On Stem Cells in the Human Breast

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Petersen and Polyak (2011) elegantly explain the developmental hierarchy of the human mammary gland as it is currently understood. It is amazing that the small pool of stem cells can be cyclically called on to give rise to the progenitors and more differentiated myoepithelial and luminal epithelial cells that are needed for expansion during monthly estrous cycles and in preparation for lactation. How do the stem cells respond so perfectly and repetitively throughout a woman's childbearing years? Do stem cells harbor internal circadian clocks that work in time with similar clocks in the endocrine system and ovaries? Or are mammary stem cells able to respond to shifting physiological needs of the organism because their functions are controlled by their microenvironment, which changes with the ebb and flow of the physiological tide? That estrous cycles can vary according to life's circumstances (e.g., changes in nutrition, exercise, or stress) and because lengths of pregnancies and lactation periods differ for each pregnancy, it seems likely that mammary stem cells are governed by an external control mechanism that interacts with systemic changes in physiology.

That stem cells and all of their progeny share identical genomes, and that stem cells reside inside niche microenvironments that are completely unique as compared to those of the surrounding tissue, suggests that microenvironments exert a tremendous influence over stem cell behavior. Even mathematical models of hematopoiesis suggested that stem cell-extrinsic regulation was the best way to explain why stem

cells responded to a wide variety of physiological needs (Loeffler and Roeder 2002; Roeder and Lorenz 2006). Experimentally, microenvironmental control of mammary progenitors, hematopoietic stem cells, embryonic stem cells, and neural progenitors has been shown by use of functional assays on arrayed combinatorial microenvironments (Flaim et al. 2005; Soen et al. 2006; LaBarge et al. 2009; Lutolf et al. 2009). And perhaps the grandest demonstration of the power of the microenvironment over stem cell function was shown repeatedly when adult stem cells from one tissue were shown to give rise to other tissues after they were placed in tissue-specific microenvironments different from their native ones (Blau et al. 2001; Boulanger et al. 2007; Booth et al. 2008). An important likelihood that arises from those experiments is that the phenotype of a stem cell is probably affected by its microenvironment (LaBarge et al. 2007). To completely understand the identity and control of mammary stem cells, we must meticulously define the microenvironment(s) they inhabit.

As Petersen and Polyak point out, the methodology used to describe the stem cell hierarchy in adult hematopoietic systems has guided many subsequent studies aimed at identifying hierarchies in epithelial tissues. Accordingly, tissues are dissociated into suspensions of single cells, fractionated with a cell sorting technology, and the fractions are assayed for stem cell activity in a number of culture assays and in vivo when possible. Demonstration that a single cell can give

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rise to the tissue in question is often referred to as the “gold standard” experiment, and it is an unfortunate burden of proof held over from the hematopoietic field. Blood is an interesting tissue in that centers for hematopoiesis shift throughout development among locations that are anatomically close to the circulation, and it is thought that in adults, blood is produced from niches in marrow and vasculature (Sacchetti et al. 2007; Hooper et al. 2009; Butler et al. 2010). Thus, it makes sense that a single hematopoietic stem cell should regenerate the blood as nothing more is being asked of it than to do exactly what it was meant to, and to do it in the perfect microenvironment. Moreover, in the hematopoiesis model, where the microenvironment was essentially perfect, it stands to reason that one would only observe different activities according to the fraction from which single cells were derived. These facts may help explain why it has taken so long for acceptance of the idea that microenvironments can control stem cell activity. By comparison, adult mammary epithelial stem cells are distinct from the neonatal stem cells that made the initial mammary rudiment, and the adult stem cells evolved within an intricate epithelial architecture that was within a tissue stroma. That a single mouse mammary stem cell could give rise to an outgrowth was shown to occur at very low frequency (Shackleton et al. 2006; Stingl et al. 2006), and it has yet to be shown that a single normal human mammary stem cell can generate an outgrowth in a murine fat pad. Given the biological differences between blood and mammary epithelium, it is no surprise that the identity of human mammary stem cells and the mechanisms that govern them are still hotly debated.

