Signal transduction in the early *Drosophila* follicle stem cell lineage

Katja Rust and Todd Nystul

The follicle stem cell (FSC) lineage in the *Drosophila* ovary is a highly informative model of *in vivo* epithelial stem cell biology. Studies over the past 30 years have identified roles for every major signaling pathway in the early FSC lineage. These pathways regulate a wide variety of cell behaviors, including self-renewal, proliferation, survival and differentiation. Studies of cell signaling in the follicle epithelium have provided new insights into how these cell behaviors are coordinated within an epithelial stem cell lineage and how signaling pathways interact with each other in the native, *in vivo* context of a living tissue. Here, we review these studies, with a particular focus on how these pathways specify differences between the FSCs and their daughter cells. We also describe common themes that have emerged from these studies, and highlight new research directions that have been made possible by the detailed understanding of the follicle epithelium.

**Address**
UCSF, United States

**Corresponding author**: Nystul, Todd (todd.nystul@ucsf.edu)


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**Introduction**

Each *Drosophila* ovary is composed of long strands of developing follicles, called ovarioles, and oogenesis begins at the anterior tip of the ovariole in a structure called the germarium (Figure 1) [1]. The germarium is divided into four regions, Regions 1, 2a, 2b, and 3 that are defined by the stage of germ cell development. Two to three germline stem cells (GSCs) reside within a niche provided by cap and terminal filament cells in Region 1 and divide during adulthood to continuously produce eggs. GSC daughter cells, called cystoblasts, undergo four rounds of mitosis with incomplete cytokinesis to become a cyst of 16 interconnected cells, with one oocyte and 15 nurse cells. During this time, the cyst moves away from the GSC niche through Regions 1 and 2a, which contain at least three types of inner germarial sheath cells (IGS cells, also called escort cells) [2**]. The IGS cells ensheathe the developing cysts and provide cues that guide their differentiation [3–6]. Next, the cysts exit the IGS cell region and become encapsulated by prefollicle cells (pFCs), which are produced by a population of follicle stem cells (FSCs) that reside in the middle of the gerarium [7]. Normally, the pFCs differentiate into one of three major cell types as the cyst buds off from the gerarium to become a follicle: main body follicle cells, which form a single layered epithelium that makes up the majority of the outer surface of the follicle; polar cells, which reside at the anterior and posterior of each follicle, and at stalk cells, which connect adjacent follicles to one another. However, several studies, discussed further below, indicate that newly produced pFCs do not differentiate immediately but instead retain the capacity to either re-enter the niche and acquire the FSC fate or to differentiate into any of the three cell types, depending on the type of signals they receive.

The GSC niche was among the first to be characterized at a single cell level and contributed significantly to the early understanding in the field of how adult stem cell niches function *in vivo* [8,9]. GSC divisions are oriented perpendicular to the niche and are inherently asymmetric, producing two daughter cells that contain unequal cytoplasmic contents and positions relative to the niche. Specifically, one daughter cell remains anchored to the cap cells through adherens junctions and retains the majority of a cytoplasmic structure called the fusome [10] while the other daughter is formed on the side of the GSC opposite the niche and thus does not have any connections to cap cells. This type of rigid niche architecture provides a straightforward mechanism for robustly segregating the stem cell and daughter cell fates at every stem cell division. In addition, these inherent asymmetries make it possible to unambiguously determine the number and location of stem cells in the tissue.

However, as more adult stem cell niches have been characterized, it is becoming clear that other types of stem cell niches do not operate in such a rigid manner. The stem cell niches in epithelial tissues have been particularly elusive, and the much more subtle differences between stem cells and daughter cells in these tissues has led to many debates over the number and position of stem cells in epithelial tissues. Nonetheless, intensive studies of stem cell-based epithelial tissues
have provided significant insights into the mechanisms that govern cell fate in epithelial stem cell lineages. In this review, we summarize the advances made in understanding how cell signaling pathways promote FSC behavior and coordinate the differentiation of pFCs.

**FSC number and location**

The FSCs were discovered by Margolis and Spradling, and their study was among the first to use site-specific DNA recombination to identify tissue-resident stem cells [7]. By inducing sparse clones during adulthood and analyzing the clone patterns at multiple time points after clone induction, they determined that there are two mitotically active FSCs per germarium and that there are a maximum of 8 divisions downstream of the FSC division. This study provided a foundation for understanding the FSC lineage and indeed, many subsequent studies are consistent with this model. However, a recent study challenged this model and instead proposed that there are 14–16 mitotically active FSCs per germarium that each contributes to a much smaller fraction of the follicle epithelium [11]. We investigated the claims of this study and identified several flaws, such as the use of an unreliable clonal marking system and the assumption that heat shock induced flippase expression causes FRT recombination to occur in every mitotic cell with 100% efficiency [12]. We also developed a method to quantify clone size throughout the entire ovariolo, and our measurements of clone size following sparse clonal labeling re-confirmed the original Margolis and Spradling model, though our data would be consistent with a range of 2–4 FSCs per germarium. In accordance, we recently showed that 2–3 cells at the Region 2a/2b boundary express low levels of Wnt4-Gal4, and these cells behave like FSCs and are capable of populating the entire follicle epithelium [2**].

