Dormant stem cells for emergencies

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Many specialized cells, such as in the skin, intestinal mucosa or blood, have a lifespan of only a few days. For these tissues to function, a steady replenishment of specialized cells is indispensable. This is the task of so-called "adult" stem cells also known as tissue stem cells.

Stem cells have two main characteristics: First, they are able to differentiate into all the different cell types that make up their respective tissue – a property called pluripotency. Second, they need to renew themselves in order to be able to supply new specialized tissue cells throughout life. These processes have best been studied in mouse bone marrow.

Up to now, scientists have assumed that adult stem cells have a low division rate. According to theory, they thus protect their DNA from mutations, which happen particularly during cell division and can lead to transformation into tumor stem cells. However, the actual number of divisions of a blood stem cell throughout an organism's lifespan has remained unknown.

Professor Dr. Andreas Trumpp and Dr. Anne Wilson have now discovered a group of stem cells in mouse bone marrow that remain in a kind of dormancy almost throughout life. Trumpp, who has been head of the Cell Biology Division at DKFZ since summer 2008, had carried out these studies at the Ecole Polytechnique Fédérale in Lausanne, Switzerland, jointly with colleagues at the Ludwig Institute for Cancer Research located in the same city.

The scientists labeled the genetic material of all mouse blood cells and subsequently investigated how long this label is retained. With each division, the genetic material is apportioned to the daughter cells and, thus, the labeling dilutes. During these studies, the investigators discovered the dormant stem cells which divide only about five times throughout the life of a mouse. Translated to humans, this would correspond to only one cell division in 18 years. Most of the time, these cells, which constitute no more than about 15 percent of the whole stem cell population, remain in a kind of dormancy with very low metabolism. In contrast, stem cells of the larger group, the "active" stem cells, divide continuously about once a month.

However, in an emergency such as an injury of the bone marrow or if the messenger substance G-CSF is released, the dormant cell population awakes. Once awakened, it shows the highest potential for self-renewal ever to be observed in stem cells. If transplanted into irradiated mice, these cells replace the destroyed bone marrow and restore the whole hematopoietic system. It is possible to isolate new dormant stem cells from the transplanted animals and these cells are able to replace bone marrow again – this can be done several times in a row. The situation is different with "active" stem cells, where bone marrow replacement can successfully be carried out only once.

"We believe that the sleeping stem cells play almost no role in a healthy organism," Trumpp explains. "The body keeps its most potent stem cells as a secret reserve for emergencies and hides them in caves in the bone marrow, also called niches. If the bone marrow is damaged, they immediately start dividing daily, because new blood cells are needed quickly." Once the original cell count is restored and the bone marrow is repaired, these stem cells go back to deep sleep. The larger population of "active" stem cells, however, keeps up the physiological balance of blood cells in the normal healthy state.

Andreas Trumpp expects that these results may give valuable impetus to our understanding of cancer stem cells: "Cancer stem cells, too, probably remain in a dormant state most of the time – we think that this is one of the reasons why they are resistant to many kinds of chemotherapy that target rapidly growing cells. If we were able to wake up these sleepers before a patient receives treatment, it might be possible to also eliminate cancer stem cells for the first time and, thus, to treat the disease much more effectively by destroying the supply basis."

In a second article*, Dr. Elisa Laurenti from Trumpp's team shows that the two cancer genes c-Myc and N-Myc play a vital role in the functioning of stem cells. The two genes provide the blueprints for what are called transcription factors, which in turn regulate the activity of other genes and are overactive particularly in cancer cells. If both c-Myc and N-Myc are switched off at the same time in mice, the animals quickly start suffering from a general lack of blood cells and quickly die.

The two genes are not only responsible for survival of nearly all blood cells, but they also jointly control the two prime characteristics of stem cells – the capability of self-renewal and the potential to produce differentiated blood cells. This result is not only relevant for our understanding of stem cells, but it also explains the damage that can be caused by overactive Myc genes. Trumpp explains: "In tumors, too, c-Myc and N-Myc are presumably responsible for the self-renewal of cancer stem cells and, thus, for uncontrolled growth."

References:

Anne Wilson; Gabriela Oser; Richard van der Wath; William Blanco; Elisa Laurenti; Maike Jaworski; Cyrille Durant; Leonid Eshkind; Ernesto Bockamp; Pietro Lio; Robson MacDonald, and Andreas Trumpp: Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. CELL 2008, DOI

10.1016/j.cell.2008.10.048

*Elisa Laurenti, Barbara Varnum-Finney, Anne Wilson, Isabel Ferrero, William E. Blanco-Bose, Armin Ehninger, Paul S. Knoepfler, Pei-Feng Cheng, H. Robson MacDonald, Robert N. Eisenman, Irwin D. Bernstein, and Andreas Trumpp: Hematopoietic Stem Cell Function and Survival Depend on c-Myc and N-Myc Activity. CELL Stem Cell 2008, DOI 10.1016/j.stem.2008.09.005

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