PRIMARY eyecare

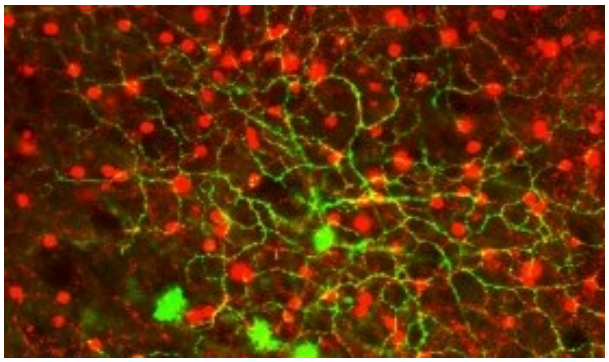
Issue 64 2021

This edition of Primary EyeCare brings you reports on recent eye health research from the US National Institutes of Health, National Eye Institute.

Gene Therapy Provides Neuroprotection To Prevent Glaucoma Vision Loss

The first study is a breakthrough investigation of gene therapy and its potential to prevent vision loss from glaucoma. The NIH funded research project is part of the Audacious Goals Initiative and opens the door to new sight-saving therapy for people diagnosed with glaucoma. Glaucoma results from irreversible neurodegeneration of the optic nerve and while current therapies can slow vision loss by lowering elevated eye pressure, some glaucoma progresses to blindness despite eye pressure being normal.

The report of the study by Guo X, et al. published in the journal Cell found that calcium modulator CaMKII protects the optic nerve in mice and preserves vision in mouse models of glaucoma. The findings suggest a way forward for developing neuroprotective therapies for glaucoma, reducing visual impairment and blindness. This would be a great development in meeting the needs of patients who currently lack treatment options.



Retinal ganglion cells under magnification

In a media statement the study's lead investigator, Bo Chen, PhD, associate professor of ophthalmology and neuroscience at the Icahn School of Medicine at Mount Sinai in New York City noted "Our study is the first to show that activating the CaMKII pathway helps protect retinal ganglion cells from a variety of injuries and in multiple glaucoma models".

The CaMKII (calcium/calmodulin-dependent protein kinase II) pathway regulates key cellular processes and functions throughout the body, including retinal ganglion cells in the eye. Yet the precise role of CaMKII in retinal ganglion cell health is not well understood. Inhibition of CaMKII activity, for example, has been shown to be either protective or detrimental to retinal ganglion cells, depending on the conditions.

Using an antibody marker of CaMKII activity, the research team discovered that CaMKII pathway signalling was compromised whenever retinal ganglion cells were exposed to toxins or trauma from a crush injury to the optic nerve, suggesting a correlation between CaMKII activity and retinal ganglion cell survival.

Searching for ways to intervene, they found that activating the CaMKII pathway with gene therapy proved protective to the retinal ganglion cells. Administering the gene therapy to mice just before the toxic insult (which initiates rapid damage to the cells), and just after optic nerve crush (which causes slower damage), increased CaMKII activity and robustly protected retinal ganglion cells.

Among gene therapy-treated mice, 77% of retinal ganglion cells survived 12 months after the toxic insult compared with 8% in control mice. Six months following optic nerve crush, 77% of retinal ganglion cells had survived versus 7% in controls.

Similarly, boosting CaMKII activity via gene therapy proved protective of retinal ganglion cells in glaucoma models based on elevated eye pressure or genetic deficiencies.

Increasing retinal ganglion cell survival rates translated into a greater likelihood of preserved visual function, according to cell activity measured by electroretinogram and patterns of activity in the visual cortex.

Three vision-based behavioural tests also confirmed sustained visual function among the treated mice. In a visual water task, the mice were trained to swim toward a submerged platform based on visual stimuli on a computer monitor.

Depth perception was confirmed by a visual cliff test based on the mouse's innate tendency to step to the shallow side of a cliff.

Lastly, a looming test determined that treated mice were more apt to respond defensively (by hiding, freezing or tail rattling) when shown an overhead stimulus designed to simulate a threat, compared with untreated mice.

