Text by Mitch Leslie
mitchleslie@comcast.net

Career guidance for stem cells

BMP pathway spurs neuron progenitors to remain undifferentiated.

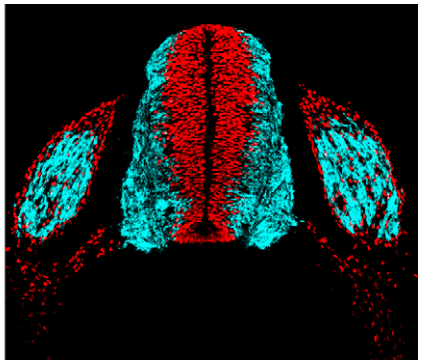
A dividing stem cell faces an existential decision—whether to differentiate or remain a stem cell. SMAD proteins steer neural stem cells toward the latter option, Le Dréau et al. reveal (1).

Three outcomes are possible when a stem cell divides (2). In self-expanding divisions, both daughter cells take after their parent, increasing the ranks of stem cells. In self-renewing divisions, one daughter can start to specialize but the other remains a stem cell, thereby maintaining the progenitor population. Finally, both daughter cells can begin to differentiate. This type of division is known as self-consuming because it depletes stem cell numbers. Which course a progenitor cell follows shapes development and affects an adult tissue's ability to renew itself (3). Researchers working on therapeutic uses for stem cells would like to have the ability to influence this choice.

For the neural stem cells that Le Dréau et al. study, researchers are just beginning to discover what dictates the division type (4). Le Dréau et al. use reporter genes to track the outcome of divisions in the developing spinal cord of chick embryos. In a previous study, the researchers revealed that all three division modes occur during spinal cord formation (5). The team also determined that the Sonic Hedgehog pathway has a big influence on the stem cells that give rise to motor neurons. Sonic Hedgehog favors the self-expanding divisions that spawn two stem cells.

In their new work, Le Dréau et al. looked for factors that control division style in the progenitors of spinal interneurons, which carry signals between neurons. They measured the activity of the Sonic Hedgehog pathway as well as Wnt and bone morphogenetic protein (BMP) signaling during early spinal cord development, when interneurons are born. The Sonic Hedgehog and Wnt pathways only operated in restricted areas of the spinal cord, whereas the BMP pathway was active in much of the structure, suggesting that it guides the fate choice of neural stem cells.

Focal Point



LAB PHOTO COURTESY OF MARTÍ LAB; IMAGE COURTESY OF GWENVAEL LE DRÉAU

(Left to right) Murielle Saade, Irene Gutiérrez-Vallejo, Elisa Martí, and Gwenvael Le Dréau probed the mechanism that controls division type in stem cells of the developing chick spinal cord. They found that two proteins in the BMP pathway, SMAD1 and SMAD5, hold back stem cells, inhibiting their differentiation into neurons. This transverse section of a 4-day-old chick embryo (right) captures neural progenitors (red) and differentiating neurons (blue).

The team showed that the activities of two BMP pathway members—SMAD1 and SMAD5—were high in stem cells going through self-expanding divisions, moderate in cells undergoing self-renewing divisions, and low in progenitors going through self-consuming divisions. When the researchers knocked down the levels of SMAD1 and SMAD5 with short-hairpin RNAs, they saw a doubling in the number of divisions that produce two neurons, whereas the number of divisions yielding two stem cells plunged by 50%. Loss of the BMP pathway members therefore caused the number of progenitors to dwindle.

> **"There might be a physiological contribution for aneuploidy in neurogenesis."**

Other studies have revealed that division style modifies the cell cycle. The team found that blocking either SMAD1 or SMAD5 shortened the cell cycle, mainly by truncating S phase. When the researchers isolated the different types of progenitors, cells undergoing self-consuming divisions stood out because their DNA content was unusual. Some of these cells were aneuploid, as were the neurons they produced. The discovery that self-consuming divisions give rise to aneuploid neurons was surprising, says senior author Elisa Martí. These cells could be beneficial because they are more diverse genetically and therefore are potentially more adaptable. "There might be a physiological contribution for aneuploidy in neurogenesis," Martí says.

The findings pinpoint the BMP pathway as one factor that decides whether neural stem cells give rise to interneurons or to more stem cells. Stronger BMP signaling boosts the number of stem cells, whereas weaker signaling promotes neurogenesis and depletes the pool of progenitors. The team's findings also suggest that a cell has already settled on its fate before there are any changes in cell cycle parameters, such as shortening of S phase. The team now wants to identify the downstream proteins in the BMP pathway that orchestrate the different division types.

1. Le Dréau, G., et al. 2014. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201307031.
2. Götz M., and W.B. Huttner. 2005. *Nat. Rev. Mol. Cell Biol.* 6:777–788.
3. Göritz, C., and J. Frisen. 2012. *Cell Stem Cell.* 10:657–659.
4. Franco, S.J., and U. Muller. 2013. *Neuron.* 77:19–34.
5. Saade, M., et al. 2013. *Cell Rep.* 4:492–503.