

Fish Eyes Offer Clues to Curing Retinal Diseases

Cells may regenerate damaged retinas in humans.

REVIEWED BY G. ASTRID LIMB, PhD, BSc, MSc

Growing evidence suggests that cells linked to regenerating the retina and restoring vision in zebrafish, even after extensive damage, may also hold the key to a cure for blindness in humans.¹ Müller glial cells, found in the adult eye, may be developed into a treatment for regenerating damaged human retinas. Müller-cell-based therapies could potentially treat age-related macular degeneration, glaucoma, and diabetic retinopathy—which are responsible for three quarters of registered blindness in the United Kingdom.

In our recent study, my colleagues and I established the existence of immortal Müller cell lines, from several human donor eyes. Because immortalization is one of the main properties of stem cells, we investigated whether these cells expressed stem cell markers. In a research project funded by the Wellcome Trust, the Medical Research Council, and the Helen Hamlyn Trust (all in London), we found that the population of Müller cells that becomes spontaneously immortalized has stem cell properties. These observations confirmed that, like the zebrafish, the adult human retina harbors a population of Müller cells with stem cell characteristics. Because human Müller cells have stem cell characteristics, we were able to develop the cells in



Figure 1. Cells that regenerate the retina in zebrafish, may hold clues to a treatment for retinal diseases in humans.

vitro into all types of neurons found in the retina. Cells that were grown as adherent monolayers responded to epidermal growth factor and could be expanded indefinitely without growth factors under normal culture conditions. They could be also frozen and thawed without losing their stem cell properties.

TESTED IN RAT MODELS

When tested in rat models with diseased retinas, we found that the cells migrated into the retina and expressed the markers of neurons present in the region where they migrated. This expression suggests that these cells may have potential use for cell-based therapies to restore retinal function.

We are currently growing the cells in the lab and transplanting them into various animal models of retinal disease to identify the best methods for potential transplantation into humans. We are also looking for ways to stimulate growth and persuade the eye to repair itself, using its own cells.

POTENTIAL TO RESTORE VISION

Müller cells with stem cell properties could potentially restore vision to someone who is losing, or has lost his or her sight due to retinal disease or damage. It might be possible to use cells from a person's own eye, which means that there is less chance of the body rejecting the treatment. It also may be possible to grow cells from donor eyes and store them in a cell bank for transplantation to other individuals subject to tissue compatibility testing (much like we already do for kidney and heart transplants).

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Although Müller glial cells with stem cell characteristics are present in the human eye, it is not clear why these cells do not automatically repair the diseased retina. It is possible that internal mechanisms exist in the normal adult retina and prevent these cells from dividing and replicating. Our next step is to identify which factor is responsible for blocking the regeneration. Once we know how this mechanism works, we will be closer to developing alternative treatments to transplantation.

We hope that a transplantation treatment will be possible within the next 5 to 10 years, for cells isolated from a person's own eye. The second approach of transplanting donor cells will take longer, as we also need to overcome the immune response. ■

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1. Lawrence JM, Singhal S, Bhatia B, et al. MIO-M1 cells and similar Müller glial cell lines derived from adult human retina exhibit neural. *Stem Cells*. 2007;8:2033-2043.

MÜLLER CELLS: A PRIMER

Three basic types of glial cells are found in the human retina, Müller cells, astroglia, and microglia. All were described by Cajal more than 1,000 years ago.

Müller cells are the principal glial cell of the retina. They form architectural support structures stretching radially across the thickness of the retina and form the limits of the retina at the outer- and inner-limiting membrane, respectively.

Müller cells contain glycogen, mitochondria, and intermediate filaments, which are immunoreactive for vimentin and, to some extent, to glial fibrillary acidic protein (GFAP). The filaments are normally in the inner half of the Müller cells and their endfeet, but after trauma to the retina, such as retinal detachment, both vimentin and GFAP are massively upregulated and found throughout the cell (described by Guerin et al in 1990; and Fisher and Lewis in 1995).

Müller cells have a range of functions all of which are vital to the health of the retinal neurons. Müller cells act in a symbiotic relationship with the neurons.

Müller cell functions include:

- Supplying endproducts of anaerobic metabolism to fuel aerobic metabolism in the nerve cells.
- They mop up neural waste products such as carbon dioxide and ammonia and recycle spent amino acid transmitters.
- They protect neurons from exposure to excess neurotransmitters such as glutamate using well-developed uptake mechanisms to recycle this transmitter. They are particularly characterized by the presence of high concentrations of glutamine synthase.
- They may be involved in both phagocytosis of neuronal debris and release of neuroactive substances such as gamma-aminobutyric acid, taurine, and dopamine.
- They are thought to synthesize retinoic acid from retinol (described by Edwards in 1994).
- They control homeostasis and protect neurons from deleterious changes in their ionic environment by taking up extracellular K⁺ and redistributing it.
- They contribute to the generation of the electroretinogram (ERG) b-wave (Miller and Dowling, 1970; Newman and Odette, 1984), the slow P3 component of the ERG (Karwoski and Proenza, 1977), and the scotopic threshold response (Frishman and Steinberg, 1989). They do so by regulation of K⁺ distribution across the retinal vitreous border, across the whole retina, and locally in the inner plexiform layer of the retina.

Source: <http://webvision.med.utah.edu/>.