REFERENCES

*Reference is also in this collection.

- Blau HM, Brazelton TR, Weimann JM. 2001. The evolving concept of a stem cell: Entity or function? *Cell* **105**: 829–841.
- Booth BW, Mack DL, Androutsellis-Theotokis A, McKay RD, Boulanger CA, Smith GH. 2008. The mammary microenvironment alters the differentiation repertoire of neural stem cells. *Proc Natl Acad Sci* **105**: 14891–14896.
- Boulanger CA, Mack DL, Booth BW, Smith GH. 2007. Interaction with the mammary microenvironment redirects spermatogenic cell fate in vivo. *Proc Natl Acad Sci* **104**: 871–876.
- Butler JM, Nolan DJ, Vertes EL, Varnum-Finney B, Kobayashi H, Hooper AT, Seandel M, Shido K, White IA, Kobayashi M, et al. 2010. Endothelial cells are essential for the self-renewal and repopulation of Notch-dependent hematopoietic stem cells. *Cell Stem Cell* **6**: 251–264.
- Flaim CJ, Chien S, Bhatia SN. 2005. An extracellular matrix microarray for probing cellular differentiation. *Nat Methods* **2**: 119–125.
- Hooper AT, Butler JM, Nolan DJ, Kranz A, Iida K, Kobayashi M, Kopp HG, Shido K, Petit I, Yanger K, et al. 2009. Engraftment and reconstitution of hematopoiesis is dependent on VEGFR2-mediated regeneration of sinusoidal endothelial cells. *Cell Stem Cell* **4**: 263–274.
- LaBarge MA, Petersen OW, Bissell MJ. 2007. Of microenvironments and mammary stem cells. *Stem Cell Rev* **3**: 137–146.
- LaBarge MA, Nelson CM, Villadsen R, Fridriksdottir A, Ruth JR, Stampfer MR, Petersen OW, Bissell MJ. 2009. Human mammary progenitor cell fate decisions are products of interactions with combinatorial microenvironments. *Integr Biol (Camb)* **1**: 70–79.
- Loeffler M, Roeder I. 2002. Tissue stem cells: Definition, plasticity, heterogeneity, self-organization and models—A conceptual approach. *Cells Tissues Organs* **171**: 8–26.
- Lutolf MP, Doyonnas R, Havenstrite K, Koeckar K, Blau HM. 2009. Perturbation of single hematopoietic stem cell fates in artificial niches. *Integr Biol (Camb)* **1**: 59–69.
- * Petersen OW, Polyak K. 2011. Stem cells in the human breast. *Cold Spring Harb Perspect Biol* doi: 10.1101/cshperspect.a003160.
- Roeder I, Lorenz R. 2006. Asymmetry of stem cell fate and the potential impact of the niche: Observations, simulations, and interpretations. *Stem Cell Rev* **2**: 171–180.
- Sacchetti B, Funari A, Michienzi S, Di Cesare S, Piersanti S, Saggio I, Tagliafico E, Ferrari S, Robey PG, Riminucci M, et al. 2007. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. *Cell* **131**: 324–336.
- Shackleton M, Vaillant F, Simpson KJ, Stingl J, Smyth GK, Asselin-Labat ML, Wu L, Lindeman GJ, Visvader JE. 2006. Generation of a functional mammary gland from a single stem cell. *Nature* **439**: 84–88.
- Stingl J, Eirew P, Ricketson I, Shackleton M, Vaillant F, Choi D, Li HI, Eaves CJ. 2006. Purification and unique properties of mammary epithelial stem cells. *Nature* **439**: 993–997.
- Soen Y, Mori A, Palmer TD, Brown PO. 2006. Exploring the regulation of human neural precursor cell differentiation using arrays of signaling microenvironments. *Mol Syst Biol* **2**: 37.

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