BRAIN AGING

Unwanted help from T cells in the aging central nervous system

Groh and colleagues investigate the age-related degeneration of axons in the optic nerve and other brain regions and show that at least part of this degeneration is due to the presence of T cells.

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Vision worsens during aging. Trees in the distance appear blurry; our arms cannot extend far enough to allow us to read small prints; the need for glasses often becomes unavoidable. Vision deterioration occurs even in the absence of eye diseases such as glaucoma or macular degeneration. Some of this decline is purely optic — reduced flexibility of the eye's lens — but some of it reflects changes in the neuronal ability to communicate visual information to the brain[1]. An unexpected finding from a new *Nature Aging* study by Groh and colleagues[2] is that intrusive immune T cells are partly responsible for vision defects and cognitive decline during aging. While the brain has been mostly regarded as an immunoprotected region secluded behind the blood–brain barrier, mounting evidence suggests that the interplay between the nervous and immune system is broader than previously thought. Recent work has described a diverse repertoire of innate and adaptive immune populations not only within the borders of the central nervous system, such as the meninges, but also inside the brain parenchyma[3–5]. Groh and colleagues find that during normal aging, T cells accumulate in brain areas rich in myelinated axons, including the optic nerve, and that these T cells are mediating structural and functional decline during aging.

The visual system is a well-studied region of the brain that shows striking changes with age, including axon number decrease, axon dystrophy and retinal decline[6]. In their study, Groh et al. first characterized the degeneration in the axon–myelin unit in mice during aging and found a significant decline in the number of axons in aged optic nerves and an increase in damaged axons. Intriguingly, the authors observed a strong temporal and spatial correlation between these axonal defects and the recruitment of cytotoxic (CD8$^+$) T cells to damaged axons in optic nerves and other white matter regions of the brain, such as the corpus callosum and the cerebellar white matter. This was accompanied by a concomitant reduction in cognitive and motor performance in old mice (24 months of age). Visual acuity, however, only declined later (28 months of age), suggesting that compensatory mechanisms maintain visual acuity in the presence of neural damage in the optic nerve.

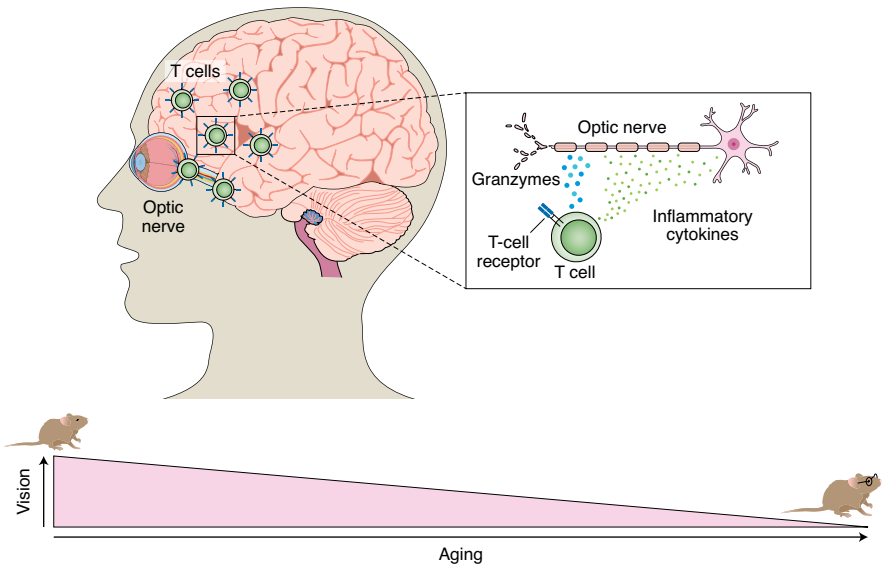

Fig. 1 | Infiltrating cytotoxic CD8$^+$ T cells contribute to axon degeneration in the aging central nervous system in mice. The study by Groh et al. suggests two possible mechanisms contributing to the damage inflicted by T cells in the aged central nervous system: direct antigen recognition followed by T-cell-mediated cell death and secretion of inflammatory cytokines leading to cytotoxicity (inset). Such damage may play a role in the loss of visual acuity associated with aging in mice and may also be relevant to humans.

To investigate the role of these infiltrating T cells, the authors used mice lacking mature B and T cells (*Rag1*$^{-/-}$) and showed that aged *Rag1*$^{-/-}$ mice exhibit less axon damage and better performance in cognitive and motor tests. Replenishing missing T cells in old *Rag1*$^{-/-}$ mice by transplanting bone marrow from wild-type mice, but not from CD8-deficient mice, was sufficient to restore the neuronal damage and motor phenotypes. These results suggest that cytotoxic CD8$^+$ T cells are key players that negatively impact the central nervous system with age.

