



Researchers find potential protein target for glaucoma treatment

A series of laboratory experiments have demonstrated that inhibition of the sCD44 molecule can improve survival of retinal ganglion cells

In recent times, a significant proportion of research into therapies for glaucoma has focused on a variety of neuro-protective agents. New American research, however, has shown that ophthalmologists may one day be able to curb the effects of glaucoma by eliminating a protein implicated in killing retinal ganglion cells and cells in the trabecular meshwork.

Although researchers still cannot pinpoint the root physiological causes of glaucoma, they do know that retinal ganglion cells and cells in the trabecular meshwork often die prematurely in patients with glaucoma.

Details of the new research appeared earlier this year in *Investigative Ophthalmology & Visual Science*, (2005;46:214-222). The researchers found that by eliminating a specific protein, they could reduce the incidence of retinal ganglion cell death and cell death in the trabecular meshwork. The protein consequently represents an attractive therapeutic target for glaucoma treatment.

The research, carried out by Dr John Choi of the Laboratory for Oculo-Cerebrospinal Investigation at Northwestern University Medical School in Chicago, reported that a soluble protein called sCD44 had a statistically significant effect on the number and viability of retina ganglion cells and on cells in the trabecular meshwork.

Higher concentrations of implicated protein in eyes of glaucoma patients

Previous research by the same group had shown that there was an increase in the concentration of sCD44 in the aqueous humour of patients with primary open angle glaucoma. With this in mind, a key question was: "Does sCD44 have a toxic effect on ocular tissues?"

To answer such a question, we must understand what we mean by "glaucoma." Physicians and researchers use the term to describe a clinically and genetically heterogeneous group of disorders that result in optic neuropathy and a progressive loss of the visual field. Often, the disorder is associated with an elevated intraocular pressure and if left untreated glaucoma can lead to total and irreversible blindness.

Glaucoma appears in a number of types and has been sub-divided in the medical literature into a variety of categories which depend on factors such as the iris-cornea angle, whether or not the glaucoma is primary or secondary in nature and the age of onset of the disease.

Traditionally, there are three major categories of glaucoma based on the classification of the disease being open angle, closed angle or congenital. As ophthalmologists well know, the terms "Open" angle and "closed" angle refer to the angle at the junction of the iris and cornea. The open angle variety is the more common and slowly progressive; the closed angle is generally more rare and often associated with a rapid rise of intraocular pressure. Congenital glaucoma, normally diagnosed before the age of three years, is often associated with ocular developmental abnormalities and a membrane obstructing the path of aqueous outflow.

Open angle glaucoma affects about half of the 70 million people in the world who have glaucoma. Primary open angle glaucoma – which includes forms of glaucoma not associated with other anatomical abnormalities of the eye or an ocular manifestation of a systemic disease – are thought to affect approximately 2% of the population over the age of 45 years.

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Glaucoma is essentially a "mechanical" disease, that is, the cause of the disorder is most likely a blockage that interrupts the balance between aqueous humour production and outflow. The blockage causes an increase in the intraocular pressure, which subsequently leads to optic neuropathy and the death of retinal ganglion cells. It has long been known that there is a hereditary component to the glaucomas, for instance, the prevalence of POAG in first-degree relatives of affected patients has been demonstrated to be seven to ten times higher than that of the general population.

Primary open angle glaucoma varies in its age of onset and has been classified into the late onset form, generally termed

"chronic open angle glaucoma," and the less frequently observed juvenile onset form, known as "juvenile open angle glaucoma."

Given the painless nature of the disease, however, this classification may be somewhat arbitrary as affected individuals may remain unaware of the disorder for many years before diagnosis.

Study verifies link between sCD44 and retinal ganglion cell death

In the recently reported research findings, primary open angle glaucoma was the form of glaucoma within which an elevated concentration of sCD44 had been observed. To determine the effect of sCD44 on retinal ganglion cells and cells of the trabecular meshwork Dr. Choi and colleagues set up cell cultures of both cell types to which sCD44 was added.

To verify that cell death was specific to the introduction of sCD44, the research team also set up, in parallel, a series of experiments that added inactive sCD44 to cell cultures. Inactivation of sCD44 was brought about through boiling sCD44 prior to addition to cells or by administering antibodies specific to sCD44 which could act like molecular sponges ensuring that sCD44 was tightly bound up and therefore unavailable.

The results demonstrated that when sCD44 was eliminated from the picture, the chances of survival of the retina ganglion cells and of the cells in the trabecular meshwork were significantly improved. Furthermore, additional tests in which cells were provided with a neuro-protective agent showed that the cytotoxic effects of sCD44 could be protected against, in some cases improving cell viability by up to 75%.

Glaucoma has similarities to neurodegenerative conditions

The authors of the study draw a number of parallels between neurodegenerative conditions such as Alzheimer's disease or Parkinson's disease. In those diseases, a toxic protein has been associated with disease pathology. The findings within the current studies on primary open angle glaucoma may consequently provide valuable data and insights not only for glaucoma but also for more general concepts of neurodegenerative disorders.

In terms of a therapeutic opportunity, the market profile of glaucoma represents an attractive investment should an appropriate technology be shown to

mediate real therapeutic benefit. With tens of millions of potential patients – and no cure – the incentives to open up such a market will insure a fiercely competitive environment.

However, before such potential approaches may be considered for pharmaceutical development, researchers need to develop:

- a better understanding of the molecular biology of aqueous humour production and outflow
- an improved understanding of the cell death pathways of retinal ganglion cells and of cells in the trabecular meshwork;
- improved control over drug delivery technology.

Though the challenges are formidable, there can be little doubt that the potential rewards in such a market will provide significant incentives for continuing high quality research and development.

Glossary

Cytotoxic: Causing injury or death to cells

Retinal ganglion cell: A specific type of retinal neuronal cell that transmits information from various other retinal cell types to the brain and therefore of critical importance in mediating normal vision

Trabecular meshwork: A pore-like structure that surrounds the entire circumference of the anterior chamber of the eye through which the aqueous humour circulates; this highly specialised structure is critical to maintaining normal fluid drainage dynamics in the eye.

Cell cultures: Isolated cells grown in dishes or containers within specialised incubators.

Antibodies: Highly specific proteins that may be produced artificially for experimental purposes but occur naturally as part of the immune system's core defence apparatus. Antibodies may act like sponges to mop up particular proteins and thereby protect host cells from damage.