OCULAR DISORDERS

Seeing the potential of targeting CCR3

A recent study in *Nature* has identified a new role for CC-chemokine receptor 3 (CCR3) in the pathogenic blood vessel growth that features in severe age-related macular degeneration (AMD), which is the most common cause of vision loss in the elderly in the developed world. As well as providing an alternative, and distinct, anti-angiogenic target to existing therapies for AMD, this role of CCR3 could also provide a basis for improved treatment through earlier detection of the disease.

The more severe, 'wet' form of AMD arises when new blood vessels grow into the macula of the retina from the surrounding choroid tissue, in a process known as choroidal neovascularization (CNV). The subsequent leakage of serum or blood damages the retina and impairs vision. Current therapies, such as ranibizumab (Lucentis; Genentech), target the pro-angiogenic cytokine vascular endothelial growth factor A (VEGFA). However, only one-third of patients benefit substantially from such treatments, and there are safety concerns about completely blocking this constitutively expressed growth factor.

In their paper, Ambati and colleagues used immunolabelling studies to show that expression of CCR3 and its ligands, CC-chemokine ligand 11 (CCL11), CCL24 and CCL26, on human choroidal endothelial cells was specific to tissue that had been isolated from patients with AMD. Although the CCR3 ligands are usually associated with eosinophil and mast cell trafficking, these cells were absent from the tissue samples studied, suggesting an inflammation-independent mechanism of disease.

The authors went on to show that CCR3 signalling has an active role in CNV: *in vitro*, CCR3 ligands stimulated proliferation of human choroidal endothelial cells; and in a mouse model of CNV involving laser injury to the eye, intraocular administration of CCR3-specific neutralizing antibodies or a small-molecule inhibitor of CCR3 reduced the laser-induced pathology compared with control mice. Furthermore, genetically engineered mice that were deficient in CCR3 or its ligands were protected to some extent from the effect of laser injury on the choroidal vasculature.

Interestingly, the CCR3-specific neutralizing antibodies were more effective than VEGFA-specific antibodies at protecting against CNV in the laser injury model, and were not associated with the modest damage to the mouse retina that is seen with such antibodies. Therefore, targeting CCR3 seems to be a promising avenue to improve the current standard of care for AMD.

Early diagnosis is also an important challenge for more effective AMD treatment. Currently, diagnosis is achieved using fluorescein angiography, but this only detects CNV after damage to the retina has begun. Using an imaging technique involving CCR3-specific antibody fragments conjugated to quantum dots, Ambati and colleagues could detect subretinal CNV in mice, suggesting a means for early detection of AMD before vision is impaired, which would improve clinical outcomes.

Katie Kingwell

ORIGINAL RESEARCH PAPER Takeda, A. *et al.* CCR3 is a target for age-related macular degeneration diagnosis and therapy. *Nature* **460**, 225–230 (2009)
FURTHER READING Narayanan, R., Kuppermann, B. D., Jones, C. and Kirkpatrick, P. Ranibizumab. *Nature Rev. Drug Discov.* **5**, 815–816 (2006)