What decides neural stem cell fate?

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Researchers at Sanford-Burnham Medical Research Institute and their collaborators found that expression of a gene called SOX2 maintains the potential for neural crest stem cells to become neurons in the peripheral nervous system. Their results, published online May 5 by the journal *Cell Stem Cell*, could help better inform therapies aimed at neurocristopathies, diseases caused by defects in the neural crest.

Early in embryonic development, the neural crest – a transient group of stem cells – gives rise to parts of the nervous system and several other tissues. But little is known about what determines which cells become neurons and which become other cell types. A team led by Dr. Alexey Terskikh at Sanford-Burnham Medical Research Institute (Sanford-Burnham) recently found that expression of a gene called SOX2 maintains the potential for neural crest stem cells to become neurons in the peripheral nervous system, where they interface with muscles and other organs. Their results, published online May 5 by the journal *Cell Stem Cell*, could help better inform therapies aimed at neurocristopathies, diseases caused by defects in the neural crest or neurons, which include microphthamia and CHARGE syndrome.

The SOX2 gene encodes a transcription factor, a type of protein that switches other genes on or off. SOX2 is one of two key genes researchers use to generate induced pluripotent stem cells (iPSCs), which are capable of differentiating into all cell types for research and potential therapeutic applications.

"In this study, we looked at SOX2's role in cells of the peripheral

nervous system and discovered that it's required to sustain multipotency – the ability to differentiate into several cell types in the peripheral nervous system, including neurons and glia," explained Dr. Terskikh, assistant professor in Sanford-Burnham's Del E. Webb Neuroscience, Aging and Stem Cell Research Center.

Using an embryonic stem cell model, Dr. Terskikh and colleagues showed that stem cells in the developing nervous system start out with SOX2, but lose it at the stage when they are considered migratory neural crest cells. Later, as neural crest stem cells aggregate at a subsequent point in development, SOX2 is regained only by those cells fated to become neurons. Neural crest stem cells that remain SOX2-free differentiate into other cell types, but never become neurons.

To determine how SOX2 controls this stage in nervous system development, the researchers looked at the genes it acts upon. They found that SOX2 switches on neurogenin-1 and Mash-1, two genes that support neuronal survival in both the central and peripheral nervous systems.

"If we prevent neural crest stem cells from re-expressing SOX2, we don't get neurons. If we try to push these SOX2-deficient cells to become neurons, they die, but they can readily give rise to glia or smooth muscle cells," Dr. Terskikh said. "We think that one function of SOX2 is to keep cells multipotent or pluripotent for one reason – if they need to become a neuron later in development. We hope this finding will be useful to researchers studying neural crest development and stem cell differentiation."

More information: Cimadamore F, Fishwick K, Giusto, Gnedeva K, Cattarossi G, Miller A, Pluchino S, Brill LM, Bronner-Fraser M, Terskikh AV. Human ESC-Derived Neural Crest Model Reveals A Key Role For SOX2 In Sensory Neurogenesis. *Cell Stem Cell.* May 5, 2011.

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