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Competition for Food Drives Stem Cell Fate in Facultative Niches

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Mechanisms regulating maintenance of the stem cell pool in facultative niches of the mammalian testis are poorly understood. In this issue of *Cell Stem Cell*, Kitadate et al. (2019) propose a minimal model in which stem cells compete for limited resources of fibroblast growth factors, which predicts their density during homeostasis and regenerative conditions.

Tissue homeostasis relies on fine-tuning the balance between the self-renewal and differentiation of stem cells. A tissue-specific specialized local microenvironment, the niche, in which stem cells reside, is critical for their long-term maintenance. The anatomy of the niche is clearly defined in some invertebrate tissues, such as the apical tip of the *Drosophila* testis, in which stem cells divide asymmetrically by mechanisms such as mitotic spindle orientation: the daughter cell physically contacting this discrete or closed niche retains stemness, while the other, moving away and escaping from its control, differentiates. In mammalian tissues, however, delineating a niche remains a challenging task owing to the complexity of the tissue or the lack of histological markers to precisely identify stem cells. Although discrete niches have been described, for example, in intestine, other tissues, such as testis, are thought to contain numerous facultative or open niches, relatively wide areas that cannot be precisely defined anatomically, in which stem cells are scattered among their progeny (Morrison and Spradling, 2008).

In the murine testicular niche, a subset of the type A undifferentiated spermatogonia lying on the basement membrane of the seminiferous tubules, the A_{single} (A_s) spermatogonia, are typically considered to be spermatogonial stem cells (SSCs) in a hierarchical model (de Rooij, 2017). Recently, a hierarchy in the A_s population was also suggested related to the high expression of the transcription factor ID4 (Helsel et al., 2017). However, an alter-

native model exists that posits that asymmetric fate is no longer achieved at each stem cell division but at the level of the population of undifferentiated spermatogonia expressing the receptor $GFR\alpha 1$ (Hara et al., 2014). In this population, cells are equipotent according to stemness, and stem cell loss following differentiation can be replaced by any cells from the $GFR\alpha 1^+$ pool, the fate of each stem cell being stochastically decided. In this issue of *Cell Stem Cell*, Kitadate et al. (2019) studied the dynamics of this population of $GFR\alpha 1^+$ spermatogonia in mutant mice for the fibroblast growth factors (FGFs) pathway during homeostasis and regenerative conditions. They show that the model of competition of stem cells for a limited supply of mitogens, here FGFs, can capture variations of their cell density in facultative niches of seminiferous tubules, which are enriched in FGF-secreting lymphatic endothelial cells.

Kitadate et al. (2019) first identified preferential expression of the growth factor FGF5 in a subset of $CD34^+$ lymphatic endothelial cells, found in regions of seminiferous tubules enriched in $GFR\alpha 1^+$ spermatogonia. FGF5 was shown to regulate *in vitro* proliferation of SSCs and the expression of some stemness genes and to be consumed *in vivo* by $GFR\alpha 1^+$ spermatogonia. Using $Fgf5^{-/-}$, $Fgf5^{+/-}$, and $Fgf5^{+/+}$ mice and a mouse strain carrying an additional copy of *Fgf5*, they observed the control of $GFR\alpha 1^+$ cell density by FGF5 in a strikingly linear dosage-dependent manner. Owing to the redundant roles of members of FGFs (FGF4 and FGF8 being

also expressed in lymphatic endothelial cells), they studied $GFR\alpha 1^+$ cell density in $Fgf4^{+/-}$ and $Fgf8^{+/-}$ heterozygote mice and in intercrosses between all these mutants. Remarkably, they observed again a correlation of $GFR\alpha 1^+$ cell density with the total dosage of *Fgf5*, *Fgf4*, and *Fgf8* genes, showing that FGF availability limits cellular behaviors. Accordingly, a decrease of testis weight and an increase of abnormal tubules were observed in mutant mice. However, proliferation, differentiation, and death of $GFR\alpha 1^+$ cells were not altered in FGF5 mutants. Thus, $GFR\alpha 1^+$ cells paradoxically appear to consume sufficient levels of FGFs to maintain their individual fate despite the variations observed on cell density at the population level in mutants.

Assuming competition between individual $GFR\alpha 1^+$ cells for the limited supply of FGFs, Kitadate et al. (2019) proposed a mathematical model that predicted the fate and dynamics of the $GFR\alpha 1^+$ cell population under homeostatic condition. In ecological systems in which resource availability is limited in the niche, fluctuations of resources can be modulated by the size of the population nested, affecting, in turn, expansion of the population. Kitadate et al. (2019) introduced here an interesting variation in the model, assuming that mitogen (i.e., stemness molecules here) levels affect the stem cell fate decision. The fluctuations between high (low stem cell density) and low (high stem cell density) stemness resources lead, respectively, to either self-renewal or differentiation (Figure 1). Their



