Cytotoxic CD4$^+$ T cells support age-associated myelopoiesis

Aging is associated with myeloid-biased hematopoiesis, which leads to the establishment of a pro-inflammatory microenvironment. We discovered that cytotoxic CD4$^+$ T cells foster this process via the CCL5–CCR5 axis and found that the clinically approved CCR5 antagonist maraviroc can rebalance immunity in aged mice.

This is a summary of:
Gabandé-Rodríguez, E. et al. Cytotoxic CD4$^+$ T cells induce age-associated myelopoiesis through CCL5–CCR5 signaling. *Nat. Aging* https://doi.org/10.1038/s43587-026-01209-9 (2026).

E.G.-R., G.S.-H. and M.M. used ChatGPT to help prepare their contribution to this Research Briefing.

Published online: 18 September 2026

The problem

As we age, the neutrophil-to-lymphocyte ratio (NLR) progressively increases, reflecting a shift in the balance between innate and adaptive immunity. NLR is a powerful and easy-to-measure indicator of immune health, and a high NLR predicts mortality in a plethora of human conditions[1]. These changes in circulating immune cells are rooted in profound changes within the bone marrow. With age, the balance between lymphoid and myeloid progenitors is gradually disrupted, favoring the production of myeloid cells at the expense of lymphoid cells.

Inspired by previous studies showing that T cells accumulate in the bone marrow under stressful conditions[2,3], we asked whether aging might similarly promote the accumulation of T cells in this tissue. This question led us to explore whether T cells in the aged bone marrow have an active role in driving hematopoietic remodeling and, ultimately, immune aging.

The discovery

Using spectral flow cytometry, we identified a distinct T cell population that preferentially accumulates in the bone marrow of aged mice. These cells were characterized by high expression of the chemokine CCL5 and the transcription factor EOMES, resembling a cell population previously described as CD4$^+$ cytotoxic T lymphocytes (CD4$^+$ CTLs) (Fig. 1a). Notably, CD4$^+$ CTLs are highly enriched in the blood of supercentenarians and have been proposed to have a protective role in healthy aging[4,5]. To define the mechanisms underlying CCL5 expression in CD4$^+$ T cells, we combined genetic and pharmacological approaches and found that accumulation of mitochondrial stress and cytosolic DNA leads to activation of the STING pathway in CD4$^+$ T cells from aged mice. STING activation in turn contributes to CCL5 expression. Notably, CCR5, the main receptor for CCL5, was markedly upregulated in aged hematopoietic stem cells. We generated mixed bone-marrow chimeras harboring wild-type and CCR5-deficient hematopoietic progenitors. Adoptive transfer of aged CD4$^+$ T cells into these mice demonstrated that T cells promote myeloid-biased hematopoiesis through the CCL5–CCR5 axis.

Next, we treated aged mice with maraviroc, a CCR5 antagonist that is approved for clinical use in individuals infected with human immunodeficiency virus (HIV). Treatment with maraviroc reduced myelopoiesis and the percentages of circulating neutrophils in aged, but not in young, mice. Compared with mice of the control group, aged mice receiving maraviroc showed NLR normalization, along with a decrease in circulating pro-inflammatory mediators and aging biomarkers. Maraviroc also reduced the numbers of tissue-infiltrating neutrophils and improved functional outcomes, including muscle strength and locomotor coordination, in aged mice (Fig. 1b).

The implications

Our findings suggest that age-associated changes in adaptive immune cells might actively promote innate immune activation, perhaps as a compensatory mechanism. Specifically, interactions between aged CD4$^+$ T cells and hematopoietic stem cells can alter the hematopoietic output and promote myelopoiesis, potentially contributing to chronic innate immune activation. In addition, our results suggest that this process can be reversed by maraviroc, a CCR5 antagonist that is already approved for use in the clinic.

Nevertheless, these findings should be interpreted with caution given three intrinsic limitations of our study. First, our experiments were performed in mice, which differ substantially from humans in terms of circulating immune cell composition. Second, our study does not exclude the possibility that cellular sources of CCL5 other than CD4$^+$ CTLs also contribute to age-associated myelopoiesis. Third, the beneficial effects of maraviroc on aging-associated phenotypes might involve mechanisms beyond rebalancing hematopoiesis, including direct inhibition of CCR5 signaling in peripheral organs.

Future research will determine whether our identified molecular mechanism is conserved in humans and whether pharmacological inhibition of CCR5 might be beneficial in specific age-associated diseases. In view of the potential broad effects of maraviroc, whether treatments that specifically target myelopoiesis can promote protection in age-associated diseases remains an open question.

Enrique Gabandé-Rodríguez, Gonzalo Soto-Heredero & María Mittelbrunn
Centro de Biologia Molecular Severo Ochoa, Madrid, Spain.