The precise location of the FSCs has also been debated. Margolis and Spradling noticed that clones originated from the border between Regions 2a and 2b of the germarium and extended toward the posterior, suggesting that the anterior-most cells in an FSC clone are the FSCs. Subsequent analysis confirmed that the anterior-most cells in FSC clones are located at the Region 2a/2b border,
at the boundary of Fas3 expression, and that these cells are typically Fas3⁻ [13–15]. In contrast, Reilein et al. proposed that FSCs are organized within three rings, one at the boundary of Fas3 expression, and two additional rings located anterior to the boundary of Fas3 expression [11]. However, this is inconsistent with several studies that have identified the Fas3⁻ somatic cells in Region 2a as IGS cells based on their distinct shape and function in promoting germ cell differentiation [3–6,15,16]. We recently re-examined the Fas3 status of cells in an FSC clone and found that all cells in the clone are Fas3⁺ in the large majority of cases [12]. In addition, we found that the FSCs expressing low levels of Wnt4-Gal4 are Fas3⁺, and that the expression profile of the Fas3⁻ somatic cells in Region 2a is distinct from that of the Fas3⁺ cells in Region 2b [2**]. Taken together, these findings indicate that each germarium contains 2–4 FSCs that are located within a single ring at the edge of the Fas3 expression boundary.

**The regulation of cell fate decisions in the FSC lineage**

The signaling pathways that regulate self-renewal, differentiation or proliferation of the FSCs or their daughter

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**Figure 2**

![Wingless signalling](image1)

(a) **Wingless signalling**
- No Wg
- Wg
- Mmp2
- Dlp
- Arm
- fz
- Apc
- Axn
- Sgg
- dsh
- pan

- FSC proliferation
- FSC competition
- FSC self-renewal
- OFF for pFC differentiation

(b) **EGFR signalling**
- Spi
- Grk
- EGFR
- Ras85D
- Lkb1
- dpERK
- AMPK
- Gro
- P

- FSC proliferation
- FSC competition
- FSC self-renewal
- Timer of pFC differentiation

Wingless and EGFR signaling pathways.
(a) Wg is provided to FSCs by IGS cells leading to high levels of Wnt pathway activity in FSCs, which changes dynamically [17*,19]. The glypicann Dlp aids to concentrate Wg in the niche region and is counteracted by Matrix metalloproteinase 2 (Mmp2). In the absence of Wg ligand, Arm is subject to proteasomal degradation induced by a destruction complex consisting of Apc, Shaggy (Sgg) and Axin (Axn). When Wg binds to its receptor Frizzled (Fz), active Dishevelled (Dsh) represses destruction complex activity allowing arm to interact with Pangolin (Pan) to activate target gene expression.
(b) The expression of the EGFR ligand Spitz (Spi) is induced by Wnt signaling in the FSC. It is unclear whether Gurken (Grk) may also function as an EGFR ligand in the FSCs. EGFR signaling is active in FSCs, uniformly low in newly produced pFCs and active again in older pFCs and main body follicle cells. In FSCs activated EGFR signaling induces the MAP-Kinase pathway resulting in the dual-phosphorylation and activation of ERK. One target of dpERK is Groucho (Gro), which is repressed by ERK-mediated phosphorylation and functions as a molecular timer regulating pFC differentiation. Active EGFR signaling is also required for the establishment of cell polarity via the Lkb1-AMPK pathway.
cells intersect in multiple ways, forming at least three distinct signaling networks. First, Wnt signaling acts upstream of EGFR signaling in FSCs and Notch signaling in pFCs (Figure 2) [17*,18*]. There is a steep gradient of Wnt signaling in the follicle epithelium, with high levels in FSCs and pFCs at the Region 2a/2b border and low or undetectable levels of pathway activity in pFCs that have moved into Region 2b [17*,19,20**]. This gradient is achieved by localized delivery of the Wnt ligand, Wingless (Wg), to the FSCs from neighboring IGS cells [17*], combined with the action of the glypican, Dally like (Dlp), that concentrates Wnt ligands in the niche region and the matrix metalloproteinase, Mmp2 [21], which degrades Dlp [22*]. In the FSCs, Wnt signaling promotes self-renewal and proliferation, at least in part, by activating expression of the EGF ligand, Spitz, which induces the MAPK pathway, presumably through activation of EGFR [17*]. EGFR signaling, in turn, functions

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**Figure 3**

(a) **Hedgehog signaling**

- FSC and pFC proliferation
- FSC competition
- FSC self-renewal
- pFC differentiation

(b) **Hippo signaling**

- FSC and pFC proliferation
- FSC self-renewal
- FSC competition
- pFC differentiation & survival

Hedgehog and Hippo signaling pathways.

