

## RESEARCH HIGHLIGHT

# Stem cell self-renewal versus differentiation: Tumor suppressor Mei-P26 and miRNAs control the balance

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Stem cells, which can self-renew and produce different cell types, have been shown to be regulated by extrinsic signals and intrinsic factors. *Drosophila* ovarian germline stem cells (GSCs), representing one of the well-studied stem cells, continuously proliferate and generate differentiated cystoblasts, which further develop into oocytes. In the *Drosophila* ovary, cap cells form the GSC niche, which produces the BMP signal for maintaining GSC self-renewal [1]. BMP signaling directly represses the transcription of *bam*, a key differentiation factor, to prevent GSC differentiation and thereby maintain self-renewal. Bam acts with its partner Bgcn to sufficiently drive GSC differentiation. Disruption of BMP signaling leads to GSC premature differentiation and loss, while elimination of *Bam/Bgcn* function results in accumulation of GSC-like cells. *mei-P26*, which was initially identified for its role in meiotic recombination, has also been shown to be required for GSC daughter differentiation since its mutant ovaries contain more GSC-like cells [2]. As expected, *mei-P26* and *bam* genetically interact with each other to regulate germ cell differentiation. *mei-P26* encodes a protein containing a RING finger B-box Coiled-Coil (RBCC) and a NHL (*NCL-1*, *HT2A*, and *Lin-41*) domain [2]. Recently, the miRNA pathway is also shown to be required for controlling GSC self-renewal since mutations in *Dicer-1*, *Ago1*, and *loquacious*, which are involved in miRNA

production and function in *Drosophila*, cause rapid loss of GSCs [3-5]. Small 23-25 nt long miRNAs can regulate gene expression through translation repression and mRNA degradation by binding to the 3' untranslated region (UTR) of their target mRNAs [6]. Interestingly, the miRNA pathway controls GSC self-renewal not by repressing *bam* [3-5]. However, it remains unclear how *mei-P26* and *bam*, suppressors of GSC-like tumors, negatively interact with the miRNA pathway to control the balance between self-renewal and differentiation. In a recent issue of *Nature*, Neumuller *et al.* have provided the missing link between *mei-P26/bam*-mediated differentiation pathway and the self-renewal-promoting miRNA pathway [7].

Neumuller *et al.* have provided three lines of evidence supporting the idea that *mei-p26* works closely with *bam* to control germ cell differentiation [7]. First, *Mei-p26* expression is developmentally delayed in comparison with *Bam*, suggesting that *Mei-P26* functions after *Bam* in the regulation of germ cell differentiation. Second, *mei-P26* is genetically epistatic to *bam*. Normally, *bam* overexpression is sufficient to induce GSC differentiation, but it fails to induce *mei-P26* mutant GSCs to differentiate, indicating that *bam* can not function without *mei-P26*. Third, *mei-P26* overexpression fails to rescue the *bam* mutant GSC-like tumor phenotype, indicating that *mei-P26* function in the

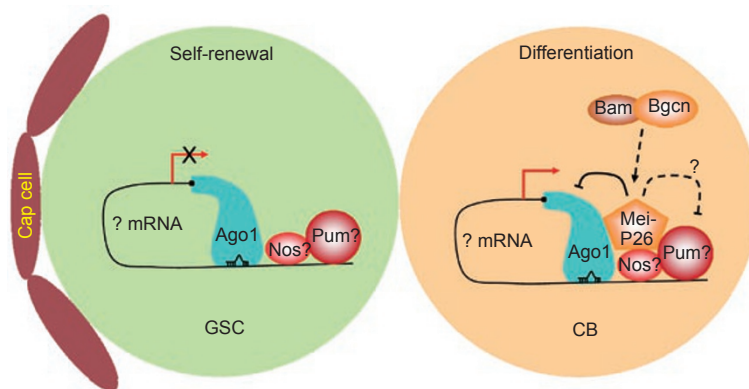
regulation of germ cell differentiation is also dependent on *bam*. These results are consistent with the previous finding that a mutation in *bam* can enhance germ cell differentiation defects of *mei-P26* mutants [2]. However, it remains unclear how *Bam* and *Mei-P26* regulate each other in germ cell differentiation.

Neumuller *et al.* then provided mechanistic insight into how the *bam/mei-P26*-directed differentiation axis affects the GSC self-renewal process [7]. Interestingly, affinity purification and co-IP experiments show that *Mei-P26*, as well as its paralog, *Brat* (brain tumor), can interact with *Agol* through the NHL domain. In addition, the NHL domain is required for *Mei-P26* function in germ cell differentiation. Although the RISC complex is involved in the regulation of miRNA-mediated translation repression or mRNA degradation [6], this study suggests that the Ago-containing RISC complex also has a role in the regulation of miRNA expression. In *mei-P26* mutant ovaries, expression levels of some miRNAs increase, while overexpression of *mei-P26* in *bam* mutants can decrease miRNA expression. *bantam*, which is known to promote proliferation and inhibit apoptosis in the *Drosophila* imaginal disc [8], can promote GSC self-renewal since its heterozygous mutant ovaries have reduced GSC number. Its expression and activity is upregulated in *mei-P26* mutant germ cells to sustain continuous germ

cell proliferation. Finally, a mutation in *loqs* can also suppress the sterility of *mei-P26* mutant female, indicating that *Mei-P26* promotes germ cell differentiation by antagonizing the self-renewal-promoting miRNA pathway. These results show that *Mei-P26* can interact with *Ago1* to inhibit miRNA expression and function during germ cell differentiation, providing important insight into how *Mei-P26* controls germ cell differentiation.

