Extensive regeneration in nerve connecting eye to brain achieved

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Damage to the optic nerve, connecting the eye with the brain, is a major cause of blindness. The most common culprit is glaucoma, estimated to affect more than 4 million Americans. There is currently no way to restore the lost vision, because the optic nerve, like other nerves in the mature central nervous system (CNS), cannot regenerate. Now, scientists at Children's Hospital Boston report achieving the greatest regeneration to date in the mammalian optic nerve.

Research in animal models has revealed many of the factors thwarting nerve regeneration in the mature CNS. The Children's scientists have now discovered that two molecular pathways, which each promote some optic nerve regeneration on their own, can work synergistically. By activating these pathways simultaneously in a mouse model, they attained about 10-fold the regeneration seen with activation of either pathway alone.

"This is really a massive change," says Larry Benowitz, PhD, a member of the Neurobiology and Neurosurgery Departments at Children's and a Professor of Surgery and Ophthalmology at Harvard Medical School. "It brings us closer to potentially restoring function after vision loss caused by optic nerve damage."

The synergistic effect, described November 17th in the Journal of Neuroscience, was achieved by simultaneously targeting the protein oncomodulin, elevating levels of the small signaling molecule cyclic adenosine monophosphate (cAMP) and deleting the gene that encodes

the enzyme PTEN. The injured retinal nerve fibers regrew over long distances, with many making it all the way from the eye down the entire length of the optic nerve and across a structure at the base of the brain called the optic chiasm-where nerve fibers from the left and right eyes partially cross. Some rare nerve fibers even reached the thalamus, a deep brain region critical for early stages of visual processing.

Oncomodulin, as discovered in 2006 by Benowitz's laboratory, is a factor secreted by immune cells in the eye in response to inflammation; it activates the intrinsic growth state of nerve cells in the retina. cAMP does not promote optic nerve regeneration by itself, but when elevated can enhance the effects of oncomodulin. PTEN is an enzyme that acts as a critical brake on cell growth; work from the Children's laboratories of Zhigang He, MD, PhD, and Mustafa Sahin, MD, PhD, showed in 2008 that deletion of the PTEN gene promotes a moderate amount of optic nerve regeneration on its own.

In the present work, Benowitz's team, including first author Takuji Kurimoto, MD, PhD, first showed that cAMP enhances regeneration by improving the ability of oncomodulin to bind to its receptors on retinal neurons. The team had some evidence that oncomodulin produced its regenerative effects via a cell growth pathway known as the PI3K pathway, and they knew that deletion of PTEN activates the same pathway. However, as Benowitz explains, "We didn't know whether the PI3K pathway was already fully activated by oncomodulin, or whether there remained brakes on it".

Their experiments showed that PTEN deletion further activates the regenerative pathway turned on by oncomodulin. "While the PI3K pathway is involved in oncomodulin's actions, it's still only partially activated. So the PTEN deletion then fully activates the PI3K pathway," Benowitz says. "And by removing all the brakes on it, we get this remarkable level of growth."

The main thrust of research on nerve regeneration has been to disable natural "brakes" on nerve growth, but the three-pronged approach tested in this study was able to achieve significant amounts of regeneration without targeting these brakes - instead, it worked by stepping on the gas, activating the intrinsic growth potential of nerve cells, Benowitz says.

Benowitz now hopes to find out whether combining the current strategy with an attack on the extrinsic growth-inhibitory factors could achieve even greater nerve regeneration, so that more nerves from the retina make it all the way to the thalamus. The lab is also investigating whether the increase in optic nerve regeneration results in improved vision in the mice.

Finally, more work remains to be done before the regenerative strategy discovered in this study can be applied to humans. For instance, researchers must find a way to deliver sufficient levels of oncomodulin to the eye over a prolonged period, or induce its production without inflammation. "We need a more clinically appropriate delivery system," says Benowitz.

In addition, assuming nerve fibers from the retina can be made to grow all the way to the thalamus, they will have go to the right places in the thalamus. "In order to have structured vision it's necessary to have topographic representation of visual space onto the brain," Benowitz explains.

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