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From Stem Cell to Progenitor and Back Again

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Under normal homeostatic conditions, tissue stem cells undergo long-term self renewal and produce progeny that differentiate into several different cell types. But what happens if the stem cells are lost? In a recent issue of *Developmental Cell*, Nakagawa et al. (2007) propose that the progeny of stem cells, called transit-amplifying progenitor cells, are able to replace lost stem cells.

A key feature of tissue stem cells is their ability to perpetuate and maintain their population over the life span of the organism. Although there may be some decline in stem cell vigor with aging, self renewal is a remarkably stable property. However, in cases where stem cells are lost, the stem cell population can be regenerated. Is this regenerated stem cell population solely replenished from equivalent stem cells, or are there additional safe guards in the system that would allow other cells to acquire stemness? A stem cell's immediate surrounding microenvironment, the niche, is crucial for its maintenance. Can an empty niche impose stem cell features on other cells, or is self renewal strictly limited to actual stem cells? Such questions get to the heart of what a stem cell is.

The mouse testis is an elegant and powerful model with which to study stem cells. Spermatogonia, which include subpopulations of stem and progenitor cells (some of which have yet to be defined), give rise to mature spermatozoa in 40 days, which then leave the seminiferous tubules (Brinster, 2002). The structural organization of the testis makes it possible to trace the progeny of individual stem cells. Furthermore, it is possible to analyze the reconstitution of the stem cell population after an insult by studying regeneration of this population or through transplantation experiments.

In an elegant study, Nakagawa et al. (2007) pulse-labeled undifferentiated cells in the mouse male germline using an inducible genetic recombination system. Recombination (and thus labeling of the cells) occurs both in the stem cells and in their immediate descendants, the transit-amplifying progenitor cells. After 3 months (that is, after several rounds of spermatogenesis), all labeled cells are derived from self-renewing stem cells and constitute 0.3% of the cells in the testis. Nakagawa and colleagues next examined reconstitution of the stem cell population after transplantation, or regeneration following an insult. Remarkably, they found that 3 months after transplantation of pulse-labeled testes into germ cell-depleted testes, close to 12% of the cells that constitute the regenerated testis were labeled (Nakagawa et al., 2007). They obtained similar results when they examined regeneration after an insult such as treatment with busulfan, which eliminates stem cells in the testis. Thus, the recombination frequency is different in the stem cells that maintain normal homeostasis and in the cells that act as long-term stem cells after transplantation or regeneration. This finding indicates that the stem cells that maintain normal homeostasis do not appear to be the same cell population that repopulates the niche after transplantation and regeneration.

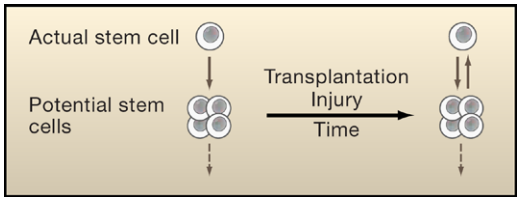

Figure 1. Stem Cells on a Round Trip
Normally, a small population of stem cells gives rise to transit-amplifying progenitor cells that differentiate to form the different cell types in the testis. Nakagawa et al. (2007) now show that when actual stem cells are lost due to an injury or perhaps naturally over time, the remaining progenitor cells or progenitor cells acquired by transplantation have the potential to acquire stem cell functions.

It has long been suspected that cells other than those that maintain homeostasis (actual stem cells) can take over stem cell function in certain situations, and they have been referred to as potential stem cells (Potten and Loeffler, 1990). Progenitor cells can take on stem cell functions when stem cells are lost in the *Drosophila* germ line (Brawley and Matunis, 2004; Kai and Spradling, 2004), but this has been difficult to establish unambiguously in mammals.

To explore whether dormant stem cells or transit-amplifying progenitor cells represent potential stem cells in the mouse testis, Nakagawa and colleagues next transplanted cells at different time points after pulse labeling. They find that it is only when cells are

transplanted shortly after labeling (i.e., shortly after recombination) that the reconstituting stem cells have a different recombination frequency than the actual stem cells (Nakagawa et al., 2007). This establishes that the cell population with the higher recombination frequency is transient, indicating that transit-amplifying progenitor cells are potential stem cells in this system (Figure 1). Furthermore, by studying mice over long time periods, Nakagawa and colleagues provide evidence that actual stem cells are lost and replaced over time (Nakagawa et al., 2007), although it is unclear whether they are replaced by potential stem cells or through symmetric divisions of actual stem cells.

An important and fortuitous feature in the system exploited by Nakagawa and colleagues is a different recombination frequency between the stem cells and progenitor cells. If the frequency were the same in both compartments, there would be no reduction in the number of recombined potential stem cells over time, as they would be replenished at the same recombination frequency from actual stem cells. The much larger absolute number of progenitor cells than actual stem cells cannot explain their results. The reason for the different recombination efficiency in these cellular compartments is unknown but could, for example, be due to different levels of expression of the transgene, different epigenetic states, or chromatin structure.

The results of Nakagawa et al. (2007) indicate that stem cell function is not strictly cell autonomous and that there is a potential for some cells to gain stemness. Strictly speaking, a lineage relationship between the actual and potential stem cells has not been established in their study, but the most plausible model is that the potential stem cells are the immediate descendants of the actual stem cells.

Stem cells are notoriously difficult to identify in tissues, which has hampered the study and use of these cells. Transplantation assays have been invaluable for the identification of stem cells in several tissues (Weissman, 2000). The results of Nakagawa et al. (2007), however, underscore the difficulty of drawing definitive conclusions regarding the identity of actual stem cells from transplantation or regeneration experiments alone. Strategies for genetic labeling similar to those used by Nakagawa and colleagues can be developed for other stem cell lineages. This may reveal whether potential stem cells are a general feature of many tissues and may aid in the identification of the actual stem cell population.

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The Sunny Side of p53

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Skin, the largest organ of our body, is often plagued by cancer because of exposure to ultraviolet radiation from the sun. A report by Cui et al. (2007) in this issue of *Cell* explains how the tumor suppressor p53 protects the skin by stimulating the suntan response.

The p53 tumor suppressor gene is one of the most frequent targets for genetic alterations in cancer. Direct mutational inactivation of p53 is observed in close to half of all human tumors. This has spurred extensive research on p53, its biochemistry, and the mechanisms whereby it suppresses cancer (Levine et al., 2006). It is now appreciated that a key role of p53 as a tumor suppressor is to prevent the emergence of cells with permanently defective genomes, which are likely to spawn cancer. To a large extent, the functions of p53 rely on its ability to act as a sequence-specific transcriptional regulator. Moreover, p53 is strategically positioned to respond to a wide array of conditions that may endanger genome integrity.

How does p53 prevent the emergence of cells with defective genomes? Initially, p53 was viewed primarily as an executioner, capable of identifying cells with severe genomic damage and eliminating them from the replicative pool,