Stem cell niche signaling goes both ways

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Abstract

Stem cell niches are well-characterized factories of signaling information, but the niche cells themselves also rely on their neighbors for fate maintenance. In this issue of *Developmental Cell*, Herra et al., (2021) reveal bi-directional communication between Drosophila testis niche "hub" cells and somatic cyst stem cells.

Text

Stem cell populations frequently rely on non-dividing signaling centers, known as "niches", in order balance the proliferative and differentiation requirements of cell lineages. Two stem cell populations in the apical tip of the Drosophila testis are regulated in such a niche environment, known as the hub: germline stem cells (GSCs) that ultimately produce sperm, and somatic cyst stem cells (CySCs) that produce somatic support cells (**Figure 1A**). Prior work had identified that niche hub cells, however, go "above and beyond" in order to maintain the CySC population: after genetic ablation of all CySCs, hub cells will exit quiescence and transdifferentiate into CySCs, regenerating the CySC population (Hétié et al., 2014). This regeneration is short-lived, however, because the CySC population cannot be sufficiently supported by the now-reduced number of hub cells, likely contributing to age-dependent physiological decay of the niche. Accordingly, there must be a mechanism that prevents unnecessary transdifferentiation of hub cells to CySCs to protect the hub cell population. The mechanism of hub cell fate control by CySCs is beautifully elucidated in a new paper by Herra et al.

Herra et al first find that the transcription factor complex E2f1/Dp is required for maintenance of the CySC population. Surprisingly, while depletion of E2f1/Dp from all CySCs led to CySC loss, CySCs mutant for *Dp* were maintained well when they had non-mutant neighboring CySCs. The authors find that the primary defect caused by depletion of E2f1/Dp from all CySCs was the loss of hub cells, which in turn led to the loss of CySCs. Based on this observation, they hypothesized that CySCs secrete a factor downstream of E2f1/Dp that maintains hub cells; in the absence of such a factor, hub cells are lost, depleting niche stemness signals and leading to the loss of CySCs.

A screen of secreted factors expressed in CySCs revealed that knockdown of the Activin inhibitor Follistatin phenocopied the Dp phenotype, suggesting that Follistatin acts downstream of Dp. Confirming this, the authors find a reduction in *Follistatin* expression in *Dp-RNAi* animals. Furthermore, addition of exogenous Follistatin fully rescued the hub cell loss found in *Dp-RNAi* animals. From these data, the authors speculate that secretion of Follistatin from CySCs maintains an Activin-low environment for hub cell maintenance. They find that the type I Activin receptor Baboon is present at the membrane of hub cells, suggesting that hub cells are receptive to surrounding Activin levels. The authors autonomously and constitutively activated Baboon in hub cells, and showed that such autonomous Activin-high signaling led to hub cell loss.

Could Activin signaling regulate the identity switch of hub cells into CySCs? Lineage tracing revealed that after autonomous Activin signaling in the hub cells, many CySCs had originated from hub cell transdifferentiation. Similarly, when *Dp* was depleted in CySCs, hub-lineage CySCs were detected at an approximately 9-fold higher rate than control samples. These CySCs that arose from a hub cell transdifferentiation event bore many of the hallmarks of normal CySCs, complete with CySC localization, marker expression, morphology, and cycling behavior.

In normal physiological conditions, total CySC ablation is unlikely. What, therefore, is the functional significance of CySC-to-hub signaling? The authors find that Follistatin expression significantly declines over the course of the fly lifetime, indicating that it may be responsible for the age-related decrease in hub cell numbers (Wallenfang et al., 2006). Age-related hub cell number loss could be blocked by overexpression of Follistatin in CySCs, as could knockdown of *baboon* or the Activin transcriptional effector *Smox* in hub cells. Therefore, the regular replacement of CySCs by transdifferentiating hub cells could be a necessary homeostatic mechanism of regulating CySC number over the course of aging.

Finally, the authors determine which of the three Activin ligands present in *Drosophila* are inhibited by CySC-secreted Follistatin. The Activin ligand Dawdle, unlike ligands Activinβ and Myoglianin, is expressed in the testis stem cell niche. *dawdle* transcription was found in both hub cells and CySCs, and *dawdle* knockdown in hub cells suppressed hub cell loss through transdifferentiation.