What is the mechanism by which T cells induce a neuronal damage phenotype? The canonical role of CD8$^+$ T cells is to induce cytotoxicity upon antigen presentation by target cells. But T cells also secrete inflammatory cytokines. To distinguish between these possibilities, the authors performed additional bone marrow transplant experiments. Replenishing the T-cell reservoir with T cells lacking granzyme B (key for cytotoxicity) or with T cells that only recognize a unique, unrelated antigen was not sufficient to

cause neuronal damage or motor defects. These results indicate that both the cytotoxic activity of CD8⁺ T cells and their antigen specificity are required for the damaging effects of T cells on the aging central nervous system. Interestingly, inducing systemic inflammation via lipopolysaccharide injection led to impaired visual acuity in old wild-type mice but not in old mice lacking CD8⁺ T cells. This suggests that T cells play a key role in mediating the ability of inflammation to trigger the decline of the visual system with age. Hence, several T-cell properties likely contribute to the various damaging effects of these immune cells on the old brain, notably the visual system (Fig. 1).

Overall, this study shows that CD8⁺ T cells play an important role in the decline of the central nervous system during aging. The mechanism responsible for the recruitment of T cells to the brain, and the optic nerve in particular, remains to be determined. The authors' experiments suggest that antigen specificity is important for inducing damage but not for the recruitment of T cells to the optic nerve. T cells may be able to infiltrate the aged brain as a result of a damaged or more leaky blood–brain barrier[7,8]. Circulating T cells may be recruited from the dural sinuses (the veins draining the brain) into the meninges, where brain-derived antigens are presented to T cells[9]. It is possible that once T cells are activated by these antigens in the meninges, they infiltrate the brain and migrate to specific regions presenting these target antigens, such as the optic nerve and other myelin-rich regions.

Antigen recognition and granzyme B both appear to be critical for the general damage induced by T cells. It will be key to determine exactly which cells or structures are attacked in the optic nerve. As this region mostly consists of axons, which show aberrant structures with age, a tantalizing possibility is that T cells are attacking axons directly. T cells could also be contributing to neuronal damage by secreting inflammatory cytokines. Interferon gamma has been shown to have deleterious effects in some regions of the brain, such as regenerative stem cell niches[3,10], during aging. It will be interesting to examine whether interferon and other inflammatory cytokines can directly induce deleterious effects on axons in the optic nerve or whether these cytokines could impact the glial cells residing in this region, which may, in turn, affect axons.

Other important questions that remain to be addressed are what antigens are T cells recognizing in the optic nerve, and are they are specific? The higher prevalence of T cells in myelin-rich areas of the brain suggests that these T cells could be attracted to myelin self-antigens, reminiscent of the damaging T cells found in multiple sclerosis[11]. An indication that T cells have recognized a specific antigen is their clonal expansion and expression of checkpoint inhibitors. Other studies have revealed clonally expanded CD8⁺ T cells expressing the checkpoint inhibitor PD-1 in old mouse brain[3] and other tissues[12], as well as in the cerebral spinal fluid of old humans (with or without Alzheimer's disease)[13]. In their study, Groh and colleagues performed single-cell RNA sequencing of CD8⁺ T cells isolated from the entire brain of old mice and showed an increase with age of CD8⁺ T cells expressing inhibitory checkpoint molecules, such as LAG3 and PD-1, corroborating that T cells in old tissues are exposed to antigens. The authors also observed an increase in the number of CD8⁺LAG3⁺ T cells in the frontal white matter of older human individuals, suggesting that their findings may be of clinical relevance. In the future, it will be exciting to characterize T-cell clonality in the visual system and compare these T cells to those from other brain regions, or even other tissues in old individuals. This type of analysis should reveal whether T cells target specific cells and structures in the optic nerve or whether they more generally recognize self-antigens.

T cells have been found to be deleterious not only in the context of aging but also in specific diseases affecting the nervous system, such as neurodegenerative diseases[13] and multiple sclerosis[11,14]. It will be interesting to compare T-cell clonality and subtypes in healthy aged optic nerves to those from patients with eye disease, such as glaucoma or macular degeneration, as well as other brain diseases. It is possible that T cells present in physiologically old brains are precursors for T cells in disease. Understanding whether the same type of T cells could give rise to diverse diseases in different contexts will have important implications to identify new therapeutic strategies, including immune-based ones, to counter age-dependent diseases.

Finally, not all T cells may be detrimental — some T cells could have neuroprotective roles[15]. In the context of multiple sclerosis, clonally expanded CD8⁺ T cells can be protective as they suppress the proliferation of myelin-specific CD4⁺ T cells[14]. In their single-cell RNA-sequencing data, Groh and colleagues find an age-related increase in the number of many CD8⁺ T-cell subgroups, some of which could be protective. This protective action could be direct by removing abnormal cells or indirect by suppressing CD4⁺ T cells. However, the role of CD4⁺ T cells in the brain and optic nerve during aging remains unknown. Future work will help to determine the roles of different T-cell subtypes during aging and the interplay between CD8⁺ and CD4⁺ T cells in the aged central nervous system.

Groh and colleagues' work adds to a growing body of evidence that points to an unsuspected interaction between the immune and nervous systems. Targeting T cells in older adults might mitigate the age-related decline in brain structure and function, and may help delay the need for glasses as we age. ❐

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Competing interests

The authors declare no competing interests.