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Scientists find gene vital to nerve cell development

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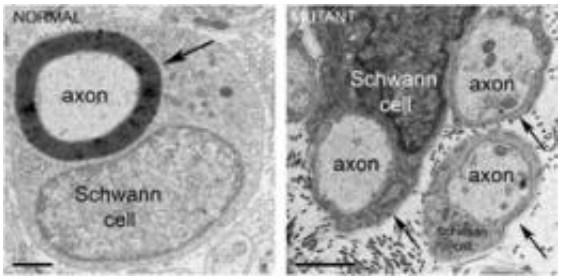

In healthy mice, individual Schwann cells wrap their membranes around a nerve cell's axon many times. A cross-section of the resulting myelin sheath is visible as a thick band surrounding the axon in the "Normal" image on the left. In mice with a mutation in Gpr126, Schwann cells cannot make myelin and no thick layer surrounding axons is visible in the "Mutant" image on the right. KELLY R. MONK

(Medical Xpress) -- The body's ability to perform simple tasks like flex muscles or feel heat, cold and pain depends, in large part, on myelin, an insulating layer of fats and proteins that speeds the propagation of nerve cell signals.

Now, scientists have identified a gene in mice that controls whether certain cells in the peripheral nervous system can make myelin. Called Gpr126, the gene encodes a cellular receptor that could play a role in diseases affecting peripheral nerves, says Kelly R. Monk, PhD, assistant professor of developmental biology at Washington University School of

Medicine in St. Louis.

“Researchers knew Gpr126 existed in humans, but no one knew what it did,” says Monk, who did this work while a postdoctoral researcher at Stanford University. “For 30 years or so, scientists have been looking for a cell receptor that controls myelination by raising levels of an important chemical messenger. We found it in zebrafish. And now we’ve shown that it’s present in mammals. It’s the first known function for this receptor, and it solved a decades-old mystery, which is exciting.”

The work is currently available online and will be published in the July 1 issue of the journal *Development*.

In a paper published in Science in 2009, Monk and her colleagues first showed that zebrafish require Gpr126 to make myelin in their peripheral nerves, but not in the brain or spinal cord of the central nervous system.

When a gene works a certain way in zebrafish, it likely works that way in mammals, according to William S. Talbot, PhD, professor of developmental biology at Stanford University and Monk’s postdoctoral advisor.

“The brain and spinal cord are fine in mice without the Gpr126 gene,” Talbot says. “But there is no myelin in the peripheral nerves, very much like in zebrafish. This is evidence that Gpr126 probably has a general role in myelin formation and nerve development in all vertebrates, including humans.”

The missing gene appears to disrupt specialized cells in the peripheral nervous system called Schwann cells, stopping those cells from enveloping and providing nutrients to the axons of nerves. Healthy Schwann cells wrap their membranes around nerve cell axons many times to form the myelin sheath that speeds the transmission of nerve

cell signals.

In zebrafish without Gpr126, Schwann cells appear to develop and arrange themselves with individual axons normally at first. But when it comes time to wrap around the axon and make myelin, they stop short.

“From zebrafish, we thought this gene controlled only one very specific step of Schwann cell development,” Monk says. “But in mice the story is more complex.”

In mice without the gene, problems begin much earlier. The Schwann cells take longer to associate with individual axons and, compared to normal mice, there are many fewer axons. Such evidence leads Monk to speculate that the delayed sorting and failure of Schwann cells to wrap around axons causes the associated neurons to die. Because of these and other problems seen in mice without Gpr126 (including defects in the lungs, kidneys and cardiovascular system), Monk proposes that it plays more diverse roles in mice than in zebrafish. Although mice without Gpr126 never lived beyond two weeks, zebrafish with the same mutation survived to reproduce.

Because of its clear role in forming myelin, Gpr126 could be a possible target for therapies to treat peripheral neuropathies, common conditions where peripheral nerves are damaged. Such damage causes an array of problems including pain and numbness in the hands and feet, muscle weakness and even problems involving functions of internal organs such as digestion. Some peripheral neuropathies are genetic, but many result from diseases of aging and poor health, including complications from diabetes or side effects of chemotherapy.

With these conditions in mind, Monk and Talbot point out that Gpr126 is a member of a large family of cell surface receptors that are common targets for most commercially available drugs, treating conditions as

diverse as allergies, ulcers and schizophrenia.

“We don’t know yet whether Gpr126 itself can be a drug target. But the fact that its relatives can,” Talbot says, “makes it especially interesting.”

Ongoing work in Monk’s lab seeks to further define the many roles of Gpr126 in mammals, including whether it could help direct Schwann cells to repair or regrow damaged myelin.

More information: Monk KR, Oshima K, Jors S, Heller S, Talbot WS. Gpr126 is essential for peripheral nerve development and myelination in mammals. *Development*. 138(13). July 2011.

Monk et al. A G protein-coupled receptor is essential for Schwann cells to initiate myelination. *Science*. 325. Sept. 2009.

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