will require identification of the key dysregulated events in each. However, it is promising that Zhang et al. could restore at least some of the programming potential of aged $CD4^+$ T cells by experimentally manipulating the balance between HELIOS, IL-2Rα and STAT5. Future studies will need to define whether restoring activities downstream of TCR signaling might synergize with dampening IL-2Rα signaling.

Zhang et al.[2] carried out their study using cells isolated from human peripheral blood, with their rationale stemming from a desire to understand how aging affects the responses of human $CD4^+$ T cells. This topic is crucially important for controlling infectious diseases in the aging human population. Although mouse models are extremely valuable tools, differences between the species have been noted in mechanistic and aging research[9,10], making it necessary to carry out these studies in people. Human studies always have caveats, including genetic diversity between individuals, limited access to tissue-resident immune cells, and wide variability in the infectious disease and general medical histories of different people. Therefore, in future studies it will be interesting to see whether any of these variables contributes to the regulation of TCR and IL-2Rα signaling balances during aging, and, if so, whether they might contribute to differences in health outcomes within human populations.

Another topic for future research will be to determine whether the HELIOS, IL-2Rα, and STAT5 balance is affected by aging in other immune-cell populations. This balance does not appear to be involved in the context of aging in regulatory $CD4^+$ T cells[2]. Yet mechanisms are often conserved across diverse immune-cell types, with cells frequently sharing similar mechanistic principles in their gene-programming potential[8,11,12]. Therefore, it will be interesting to define the expression profiles for these factors in a variety of young and old immune cells, and to determine how this affects gene programming in unique cell populations. Overall, the findings of Zhang et al. have opened new mechanistic directions to explore in the pursuit to understand the events that contribute to age-associated changes in human immune-cell differentiation and function.

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Competing interests

The author declares no competing interests.