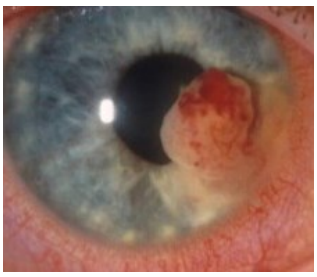
"If we make retinal ganglion cells more resistant and tolerant to the insults that cause cell death in glaucoma, they might be able to survive longer and maintain their function," Chen concluded.

This study was supported by NEI grants R01EY028921, R01EY024986. NEI is part of the National Institutes of Health and reported in NEI media by Kathryn DeMott.

Reference:
Guo X, Zhou J, Starr C, Mohns EJ, Li Y, Chen E, Yoon Y, Kellner CP, Tanaka K, Wang H, Liu W, LR, Demb JB, Crair MC, and Chen B. "Preservation of vision after CaMKII-mediated protection of retinal ganglion cells." Published online July 22, 2021 in Cell. DOI: 10.1016/ j.cell.2021.06.031

Melanoma of the eye: preclinical tests show path toward treatment

Uveal Melanoma is a rare and deadly cancer of the eye, and the mortality rate has remained unimproved for 40 years. Half of the melanomas spread to other organs of the body, causing death in less than a year, so new treatments to preserve vision and prevent death are an urgent need.



A breakthrough has appeared in a new preclinical study by researchers at the University of Alabama at Birmingham, Emory University, Atlanta, and the University of Houston (reported by Jeff Hansen, on the UAB media site) which is offering hope that a treatment could be developed for people with UM. A small-molecule inhibitor has been identified that dampens the potent drivers of this tumour. In mouse models, **this inhibitor, KCN1, strongly limited primary disease in the eye and metastatic tumour dissemination to the liver, and animals survived longer, without overt side effects.** *(emphasis added)*

In the paper published in the journal Oncogene, the researchers note that "preclinical studies support the further translation of the KCN1 arylsulfonamide scaffold toward a novel treatment for patients with metastatic uveal melanoma."

The report explains that prior to this study, it was known that: 1) a hypoxia gene signature, indicative of low oxygen levels in the tumour, is associated with poor prognosis and a high metastatic rate in uveal melanoma; 2) the hypoxia-inducible transcription factor (HIF) turns on a large number of gene products with critical roles in cancer growth and metastasis; and 3) for UM specifically, HIF promotes tumour progression by regulating proliferation, migration, invasion and adhesion of tumour cells, as well as promoting blood vessel growth to feed the tumour.

Hypoxia-Inducible Transcription Factor (HIF)

Little was known of the role of HIF in directing pro-invasive extracellular matrix remodelling in UM. Changes in the extracellular matrix, including increased collagen deposition and reorganization of collagen fibres outside the cell, is known to aid cancer progression and tumour cell invasion.

Hypoxia promotes collagen deposition, in part, because HIF increases the production of two gene products, P4HA1 and P4HA2, that are part of an enzyme complex that adds hydroxyl residues to prolines in procollagen. Procollagen is a precursor protein in the complex maturation process that collagen undergoes.

In their study, Van Meir, Grossniklaus and colleagues decided to evaluate the expression of the P4HA1/2 genes concerning UM patient prognosis and to determine whether inhibiting hypoxia-induced P4HA1/2 expression in a preclinical model of metastatic UM would yield therapeutic benefit.

They found that P4HA1 and P4HA2 were induced by hypoxia in human UM cell lines, and this induction was reduced by KCN1.

Comparison of 46 patients with non-metastatic UM and 46 with metastatic UM showed that P4HA1/2 were significantly overexpressed in patients with metastatic disease. Also, P4HA1/2 expression correlated with poor overall survival in UM patients. This suggests that P4HA1 and P4HA2 can serve as prognostic markers in UM and that they may be important for the malignant progression of the disease and patient survival.

Intervention with KCN1 in Animal Models

Using preclinical animal models of UM the researchers showed that KCN1 was abundantly taken up in the liver and the eyes after intraperitoneal injection. It dampened tumour growth and disease burden at the primary site of the eye, as well as reduced distant metastases in the liver.

KCN1 also increased survival in three different models that test the growth of human UM after injection in mice uvea. The inhibitor was most effective at reducing metastases when it was administered early.

