Stress pathway identified as potential therapeutic target to prevent vision loss

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A new study identifies specific cell-stress signaling pathways that link injury of the optic nerve with irreversible vision loss. The research, published by Cell Press in the February 9 issue of the journal *Neuron*, may lead to new strategies that will help to protect vulnerable neurons in the retina after optic nerve damage and diseases.

Retinal ganglion cells (RGCs) send visual information from the retina to the brain through long processes called axons. The axons of the RGCs are bundled together to form the optic nerve. "RGCs are highly vulnerable when then optic nerve is damaged," explains senior study author, Dr. Zhigang He, from Children's Hospital and Harvard Medical School. "For example, optic nerve injury and subsequent loss of RGCs occur often in the setting of head injury and other types of retinal pathology, such as glaucoma."

Previous work has linked a cell-death pathway, called apoptosis, with trauma-related RGC death. However, targeting apoptosis is not seen as an efficient therapeutic strategy because apoptosis is likely to be one of the last steps in the disease process. In the current study, Dr. He and colleagues used an optic nerve crush model to investigate signals that are farther upstream of RGC death. The researchers discovered that optic nerve crush induced activation of distinct pathways of the unfolded protein response (UPR). The UPR is a cellular stress response that can be protective in some cell types.

The researchers went on to show that diverse UPR pathways are activated by axon injury and that the way these pathways function in neurons may be quite different from other cell types. Specifically, they suggest that axonal damage results in pro-cell-death UPR activation, which might contribute to irreversible cell death associated with optic nerve injury and glaucoma.

"Importantly, such differential activations of UPR pathways and their distinct effects on neuronal cell death are also observed in RGCs with other types of axonal insults, such as intraocular pressure elevation," concludes Dr. He. "This suggests a new protective strategy for optic nerve injury and diseases. In addition, as axonal damage is common in different neurodegenerative diseases, it would be interesting to see whether what we learned from optic nerve injury models is applicable to other types of neurodegeneration."

More information: Hu et al.: "Differential Effects of Unfolded Protein Response Pathways on Axon Injury-Induced Death of Retinal Ganglion Cells." *Neuron*, DOI:10.1016/j.neuron.2011.11.026

Abstract

Loss of retinal ganglion cells (RGCs) accounts for visual function de?cits after optic nerve injury, but how axonal insults lead to neuronal death remains elusive. By using an optic nerve crush model that results in the death of the majority of RGCs, we demonstrate that axotomy induces differential activation of distinct pathways of the unfolded protein response in axotomized RGCs. Optic nerve injury provokes a sustained CCAAT/enhancer binding homologous protein (CHOP) upregulation, and deletion of CHOP promotes RGC survival. In contrast, IRE/XBP-1 is only transiently activated, and forced XBP-1 activation dramatically protects RGCs from axon injury-induced death. Importantly, such differential activations of CHOP and XBP-1 and their distinct effects on neuronal cell death are also observed in RGCs with other types of axonal insults, such as vincristine treatment and intraocular pressure elevation, suggesting a new protective strategy for neurodegeneration associated with axonal damage.

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