MODELING PATHOLOGY WITH IPS CELLS

A collaboration between the University of Wisconsin–Madison and the University of Missouri has led to the generation of induced pluripotent stem (iPS) cells from the fibroblasts of a patient with spinal muscular atrophy (SMA), an inherited disorder in which mutations in the *SMN1* gene cause selective loss of lower motor neurons, and lead to death in infancy. The iPS cells differentiated to form motor neurons, which retained the disease phenotype. This research, published in *Nature*, suggests that iPS cells can be used to model the specific pathology of genetic diseases.

"We are interested in disease modeling using stem cells," says lead author Allison Ebert. "We want to use these cells to better understand the mechanisms involved in motor neuron death in SMA and try to develop ways to stop the neurons from dying, either through drug development or gene therapy techniques." The researchers generated iPS cells from skin fibroblasts isolated from a child with SMA. They used viruses expressing *OCT4*, *SOX2*, *NANOG* and *LIN28* to overexpress the pluripotency genes and thereby reprogram the fibroblasts to become iPS cells. They then generated neural stem cells, and lineage-restricted these cells to make motor neurons. Initially, the neurons derived from iPS-SMA cells developed normally, "but with more time in culture, they became smaller, fewer in number, and didn't show synapsin staining as the wild-type motor neurons did," says Ebert. "This would indicate that the iPS-SMA cells can produce motor neurons, but that there is something that is preventing them from surviving long-term."

The iPS-SMA neurons were deficient in SMN protein, but began to express SMN in response to drug treatment, suggesting that the iPS-derived neurons could be used in drug development screens.

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