How injured nerves grow themselves back

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Unlike nerves of the spinal cord, the peripheral nerves that connect our limbs and organs to the central nervous system have an astonishing ability to regenerate themselves after injury. Now, a new report in the October 1st issue of *Cell* offers new insight into how that healing process works.

"We know a lot about how various cell types differentiate during development, but after a serious injury like an amputation, nerves must re-grow," said Allison Lloyd of University College London. "They need a new mechanism to do that because the developmental signals aren't there."

That kind of regrowth isn't easy to pull off. Peripheral nerves are long cells; their nucleus is in the spinal cord and the axons that extend from them and relay nerve messages can reach all the way down a leg. "When a nerve gets cut, all the axons downstream degenerate," Lloyd said. Regrowth requires that the two ends somehow find their way back to each other through damaged tissue.

Scientists knew that Schwann cells were important to that process. Those cells are found wrapped around axons, where under normal circumstances they are rather "quiet" cells. All of that changes when an injury occurs; those Schwann cells de-differentiate back to a stem-cell-like state and play an important role in bridging the gap to repair damaged neurons.

"Schwann cells could sit on a nerve for years and then, at any point,

switch states," Lloyd said. "They are quite unusual cells." (There are other examples of cells that can return to a stem-cell-like state, she said. For instance, cells in the liver and the endothelial cells that line blood vessels.)

But, the new study shows, the Schwann cells need help to repair the nerves properly. That help comes from a well-studied cell type known to play a role in wound healing: fibroblasts.

"This is a new role for fibroblasts," Lloyd said, an exciting find given that the cells are the type that grows when you place animal tissue in cell culture and have been very well studied as a result. "There is lots known about them, and they are always present at wounds. This shows that they act in a completely new way."

The fibroblasts send a signal to the Schwann cells, causing them to sort themselves into clumps, or cords, that make their way out of the nerve stump as a group. Those cords guide the regrowth of axons across the wound. Lloyd's team found that the response to the so-called ephrin-B signal issued by the fibroblasts depends on a factor called Sox2, best known for its central role in embryonic stem cells. Sox2 is also one of a handful of ingredients that can help reprogram adult cells to behave like embryonic stem cells.

Without the ephrin-B signal, Schwann cells fail to migrate in an organized fashion and the axons don't grow back properly.

Lloyd said the new findings might lead to ways to improve the repair of peripheral nerves, noting that the natural process isn't all that efficient. "It's not perfect, but if a hand is cut off and sewn back on, you can get some movement," Lloyd said. Her team is actively exploring ways to improve upon the natural nerve-healing mechanism now.

The researchers also have plans to investigate whether similar mechanisms might be involved in the movement and spread of cancers of the peripheral nervous system. "We don't know yet, but it wouldn't be surprising if this is relevant to the movement of other cells," Lloyd said.

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