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A Competitive Cell Fate Switch

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Whereas tissue development and homeostasis depend on stem cell self-renewal and differentiation, the mechanisms that balance these processes remain incompletely understood. Pan et al. (2014) now show that competitive protein-protein interactions between Bam and COP9 signalosome components regulate cell fate decisions within the *Drosophila* ovarian germline stem cell lineage.

Tissue development and homeostasis depend on the highly regulated activity of self-renewing stem cells and their differentiating progeny. Stem cells often reside in specialized microenvironments called niches (Morrison and Spradling, 2008). Cells that comprise the niche produce a variety of factors that keep resident stem cells in an undifferentiated state. When a stem cell divides, any daughter cell displaced outside of the niche can undergo the process of differentiation to take on a more specialized function within the tissue. Understanding how stem cell progeny switch their gene expression programs at the onset of differentiation remains a fundamental goal in the field. Recent work from Xie and colleagues (Pan et al., 2014) provides molecular insights into how this switch occurs in the *Drosophila* ovary.

The *Drosophila* ovary has emerged as an outstanding model for studying molecular interactions between niche cells and stem cells (Figure 1) (Slaidina and Lehmann, 2014). Within the ovary, germline stem cells (GSCs) maintain close contact with a group of somatic cells called cap cells, which produce a variety of growth factors, including a bone morphogenic protein (BMP) family member called Decapentaplegic (Dpp). Activation of a canonical BMP signal transduction pathway in GSCs results in the transcriptional silencing of a gene called *bag-of-marbles* (*bam*). Upon division, GSC daughters displaced away from the cap cell niche, referred to as cystoblasts, no longer experience BMP signaling and transcribe *bam*, resulting in differentiation. Loss of *bam* results in tumor formation, marked by the accumulation of germ cells arrested in a precystoblast-like state. By contrast, ectopic expression of *bam* within GSCs results in their precocious differentiation. Therefore, Bam is both necessary and sufficient for germ cell differentiation in the *Drosophila* germline.

The function of Bam protein remains poorly understood. Bam exhibits a high degree of amino acid sequence divergence even among closely related species. Furthermore, a limited number of cells within the ovary express Bam, precluding the use of biochemical approaches to characterize its molecular function. Despite these obstacles, several previous studies have provided important clues about the function of this enigmatic protein. For example, Bam binds to a protein called Benign gonial cell neoplasm (Bgcn), which contains an RNA helicase-associated domain (Li et al., 2009; Ohlstein et al., 2000). Loss of *bgcn* results in the same germ cell tumor phenotype as *bam* mutants (Ohlstein et al., 2000), and expression of *bam* in a *bgcn* mutant background fails to drive GSC differentiation (Lavoie et al., 1999). Thus, Bam and Bgcn likely act together to promote differentiation. Additional studies indicate that Bam acts to repress the expression and activity of stem cell maintenance factors like *nanos* and *pumilio*, giving rise to a model whereby Bam and Bgcn drive germ cell differentiation by turning off gene expression programs that foster GSC self-renewal (Slaidina and Lehmann, 2014).

Xie and colleagues, reporting in Nature (Pan et al., 2014), now reveal that Bam also interacts with a component of the COP9 signalosome (Csn). Csn complex members were originally discovered in genetic screens as repressors of photomorphogenesis in *Arabidopsis* (Wei and Deng, 2003). Subsequent analyses showed that the complex is typically composed of eight different subunits (Csn1–Csn8), many of which exhibit conservation from yeast to mammals (Wei and Deng, 2003). The Csn complex has a variety of conserved functions, including inactivation of Cullin-RING E3 ubiquitin ligases. In *Drosophila*, loss of *Csn4* and *Csn5* results in a variety of defects during oogenesis, some of which can be traced to a failure to properly degrade cyclin E (Doronkin et al., 2003).