Together, these data – including many well-designed controls too numerous to list in this Preview – present an elegant view of bi-directional niche-stem cell signaling in the Drosophila testis. As controlled by the transcription factor complex Dp/E2f1, CySCs will typically express and secrete Follistatin, inhibiting local Dawdle ligands and maintaining an Activin-low environment (**Figure 1B**). In the absence of CySCs, insufficient Follistatin is produced, and Dawdle ligands activate Baboon receptors present on hub cells. Responding to this Activin signal, hub cells will transdifferentiate, adopting a CySC fate: simultaneously resulting in a regeneration of lost CySCs and a loss of necessary hub cells (**Figure 1C**).

Follistatin/Activin signaling has been demonstrated to play a role in stem cell and regenerative contexts in many species, including axolotl (Bryant et al., 2017) limb regeneration; zebrafish cardiomyocte repair (Dogra et al., 2017); and planarian whole-body regeneration (Cloutier et al., 2021; Tewari et al., 2018), among others. Though understudied relative to other TGFβ ligands, Follistatin/Activin are frequently uniquely capable of generating tight signaling environments through secreted activator-inhibitor networks. Herra et. al. now add regulation of niche cell fate to the list of important stem cell behaviors mediated by Follistatin/Activin.

Could other quiescent niche cells be capable not only of maintaining their resident stem cell populations, but also of serving as the cellular source for stem cell regeneration after loss? There is precedent elsewhere: Paneth cells, which serve as niches for $Lgr5^+$ intestinal stem cells (SCs), can generate $Lgr5^+$ SCs after irradiation-induced loss (Yu et al., 2018). Notably, hub cells and CySCs share a common developmental lineage (Okegbe and DiNardo, 2011), and Paneth cells are direct differentiation progeny of $Lgr5^+$ SCs. Such lineage relationships could potentially prime these pairs for some degree of fate interconversion in the adult not available to developmentally divergent niche/stem cell pairs (e.g., hub cells and GSCs). Nevertheless, this work highlights the necessity of questioning the exclusive primacy of stem cell self-renewal in maintenance of many stem cell populations.

These and other questions remain, and the advances described here by Herra et. al. provide an excellent framework to truly understand the complexities of stem cell niche dynamics.

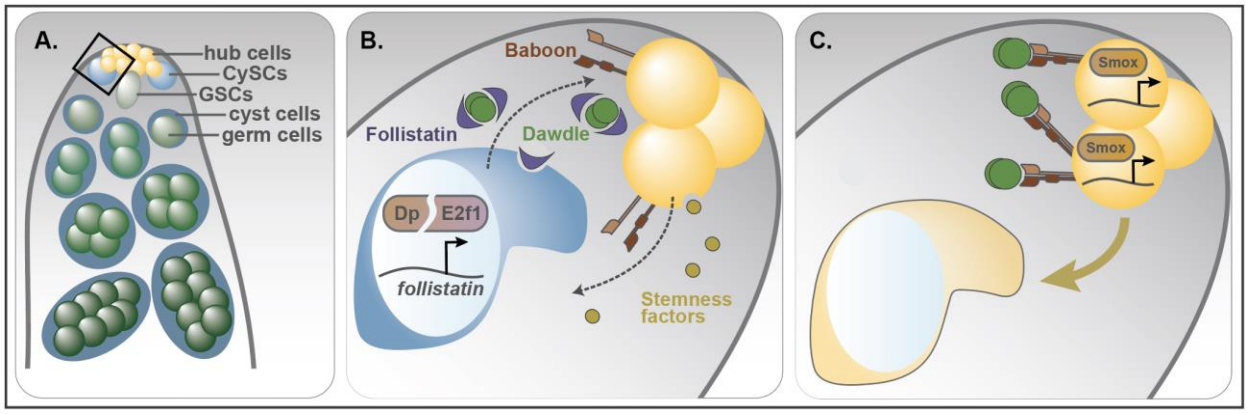

Figure 1. Model for bi-directional hub communication. A. The Drosophila apical testis. Hub cells at the tip are contacted by cyst stem cells (CySCs) and germline stem cells (GSCs). Differentiating cyst cells provide support to the differentiating germ cells through encapsulation. **B.** Bi-directional communication. In intact testes, CySCs produce Follistatin under the control of Dp/E2f1. Secreted Follistatin inhibits the local Activin ligand Dawdle, which fails to activate the Activin receptor Baboon on hub cells. Hub cells remain quiescent and continue to secrete stemness factors to maintain CySC fate. **C.** In the absence of functional CySCs, there is insufficient Follistatin expression to inactivate Dawdle, which in turn activates Baboon. Positive Activin signaling in hub cells, mediated by Smox, leads to a loss of hub cell quiescence and hub-to-CySC transdifferentiation.

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