EXPERT OPINION

"Gabandé-Rodríguez et al. describe a previously unrecognized mechanism driving enhanced myelopoiesis during aging, through cytotoxic T cells that recirculate to the bone marrow and overproduce CCL5, thereby skewing hematopoiesis towards myelopoiesis and granulopoiesis. This mechanism can be blocked through the CCL5 receptor CCR5, which can rejuvenate some features in aged mice. These are very exciting findings and are overall well supported." **Simon Mendez-Ferrer, University of Cambridge, Cambridge, UK.**

FIGURE

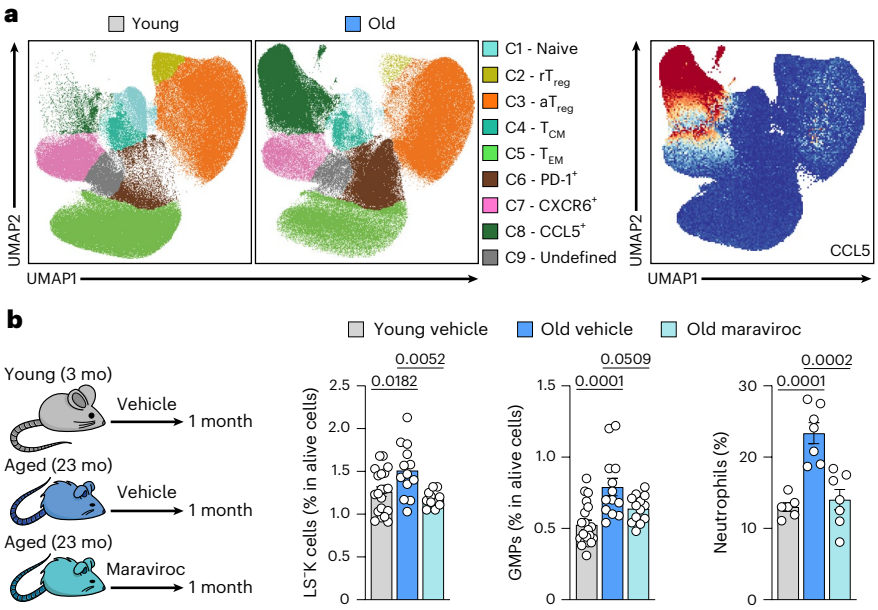

Fig. 1 | Targeting the CCL5–CCR5 axis ameliorates age-associated hematopoietic dysfunction associated with cytotoxic CD4$^+$ T cell accumulation. **a**, Bone marrow profiling of young (3-month-old) and aged (24-month-old) mice revealed an accumulation of CCL5-expressing cytotoxic CD4$^+$ T cells with age. UMAP, uniform manifold approximation and projection. **b**, Treatment of aged (23-month- old) mice with the CCR5 antagonist maraviroc for 1 month reduced age-associated myeloid skewing and circulating neutrophil levels. LS$^-$K, Lin$^-$Sca-1$^-$c-Kit$^+$; GMP, granulocyte–monocyte progenitor; rT$_{reg}$, resting regulatory T cells; aT$_{reg}$, activated regulatory T cells; T$_{CM}$, central memory T cells; T$_{EM}$, effector memory T cells.

BEHIND THE PAPER

This journey began almost 6 years ago, inspired by findings linking a high NLR with age-associated diseases and mortality, as well as with skewed differentiation of hematopoietic progenitors in the aged bone marrow[1]. Our longstanding interest in T cells, together with excellent work by former members of our lab and other groups, set the stage for a long journey of effort and resilience during which we explored a still poorly characterized subset, the cytotoxic CD4$^+$ T cells, and their role in driving age-associated myelopoiesis.

A major challenge throughout this research was the intrinsic difficulty of working with aged mice. Their long lifespan limits the availability of experimental cohorts, especially when they involve the generation of new genetically modified mouse models. Thus, not all mechanistic questions can be addressed within the tight time constraints of a research project. This challenge was compounded by the narrow deadlines of funding programs designed to support early-career researchers. As a result, pursuing mechanistic questions in aged animals required considerable patience, persistence and resilience. In this landscape, we are deeply grateful for the inspiring work that preceded ours and to all the members of our lab and our families for their crucial support throughout the sometimes stressful journey of bringing this paper to publication. **E.G.-R., G.S.-H. & M.M.**

REFERENCES

1. Pellegrino, R. et al. Neutrophil, lymphocyte count, and neutrophil to lymphocyte ratio predict multimorbidity and mortality—results from the Baltimore Longitudinal Study on Aging follow-up study. *Geroscience* **46**, 3047–3059 (2024). **This paper reports that NLR is a predictor of all-cause mortality and multimorbidity based on a cohort of 1,769 aged participants.**
2. Chongsathidkiet, P. et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat. Med.* **24**, 1459–1468 (2018). **This paper reports sequestration of CD4$^+$ T cells into the bone marrow of humans and mice with intracranial tumors.**
3. Shi, K. et al. Bone marrow hematopoiesis drives multiple sclerosis progression. *Cell* **185**, 2234–2247 (2022). **This paper reports that autoreactive CD4$^+$ T cells drive myelopoiesis during autoimmune neuroinflammation by secreting CCL5.**
4. Hashimoto, K. et al. CD4 CTLs in supercentenarians: signs of adaptive expansion in healthy aging. *Cell Rep.* https://doi.org/10.1016/j.celrep.2026.117728 (2026). **This paper shows that CD4$^+$ CTLs expand in supercentenarians owing to persistent exposure to tumor antigens, potentially contributing to longevity through cancer suppression.**
5. Hasegawa, T. et al. Cytotoxic CD4$^+$ T cells eliminate senescent cells by targeting cytomegalovirus antigen. *Cell* **186**, 1417–1431 (2023). **This paper shows that senescent cells in the human skin upregulate HLA-II and human cytomegalovirus glycoprotein B, becoming targets of cytotoxic CD4$^+$ T cells.**

FROM THE EDITOR

"The reshaping of both adaptive and innate immunity during aging has important systemic consequences. The mechanism identified in this work sheds light on the deleterious interplay between these arms during aging by linking cytotoxic CD4$^+$ T cell accumulation to enhanced myelopoiesis, as well as showing it is pharmacologically modifiable, improving readouts of healthspan in old mice." **Hannah Walters, Senior Editor, *Nature Aging*.**