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One step closer to closure: Neuroscientists discovery key to spinal cord defects

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Spinal cord disorders like spina bifida arise during early development when future spinal cord cells growing in a flat layer fail to roll up into a tube. In the Dec. 6 issue of *Nature Cell Biology*, researchers from the Johns Hopkins University School of Medicine team with colleagues at the University of California, Berkeley to report a never-before known link between protein transport and mouse spinal cord development, a discovery that opens new doors for research on all spinal defects.

"What I love about this discovery is the total surprise — we never before would have linked defects in the protein-secretion machinery and neural tube closure," says David Ginty, Ph.D., professor of neuroscience and Howard Hughes Medical Institute investigator.

The team originally set out to find new genes that instruct proper wiring of the hundred billion neurons in the nervous system. To do that, they randomly generated mutations in mouse genes, bred the mice and examined offspring for defects in nervous system development. One of the thousands of mouse embryos examined by graduate student Janna Merte had a spinal cord that had failed to close into a tube. Whereas conditions like spina bifida arise from failure of the tail end of the spinal cord to close, these new mice had a more severe condition, where the entire length of the spinal tube had failed to close.

Intrigued, Janna then identified the mutated gene in this mouse as Sec24b, a gene already known to play a role in the process where cells package newly made proteins that are destined to be delivered to the cell

membrane or sent to the outside of the cell. But all genes known to instruct normal spinal tube closure are known to orient cells in a flat sheet, similar to patterning of the hair follicles in skin.

"We didn't really know what to do with Sec24b at first," says Ginty. His team consulted and eventually teamed up with Berkeley professor Randy Schekman, who discovered the Sec24 gene in yeast.

Another gene, Vangl2, when mutated causes remarkably similar defects in spinal closure, so the team set out to see if Vangl2 and Sec24b interact with each other. They first engineered mice to contain mutations in both genes and found that 68 percent of mice had spina bifida and more than half of the mice died within four weeks after birth, strongly suggesting the two genes interact with each other.

Because both proteins are involved in neural tube closure, the team reasoned that perhaps mutations in Sec24b might affect the packaging of Vangl2. Mixing cell components and Vangl2 in a test tube, the team added either Sec24b or other related proteins. Only tubes containing Sec24b were able to package Vangl2; other related proteins could not. The team showed that even small changes in the Vangl2 protein prevented Sec24b from properly sorting Vangl2. Instead, Vangl2 was found clumped inside the cell.

Proper cell patterning, explains Ginty, probably is established with very early stage cellular processes that regulate protein production and transport. And the high prevalence of spina bifida in mice with altered Sec24b and Vangl2 suggests that defects in Sec24b and perhaps other Sec genes might be at the root of spinal cord defects in humans. "It will be interesting to see if that is in fact the case," he says.

More information: Nature Cell Biology: www.nature.com/ncb/index.html

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