For Stem Cells, Practice Makes Perfect

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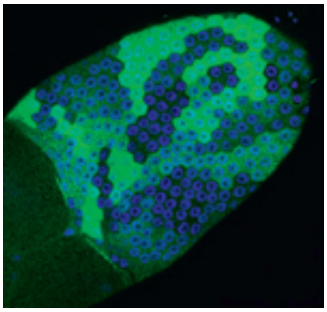

Follicle cells show variable gene expression

(PhysOrg.com) -- Multipotent stem cells have the capacity to develop into different types of cells by reprogramming their DNA to turn on different combinations of genes, a process called "differentiation." In a new study, researchers from the Carnegie Institution for Science have found that reprogramming is imperfect in the early stages of differentiation, with some genes turned on and off at random. As cell divisions continue, the stability of the differentiation process increases by a factor of 100. The finding will help scientists understand how stem cells reprogram their genes and why fully differentiated cells are very hard to reprogram, knowledge with potential impacts on aging, regenerative medicine, and cancer research.

Allan Spradling and Andrew Skora of the Carnegie Institution's Department of Embryology studied stem cells in the ovaries of the fruit fly Drosophila. The stem cells develop into specialized cells, called

follicle cells, over a series of nine generations of cell divisions. Using a biochemical method known as a GAL4-UAS reporter gene, the researchers were able to keep track of genes located at many different sites on the chromosomes as the follicle cells developed. If the programming of a reporter gene was perfectly transmitted from parent to daughter cell, then the follicle cells would express the gene at the same level after each division. But the researchers found that in the first division alone random changes occurred 41% of the time. By the fifth division changes took place about 8% of the time. By the ninth division, however, such changes happened only 0.37% of the time, a stability increase of more than 100-fold.

The instability of epigenetic information during the early differentiation of ovarian stem cells surprised the researchers. They speculate that stem cells may be deficient in epigenetic inheritance machinery in order to prevent them from differentiating prematurely, and thereby to help maintain the flexibility to give rise to many different cell types. "Stem cells appear unable to faithfully pass on a particular genetic program to their daughter cells," says Spradling. "Apparently, before one particular kind of cell can differentiate from a stem cell, its progenitors have to learn how to maintain and transmit epigenetic (programming) information."

Spradling explains that the mechanism by which the reprogramming and stabilization occurs is not well understood, but their research confirmed the expectation that at least some of the critical changes take place in the gene-bearing chromosomes themselves, rather than in external factors such as the cell's environment or signals from other cells. Most likely the reprogramming alters proteins on the chromosome which package the DNA and control which genes are expressed. Changes in chromosome structure, as opposed to changes in the genes themselves, that can be passed on from one generation to the next are called epigenetic changes. The researchers hope that their research will provide a way to learn more

about the methods cells use to transmit epigenetic information faithfully during cell division.

"Epigenetic inheritance underlies the ability of multi-celled organisms to develop from single-celled zygotes to complex creatures with an array of specialized cells and tissues," says Spradling. "But the amount of epigenetic information transmitted at different stages of cellular differentiation remains little known. Applying the GAL4-UAS system within a defined stem cell lineage allows us to measure the stability of epigenetic information quantitatively, and to follow how it changes during development. This will have an impact across a broad swath of stem cell research."

The results of this research are published in the *Proceedings of the National Academy of Sciences.*

Provided by Carnegie Institution