INNATE IMMUNITY

The NLRP3 inflammasome — a good site for sore eyes

A recent study in *Nature Medicine* has described a beneficial role for inflammasomes in the injured eye, showing that activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome has protective effects in a mouse model of age-related macular degeneration (AMD).

AMD is the main cause of vision loss in the elderly and is characterized by the accumulation of extracellular protein aggregates — known as drusen deposits — between the retina and choroid of the eye. This 'dry' form of AMD can further progress to a more severe 'wet' form, in which neovascularization of the choroid leads to blindness. As particulate materials are known to activate the inflammasome, the authors hypothesized that drusen might show similar properties. They found that drusen isolated from patients with AMD could drive the cleavage of procaspase 1 and the production of active interleukin-1β (IL-1β) and IL-18 — the classical hallmarks of inflammasome activation — in human and mouse leukocytes. *In vitro* treatment with drusen promoted IL-1β production in lipopolysaccharide (LPS)-primed myeloid cells from wild-type mice. However, LPS-primed NLRP3-deficient myeloid cells did not produce IL-1β in response to drusen, indicating that drusen triggers pro-inflammatory cytokine production via the NLRP3 inflammasome.

> "a beneficial role for inflammasomes in the injured eye"

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The authors next explored whether any specific components of drusen are especially important for inflammasome activation. They found that carboxyethylpyrrole (CEP) protein adducts — which arise due to oxidative stress and are abundant in the drusen and serum of patients with AMD — could prime mouse macrophages for inflammasome activation in a Toll-like receptor 2-dependent manner. Furthermore, complement component C1q, which is also found in drusen, promoted IL-1β production by primed wild-type macrophages, but not by primed NLRP3-deficient macrophages. Thus, host-derived proteins that accumulate in drusen can prime and activate the NLRP3 inflammasome.

To assess the physiological relevance of inflammasome activation in the injured eye, the authors used mouse models of AMD. In a model of dry AMD, which was induced by immunizing mice with a CEP-adducted protein, macrophages positive for NLRP3 and cleaved caspase 1 were detected in the retina and choroid of the eye. Activated macrophages were also detected in the injured retinas of mice with wet AMD, in which a laser was used to induce focal burns and choroidal neovascularization. Notably, increased choroidal neovascularization and subretinal haemorrhaging occurred in NLRP3-deficient mice compared with in wild-type mice, pointing to a protective role for the NLRP3 inflammasome in wet AMD. IL-1 receptor-deficient mice developed similar laser-induced injuries to wild-type controls, suggesting that NLRP3-mediated production of IL-18 may be important for protection in the wet AMD model. In support of this, IL-18-deficient mice or mice injected intravitreally with IL-18-specific neutralizing antibodies had increased laser-induced choroidal neovascularization compared with wild-type controls.

The authors propose that the anti-angiogenic properties of IL-18 account for the protective role of NLRP3 inflammasome activation in wet AMD. They suggest that IL-18 delivery to the eye may be a useful clinical strategy for preventing choroidal neovascularization and consequent blindness in patients with wet AMD.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Doyle, S. L. *et al.* NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. *Nature Med.* 8 Apr 2012 (doi:10.1038/nm.2717)