Although it remains unclear how the miRNA pathway controls GSC self-renewal, this study on *Mei-P26* has offered some insight into how the miRNA pathway and *Bam/Mei-P26* regulate the balance between self-renewal and differentiation [7]. *Brat* is known to interact with a *Pum/Nos* complex through its NHL domain and function as a translational repressor [9]. Interestingly, *Pum* and *Nos* are required for controlling GSC self-renewal by preventing differentiation [10, 11]. In *C. elegans*, a *pum* homolog, *puf-9*, and *let-7* miRNA directly bind to the 3'UTR of *hunchback* mRNA to suppress its expression [12]. Since *Ago1* along with miRNAs binds to 3'UTRs of target mRNAs to repress translation or trigger mRNA degradation, it raises an interesting possibility that the target mRNAs, which encode protein products important for germ cell differentiation, may contain *Pum/Nos* binding sites and miRNA binding sites at their 3'UTRs, which bring together the *Pum/Nos* complex and the *Ago1*-containing RISC complex. In order to trigger germ cell differentiation, *Mei-P26* can interact with *Ago1* to antagonize the miRNA/*Pum/Nos*-mediated translation repression and thus turn on expression of germ cell differentiation-promoting proteins. This model can explain how the miRNA pathway and the *Pum/Nos* complex promote GSC self-renewal, and how *Mei-P26/Bam* inhibit GSC self-renewal and thus promote differentiation (Figure 1).

Since *Mei-P26* and *Brat*, two NHL-containing proteins, function as tumor



**Figure 1** miRNA/*nos/pum* self-renewal pathway and *bam/mei-P26* differentiation pathway control the balance between GSC self-renewal and differentiation. *nos* and *pum* maintain GSC self-renewal by preventing differentiation. *mei-P26* works with *bam/bgcn* to promote cystoblast (CB) differentiation by interacting with *Ago1*, or possibly *Nos* and *Pum* to turn on target gene expression.

suppressors by interacting with *Ago1* to repress stem cell activities in the *Drosophila* ovary and the brain, respectively, this study by Neumuller *et al.* sheds new light on how tumor suppressors and miRNAs control stem cell function and cell proliferation at the molecular and cellular level [7]. This study has also provided significant insight into how miRNA-mediated translational repression can be relieved and the translation process resumes. However, it remains unclear how *Mei-P26* can mechanistically inactivate miRNA-mediated translational repression through interacting with *Ago1*. Further revelation of the detailed mechanism underlying the antagonizing functions between *Mei-P26* and miRNAs will surely boost our understanding of the miRNA pathway in tumorigenesis, and lead to possible new cancer treatments.

## References

- 1 Kirilly D, Xie T. The *Drosophila* ovary: an active stem cell community. *Cell Res* 2007; **17**:15-25.
- 2 Page SL, McKim KS, Deneen B, Van Hook TL, Hawley RS. Genetic studies of *mei-P26* reveal a link between the processes that control germ cell proliferation in both sexes and those that control meiotic exchange in *Drosophila*. *Genetics* 2000; **155**:1757-1772.
- 3 Yang L, Chen D, Duan R, *et al.* Argonaute 1 regulates the fate of germline stem cells in *Drosophila*. *Development* 2007; **134**:4265-4272.
- 4 Park JK, Liu X, Strauss TJ, McKearin DM, Liu Q. The miRNA pathway intrinsically controls self-renewal of *Drosophila* germline stem cells. *Curr Biol* 2007; **17**:533-538.
- 5 Jin Z, Xie T. Dcr-1 maintains *Drosophila* ovarian stem cells. *Curr Biol* 2007; **17**:539-544.
- 6 Valencia-Sanchez MA, Liu J, Hannon GJ, Parker R. Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes Dev* 2006; **20**:515-524.
- 7 Neumuller RA, Betschinger J, Fischer A, *et al.* *Mei-P26* regulates micro RNAs and cell growth in the *Drosophila* ovarian stem cell lineage. *Nature* 2008; in press.
- 8 Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. *bantam* encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene *hid* in *Drosophila*. *Cell* 2003; **113**:25-36.
- 9 Sonoda J, Wharton RP. *Drosophila* Brain Tumor is a translational repressor. *Genes Dev* 2001; **15**:762-773.
- 10 Forbes A, Lehmann R. *Nanos* and *Pumilio* have critical roles in the development and function of *Drosophila* germline stem cells. *Development* 1998; **125**:679-690.

- 11 Wang Z, Lin H. Nanos maintains germline stem cell self-renewal by preventing differentiation. *Science* 2004; **303**:2016-2019.
- 12 Nolde MJ, Saka N, Reinert KL, Slack FJ. The *Caenorhabditis elegans* pumilio homolog, puf-9, is required for the 3'UTR-mediated repression of the let-7 microRNA target gene, hbl-1. *Dev Biol* 2007; **305**:551-563.