MacularNEWS

Spring 2022 : Edition 25

Tackling retinal scarring

Neovascular ("wet") age-related macular degeneration (nAMD) causes 80% of blindness in AMD. It is currently treated with drugs to stop abnormal blood vessel leaking and bleeding. However, patients with nAMD may also lose vision from the development of scar tissue (fibrosis) under the retina, which is irreversible once established and cannot be efficiently treated. Researchers urgently need to develop a new cure to prevent the development of fibrosis, thus saving patients from blindness.

The Macula Research Group has recently established a novel transgenic (i.e., genetically modified) mouse model (JR5558) of retinal scarring. This mouse model spontaneously develops the same key features of nAMD, such as subretinal lesions. The growth and development of these lesions begin from four weeks of age before becoming established at 12 weeks. This provides an excellent model for studying the disease progression of the early and late stages of subretinal fibrosis.

Through our mouse model, we have found that in the early stage of retinal fibrosis, the normal behaviour of the amino acid, glycine, is significantly changed. This amino acid is an important composition for scar tissue formation. Further investigation into this phenomenon has found that the production of glycine is increased during the early stage of retinal fibrosis. This suggests that glycine production may be strongly involved in forming scars, which may lead to novel therapeutic targets.

Director's Message

This issue of MacularNEWS, focuses on our laboratory's studies on how to prevent retinal scarring, which is a major cause of blindness in people with advanced macular degeneration

Thank you for your continued interest in our work.

Professor Mark Gillies
Macula Research Group

MacularNEWS is now available digitally!
To subscribe, visit http://tinyurl.com/macularnews

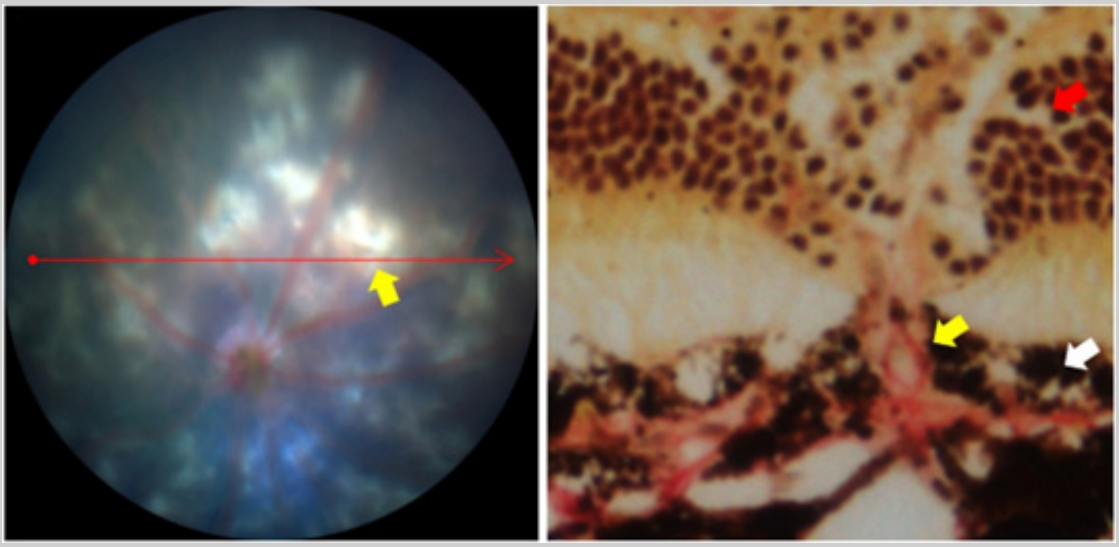

Figure 1: The Macula Research Group has characterised a mouse model of subretinal fibrosis which can be used to screen anti-fibrotic drugs.
Yellow arrows: Fibrotic scars, one of the most common causes of poor outcomes for nAMD patients, in a mouse retina are similar to humans.
Red arrow: Retina.
White arrow: Pigmented cell layer at the base of the retina.

The Macula Research Group has also established a system to evaluate and quantify fibrotic lesions in this mouse model over time. We have been able to use this system to monitor the effect of different treatments on the development of these lesions. This system enables us to locate and identify the same lesions at varying time points. This evaluation system also includes a set of fibrosis biomarkers that indicate the treatment effects at the molecular level. Ultimately, this would allow us to measure the overall actual effect of these treatments on retinal fibrosis.

Aflibercept, a vascular endothelial growth factor (VEGF) inhibitor widely used to treat choroidal neovascularisation (CNV), would be expected to prevent the development of fibrosis by inhibiting the growth of the CNV itself. We found that Aflibercept inhibited the development of subretinal fibrosis, thereby establishing the system's utility in evaluating other potential treatments. Using this evaluation system, we are now testing one anti-fibrotic drug in a clinical trial for lung fibrosis. This drug targets an enzyme that prevents the cross-linking of collagen, an essential process to form the scar. Any positive results from this test will be swiftly translated into clinical trials to treat subretinal fibrosis.

Publication news

The Macula Research Group published a scientific paper in a high-impact journal, *Redox Biology*, in July. This research studies the role of the Pentose Phosphate Pathway (PPP). This is a chemical reaction in Müller cells, the supporting cells in the retina. Transketolase (TKT) is an important enzyme that controls the speed and extent of PPP and plays an important antioxidant role in the retina. We found that disruption of TKT led to impaired glucose metabolism and reduced antioxidative capacity in Müller cells and made them more vulnerable to stress and ageing. Boosting TKT may be a way to prevent retinal degeneration.

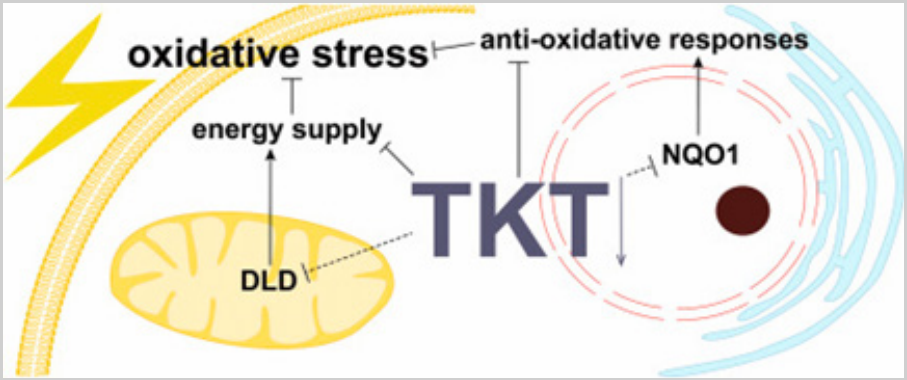

Figure 2: Transketolase in human Müller cells is important for combatting oxidative stress.

If you would like to make a tax-deductible donation or discuss leaving a bequest to support macular research please visit our website **sydney.edu.au/medicine/eye,** call us on **(02) 9382 7309** or post a cheque to: Save Sight Institute, South Block, Sydney Eye Hospital, 8 Macquarie Street Sydney NSW 2000 made out to 'The University of Sydney'

Save Sight Institute is a centre of The University of Sydney.

THE UNIVERSITY OF SYDNEY