Using a yeast two-hybrid screening strategy, Pan et al. (2014) identified Csn4 as a potential interacting partner of Bam. Further biochemical experiments confirmed this interaction in vivo. Interestingly, direct coimmunoprecipitation experiments failed to detect physical interactions between Bam and Csn5, suggesting that association of Bam with Csn4 may be outside the context of the COP9 complex. Mapping interaction domains revealed that Bam binds Csn4 through the same domain used to bind to Bgcn. The authors further showed that increasing amounts of Csn4 in cultured cells decreased the interaction between Bam and Bgcn. Likewise, interactions with Bam weakened the association of Csn4 with Csn5, Csn6, and Csn7, but they did not affect binding between Csn6 and other Csn components. These results suggest that Bgcn and Csn4 compete for Bam binding and that Bam sequesters Csn4 away from the COP9 complex.

Consistent with this hypothesis, the authors found that Csn4 and Bam genetically antagonize one another. Heterozygous *Csn4* mutations suppressed the differentiation defects exhibited by *bam* mutants. Consistently, overexpression of *Csn4* in a *bam* heterozygous mutant background resulted in an increased number of undifferentiated cystoblasts

and two-cell cysts compared to *Csn4* overexpression in an otherwise wild-type background. Furthermore, *Csn4* overexpression suppressed the GSC loss phenotype caused by ectopic *bam* expression in GSCs. Together, these data suggest that Bam-mediated sequestration of Csn4 promotes GSC differentiation.

Bam binding to Csn4 appears to act as a molecular switch between GSC self-renewal and differentiation. Homozygous *Csn4* and *Csn5* mutant GSCs were lost from the niche over time more rapidly than controls, indicating that their function is required for GSC maintenance. Immunofluorescence staining indicated that the function of the COP9 complex in GSCs is likely independent of two other well-established mechanisms that govern GSC maintenance: BMP signaling and E-cadherin-dependent adhesion to the niche. In addition, *Csn5* mutant GSC progeny failed to differentiate normally. Similarly, loss of other Csn members, with the exception of Csn4, resulted in an increase in the number of undifferentiated germ cells. Together, these findings suggest that the COP9 complex carries out two distinct and opposing functions in the early *Drosophila* germline. When bound to Csn4, the complex promotes GSC maintenance. By contrast, sequestration of Csn4 by Bam frees the signalosome to drive germ cell differentiation.

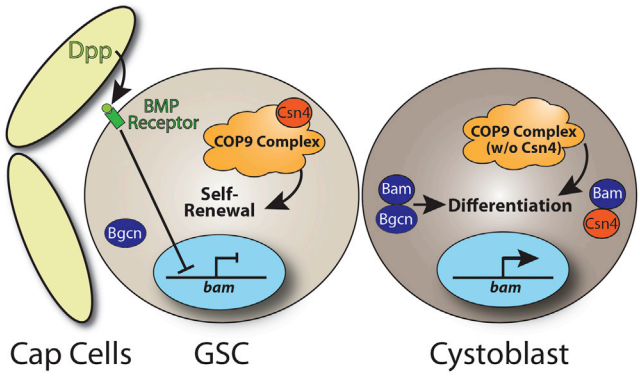

Figure 1. Model for How Bam Binding to Csn4 Switches the Activity of COP9 Complex from GSC Self-Renewal to Differentiation

Pan et al. (2014) provide evidence that Bam competes with other COP9 components for Csn4 binding. Sequestration of Csn4 away from the COP9 complex may change the activity or substrate specificity of the complex to promote differentiation. Identifying specific targets of COP9 in GSCs and cystoblasts remains important work for the future.

Although the specific targets of Csn4-bound (GSCs) and Csn4-free (differentiating progeny) COP9 complexes remain unknown, the Pan et al. (2014) study highlights a novel mechanism that underlies changes in cell fate within the *Drosophila* germline. Although competition between transcription factors for specific elements within the promoters of target genes represents a well-studied mechanism for orchestrating changes in gene expression programs within somatic stem cell lineages (Zon, 2008), these new results suggest that sequestration of specific proteins may also change the activity or target specificity of their binding partners. Given that components of complexes that govern cell fate decisions are often present in both stem cells and their differentiating progeny, the tug-of-war between Bam and Csn4 may represent just one example by which competition between proteins helps to pull cells toward one fate over another.

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