These autologous T cell–tumour organoid co-cultures were then used to assess T cell-mediated tumour destruction. By quantifying the number of live tumour cells by flow cytometry and using a probe for caspase activation, the authors showed that co-culture with autologous T cells results in increased apoptosis and decreased size of tumour organoids, but not autologous healthy organoids.

The ability to establish tumour organoids from small amounts of biopsy tissue and to expand tumour-specific $CD8^+$ T cells from peripheral blood (rather than requiring the isolation of tumour-infiltrating lymphocytes) provides a minimally invasive method to study patient-specific immune responses and sensitivity to various therapies. It might also enable the unbiased generation of a personalized T cell product for adoptive cell therapy.

Kirsty Minton

ORIGINAL ARTICLE Dijkstra, K. K. et al. Generation of tumor-reactive T cells by co-culture of peripheral blood lymphocytes and tumor organoids. *Cell* https://doi.org/10.1016/j.cell.2018.07.009 (2018)

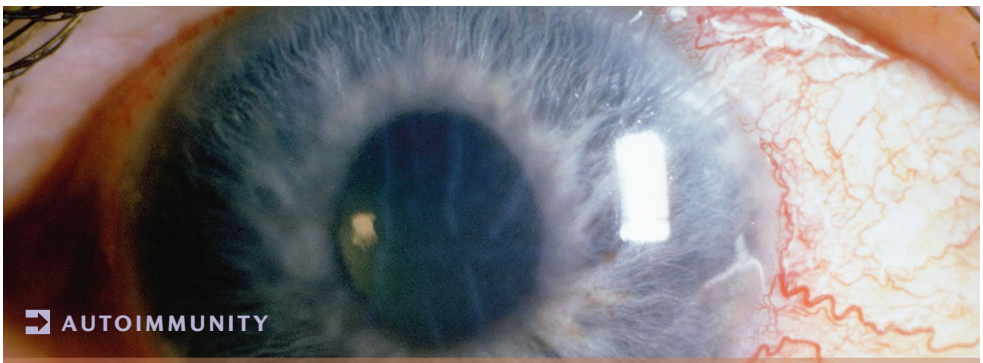
IL-17 and IFNγ responses following allergen challenge were also reduced by the absence of *Pad4*, together supporting a role for cytoplasts in promoting neutrophilic lung inflammation.

Studies using in vitro cultures indicated that cytoplasts were more efficient than neutrophils at promoting dendritic cell (DC)-induced T_H17 cell differentiation. This effect required direct contact between cytoplasts and DCs, as it was not maintained in a transwell culture system.

Finally, of relevance to human disease, DNA and hypercitrullinated histones were detected in BALF from a subset of individuals with severe asthma associated with higher neutrophil counts. Moreover, BALF cytoplasts and neutrophils positively correlated with BALF IL-17 levels, suggesting that cytoplasts promote T_H17 cell responses to propagate lung neutrophilia in some patients with asthma.

Lucy Bird

ORIGINAL ARTICLE Krishnamoorthy, N. et al. Neutrophil cytoplasts induce T_H17 differentiation and skew inflammation toward neutrophilia in severe asthma. *Sci. Immunol.* **3**, eaao4747 (2018)



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AUTOIMMUNITY

Bacteria-primed T cells identified as culprit in glaucoma

Glaucoma is characterized by the progressive degeneration of retinal ganglion cells (RGCs), leading to blindness. The most prominent risk factor is elevated intraocular pressure (IOP), but an autoimmune component to disease pathology has long been suspected. Now, reporting in *Nature Communications*, Chen et al. show that a transient elevation in IOP can induce infiltration of autoreactive T cells into the retina and demonstrate that these T cells are pre-sensitized by the commensal microflora.

The authors used a mouse model in which glaucoma is induced by microbead injection into the eye, which induces a temporary elevation in IOP, as well as mice that develop glaucoma in response to a spontaneous elevation of their IOP. In both models, they found that the elevation of IOP was followed by degeneration of axons and RGCs and an infiltration of the RGC layer by interferon-γ-secreting $CD4^+$ T cells.

Neurodegeneration appeared to occur in two stages: the acute initial phase (lasting approximately 2 weeks) during which the IOP is elevated and RGCs and axons are damaged, likely by physical stress, and a prolonged (progressive) phase during which the IOP is back to normal but loss of RGCs and axons continues (weeks 2-8).

In order to investigate the role of immune cells in this process, the authors subjected mice deficient in αβ T cells (*TCRβ*$^{-/-}$ mice), B cells (*Igh6*$^{-/-}$ mice) or both (*Rag1*$^{-/-}$ mice) to microbead injection. An initial phase of axon and RGC degeneration was observed in all mice, but mice lacking T cells did not experience the progressive phase of neurodegeneration. Adoptive transfer experiments confirmed a causal role of $CD4^+$ T cells: microbead-treated *Rag1*$^{-/-}$ mice that received $CD4^+$ cells from glaucomatous mice had progressive degeneration of their RGCs. $CD4^+$ T cells from non-glaucomatous mice, or injection of total IgG from glaucomatous mice, did not have the same effect — indicating that the progressive phase of neurodegeneration is mediated by conditioned $CD4^+$ T cells.

Next, the authors sought to identify the autoantigens recognized by the $CD4^+$ T cells. Previous studies had implicated the heat shock proteins HSP27 and HSP60 as potential antigens. Indeed, these proteins were found to be upregulated on RGCs in response to elevated IOP, and significantly higher levels of serum HSP27-specific autoantibodies were found in mice that had experienced elevated IOP compared to mice that had not. Further assays confirmed increased levels of HSP27-specific $CD4^+$ T cells in mice after IOP elevation. These cells appeared to accumulate in the retina and mediate the prolonged phase of neurodegeneration.

The authors then asked how T cell responses to HSPs are induced by IOP elevation. As HSPs are highly conserved from bacteria to humans, they hypothesized that mice may harbour HSP-specific memory T cells that were originally induced by commensal bacteria. Indeed, they found that mice housed under germ-free conditions do not experience any neurodegeneration after microbead injection into the eye or in response to a spontaneous elevation of IOP.

Collectively, these results suggest that glaucoma is caused by bacteria-primed $CD4^+$ T cells that enter the eyes after the blood–retina barrier is compromised through pressure and cause neurodegeneration by cross-reacting with HSP-expressing RGCs. The authors found that patients with open-angle or normal tension glaucoma also have increased frequencies of HSP27-specific and HSP60-specific T cells, indicating that these findings are likely to be of human relevance.

Alexandra Flemming

ORIGINAL ARTICLE Chen, H. et al. Commensal microflora-induced T cell responses mediate progressive neurodegeneration in glaucoma. *Nat. Commun.* **9**, 3209 (2018)