A role for IL-17 in age-related macular degeneration

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In a recent article¹, Ambati and colleagues discussed the immunological aspects of age-related macular degeneration (AMD) pathogenesis and inflammation-directed therapeutics to treat AMD.

Based on the current literature and evidence, they deliberated that AMD could be caused by various factors, such as immune-mediated retinal damage (for example, interleukin-1 β (IL-1 β), IL-6 and IL-18), the pro-inflammatory components of drusen (for example, β -amyloid), complement activation (for example, C1q, C3 and C5 activation), proliferative angiogenic responses causing neovascularization (for example, IL-1 β , IL-6, tumour necrosis factor (TNF) and vascular endothelial growth factor A (VEGFA)), and geographic atrophy caused by prolonged VEGFA-specific antibody therapy¹. However, we would like to add that the IL-17 signalling pathway is also likely to be important in the pathogenesis of AMD.

IL-17 is a signature cytokine of the T helper 17 (T_H17) cell subset and has a crucial role in promoting inflammation in various autoimmune and inflammatory diseases². In addition to T_H17 cells, $\gamma\delta$ T cells and innate lymphoid cells (ILCs) also produce IL-17. Recently, several reports have demonstrated the involvement of IL-17 in the pathogenic inflammation of AMD^{3–5}. Liu *et al.*³ reported that complement component 5a (C5a) is increased in the circulation of AMD patients and that it promotes IL-17 and IL-22 expression by human CD4⁺ T cells. These authors found significantly elevated levels of IL-17 and IL-22 in patients with AMD compared with control individuals who did not have AMD. Furthermore, in laser-induced experimental choroidal neovascularization — which has characteristic features of AMD — Hasegawa *et al.*⁴ showed that IL-17 has a strong potential for stimulating neovascularization in a VEGF-independent manner. Importantly, the authors reported that $\gamma\delta$ T cells and THY1⁺ ILCs, but not T_H17 cells, were the relevant source of IL-17. In line with the findings of Liu *et al.*³, IL-1 β in

combination with high-mobility group box 1 (HMGB1) induced IL-17 production by $\gamma\delta$ T cells. Tuo *et al.*⁵ demonstrated that intravitreal administration of recombinant TNF-inducible gene 6 protein (TSG6) could stabilize retinal lesions in mice that are deficient in both CC-chemokine ligand 2 (CCL2) and CX₃C-chemokine receptor 1 (CX₃CR1) by modulating the expression of several ocular immunological genes and, in particular, *Il17a*. IL-17 is also known to promote VEGF-mediated angiogenesis by enhancing VEGF-induced growth of vascular endothelial cells⁶.

All of these reports point towards the possibility that IL-17 could be involved in the pathogenesis of AMD by promoting retinal angiogenesis and neovascularization. Therefore, as a proof-of-concept, IL-17-targeted therapies could be explored, at least in experimental models.

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Competing interests statement

The authors declare no competing financial interests.