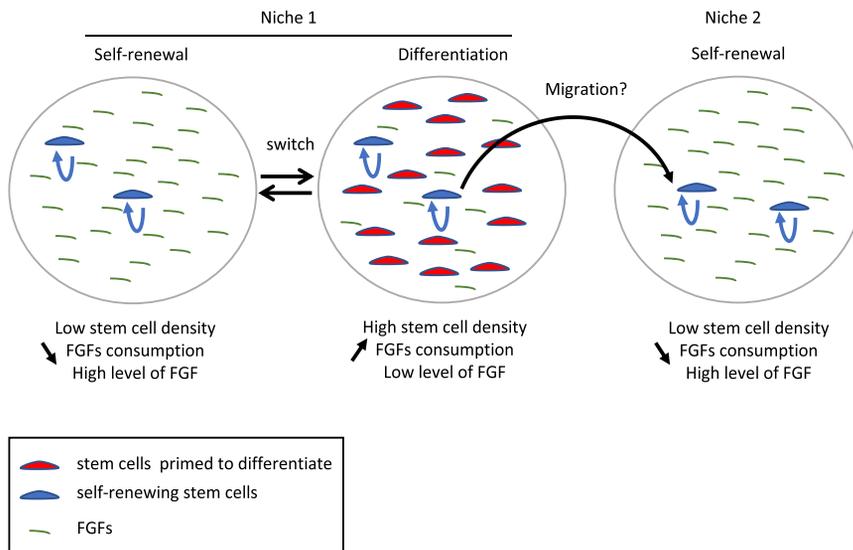


Figure 1. Stem Cell Density Modulates Stemness Resources and the Fate of the Population of Stem Cells in Facultative Niche with a Limited Supply of FGFs

In differentiation-prone niche 1 with high cell density, some stem cells retain stemness to replace lost neighbor stem cells committed to differentiation, and niche 1 switches to a self-renewal state owing to feedback to a low stem cell density. Then, stem cell density increases, and niche 1 returns to the differentiation state. Alternatively, stem cells from niche 1 could also migrate to another niche prone to self-renewal (niche 2) to maintain the stem cell pool.

mathematical model of mitogen competition emulated the variations of $GFR\alpha 1^+$ cell density observed experimentally according to FGF supply. This model proved to be valid regardless of the paradigm of stem cells used (hierarchical or equipotent $GFR\alpha 1^+$ cells) or competition of $GFR\alpha 1^+$ cells with progenitors for FGF resource. Remarkably, their model also predicts the dynamics of recovery of the $GFR\alpha 1^+$ cell density that was observed after tissue injury, i.e., an acute stem cell depletion followed by decaying oscillations of the stem cell density up to the return to the steady-state level. Finally, they observed that FGFs also regulate $GFR\alpha 1^+$ cell density in new “artificial niches,” created by implantation of FGF5-soaked beads near seminiferous tubules, integrating also in their model the property of migration of $GFR\alpha 1^+$ cells and the biased localization of stem cells in the FGF-rich areas.

The capture of the complex regulation of stem cell fate by a minimal model of competition for consumption of a single family of growth factor was quite unexpected. Can stem cell population fate be regulated also by competition to other stemness resources in the niche? Challenging the model of mitogenic competition with GDNF, a ligand for $GFR\alpha 1$ recep-

tor and a crucial growth factor for SSCs expressed cyclically in testis, might be very instructive (Sharma and Braun, 2018). The wide areas of testicular tissue enriched in FGF-secreting cells could also be viewed as a multitude of “discrete niches,” even if they do not fit to all the criteria. Indeed, these niches would exhibit a certain plasticity, switching regularly from a self-renewal-prone state to a differentiation-prone state according to resource levels. Moreover, this activity infers that stem cells would resume the power on their fate with respect to their microenvironment, as their own cell densities regulate niche resources.

Can this model explain the expansion of tumor-initiating cells in cancer? Mutations making transformed stem cells independent of one key component of the niche should give an increased competitive fitness for mitogen competition. Transformed stem cells, in niches with a high density of mutant and normal stem cells and low levels of shared resource, could hence overwhelm progressively normal stem cells by pushing them to differentiation. Interestingly, if we refer to the role of the FGF pathway in SSCs (Ishii et al., 2012), activating mutations of *FGFRs* in human SSCs are thought to be at the origin of spermatocytic seminoma in the

testis (Goriely et al., 2009). In addition, *FGFR* mutations have also been associated with an increased risk for spontaneous Apert syndrome and achondroplasia congenital disorders in offspring when the age of fathers increases (Goriely et al., 2009). This paternal age effect is assumed to result from the clonal expansion of mutant SSCs with age (Martin et al., 2014). Hence, extrapolating the mitogenic competition model to study the evolution of heterogeneous populations of normal and *FGFR* mutant SSCs, co-existing in the niche, could also bring new insights in some pathological contexts. Moreover, future studies on other tissues will undoubtedly allow to ascertain whether mitogenic competition can constitute a general rule driving stem cell density in niche.

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