At the molecular level, treatment with KCN1 to inhibit the hypoxic induction of P4HA1/2 decreased the hydroxylation of proline amino acids in the procollagen. It also caused cleavage of the collagen and disordered the structure of collagen VI, a mature structural component of the extracellular matrix. These collagen changes correlated with a reduction in tumour cell invasion.

“Our study,” Van Meir and Grossniklaus concluded, “suggests that KCN1 has desirable properties as a suppressor of metastasis: It is well tolerated, has excellent distribution to the eye and the liver, and is thus ideally suited for treating metastatic UM.”

Reference:
Kaluz S, Zhang Q, Kuranaga Y, Yang H, Osuka S, Bhattacharya D, Devi NS, Mun J, Wang W, Zhang R, Goodman MM, Grossniklaus HE, Van Meir EG. Targeting HIF-activated collagen prolyl 4-hydroxylase expression disrupts collagen deposition and blocks primary and metastatic uveal melanoma growth. Oncogene. 2021 Jul 3. doi: 10.1038/s41388-021-01919-x. Epub ahead of print. PMID: 34218269.

[Co-first authors of the report: Grossniklaus HE, Van Meir EG, Kaluz S, Zhang Q]

What makes us sneeze?

And just for a bit of light relief, we include a report of research by Li F, et al. from the journal Cell, published online June 15, 2021, and featured on the web page of Washington University School of Medicine attributed to Jim Dryden, Director of Broadcast & Podcasts.

A team led by researchers at Washington University School of Medicine in St. Louis has identified, in mice, specific cells and proteins that control the sneeze reflex. The lead author of the study, Qin Liu, PhD, noted

“We study the neural mechanism behind sneezing because so many people, including members of my own family, sneeze because of problems such as seasonal allergies and viral infections. Our goal is to understand how neurons behave in response to allergies and viral infections, including how they contribute to itchy eyes, sneezing and other symptoms. Our recent studies have uncovered links between nerve cells and other systems that could help in the development of treatments for sneezing and for fighting infectious respiratory diseases.”

Sneezing is the most forceful and common way to spread infectious droplets from respiratory infections. Scientists first identified a sneeze-evoking region in the central nervous system more than 20 years ago, but little has been understood regarding how the sneeze reflex works at the cellular and molecular level.

In the new study, Liu and her team established a mouse model in an attempt to identify which nerve cells send signals that make mice sneeze. The researchers exposed the mice to aerosolised droplets containing either histamine or capsaicin, a pungent compound made from chilli peppers. Both elicited sneezes from the mice, as they do in people.

By examining nerve cells that already were known to react to capsaicin, Liu’s team was able to identify a class of small neurons linked to sneezing that was caused by that substance. The researchers then looked for neuropeptides that could transmit sneeze signals to those nerve cells and found that a molecule called neuromedin B (NMB) was required for sneezing. Eliminating the NMB-sensitive neurons in the part of the nervous system that evoked sneezes in the mice blocked the sneeze reflex. Those neurons all make a protein called the neuromedin B receptor. In mice without that receptor, sneezing was also greatly reduced.

“Interestingly, none of these sneeze-evoking neurons were housed in any of the known regions of the brainstem linked to breathing and respiration,” Liu said. “Although we found that sneeze-evoking cells are in a different region of the brain than the region that controls breathing, we found that the cells in those two regions were directly connected via their axons.”

Because many viruses and other pathogens — including the majority of human rhinoviruses and coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2, the coronavirus that causes COVID-19 — are spread in part by aerosolized droplets, Liu said it may be possible to limit the spread of those pathogens by targeting NMB or its receptor to limit sneezing in those known to be infected.

“A sneeze can create 20,000 virus-containing droplets that can stay in the air for up to 10 minutes,” Liu explained. “By contrast, a cough produces closer to 3,000 droplets, or about the same number produced by talking for a few minutes. By identifying neurons that mediate the sneeze reflex, as well as neuropeptides that activate these neurons, we have discovered targets that could lead to treatments for pathological sneezing or strategies for limiting the spread of infections.”

Reference:
Li F, et al. Sneezing reflex is mediated by a peptidergic pathway from nasal sensory neurons to brainstem respiratory neurons. Cell, published online June 15, 2021.

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