(a) Hh signaling in the early follicle cell lineage. Hh is provided for FSCs from terminal filament cells, cap cells, and IGS cells. Brother of ihog (Boi) regulates hh release by sequestration. Under rich diet, cholesterol binds and activates the negative regulator of boi, Hormone receptor 96 (Hr96), allowing hh release. The micro-RNA family mir-310 represses Hh release by targeting Hr96, and Rab23, which functions in Hh transport. In canonical Hh signaling extracellular hh binds to its receptor Patched (Ptc) and prevents Ptc-mediated repression of Smoothened (Smo). This allows Costal (Cos), which interacts with Fused (Fu) and Suppressor of fused (Su(fu)), to induce proteolytic cleavage of the transcription factor Cubitus interruptus (Ci), producing the repressive form (CiR). CiR acts as a repressor of Hh target gene expression. In the presence of Hh, Smo represses Cos allowing the active form of Ci (CiA) to activate Hh target gene expression.

(a) Core components of the Hippo signaling pathway. When Hippo signaling is active the Hippo (Hpo) kinase phosphorylates itself and the components of the kinase cassette: Salvador (Sav), which acts as a scaffold between Hippo and Warts (Wts), as well as the Warts cofactor Mob as tumor suppressor (Mats). The activated Warts kinase phosphorylates Yorkie (Yki) and prevents its nuclear translocation. When the kinase cassette is inactive, Yki enters the nucleus and acts as a transcriptional cofactor to induce target gene expression. In the FSC, Yki is regulated by the Hh signaling pathway both transcriptionally as well as post-transcriptionally and induces the expression of the cell cycle gene Cyclin E [24,76].
upstream of the Lkb1-AMPK pathway to regulate cell polarity [23] and represses the transcriptional corepressor, groucho (gro) through phosphorylation by dpERK [18*]. In pFCs, the active (unphosphorylated) form of Gro promotes Notch signaling in differentiating pFCs. Interestingly, the phosphorylated form of gro persists for a short period of time after pFCs exit the niche and downregulate dpERK. This may provide these cells with a molecular 'memory' of niche signaling that delays differentiation and allows these cells to participate in stem cell replacement or to increase in number before committing to a cell fate choice [18*].

In the early pFCs, low levels of Wnt signaling promote receptivity to Notch signaling [20**]. pFCs at this stage that are correctly positioned to receive a Delta signal from the germline activate the Notch pathway and progress toward the polar cell fate, whereas pFCs that do not receive a Delta signal before they downregulate Wnt signaling become refractory to Notch signals [20**]. Thus, Wnt signaling must be high in FSCs to promote self-renewal and downregulated in pFCs to allow for differentiation, suggesting that a steep gradient of Wnt signaling is important for controlling FSC number and position.

Second, Hedgehog (Hh) signaling controls proliferation and differentiation in the FSC lineage by regulating Yorkie (Yki), the downstream effector in the Hippo signaling pathway, leading to Yki nuclear accumulation and activation of target genes, like Cyclin E (Figure 3) [24]. The Hh ligand is produced by cap cells, terminal filament cells, and IGS cells in a gradient that decreases in an anterior-to-posterior direction [19,25]. RNAi knockdown of Hh in either cap cells and terminal filament cells or IGS cells causes follicle formation phenotypes [19,26], indicating that Hh is required from multiple sources for optimal performance of the tissue. In cap and terminal filament cells, the release of Hh from the apical surface of the cells is inhibited by the transmembrane protein, Brother of ihog (Boi) [26]. This is counteracted by cholesterol in the diet, which binds to the nuclear hormone, Hr96 in cap and terminal filament cells and stimulates the release of Hh from Boi, thus helping to coordinate egg production with nutrient availability [27]. The mir-310 family of microRNAs also help to coordinate the level of Hh signaling in response to dietary cues by repressing Hr96 and vesicle trafficking of the Hh ligand [28*]. The gradient of Hh ligand availability produces a steep gradient of Hh pathway activity in the FSC lineage, with high levels in the FSCs and rapidly decreasing levels in newly produced pFCs [20**,29,30]. Hh signaling regulates early pFC differentiation through a network of mutually repressive interactions with two transcription factors, castor and eyes absent [31,32]. However, the gradient of Hh activity in pFCs appears not to be important for spatial patterning of pFC fate [33]. These observations indicate that Hh signaling regulates follicle cell production, FSC self-renewal, and early pFC differentiation but is unlikely to play a direct role in the specification of FSC number or position. Interestingly, several studies suggest that Hh signaling in the FSC does not function via the canonical pathway: mastermind, which is usually a Notch signaling component, is a positive regulator of Hh signaling in FSCs [34], and Hh signaling in the FSC (but not pFCs) is independent of fused [35]. In addition, some types of Hh signaling in the FSC lineage appear to be independent of Smo [36**]. Further, unlike in embryogenesis, Hh signaling does not interact with Wingless signaling in the FSC [30].

Third, Notch signaling cooperates with JAK-STAT signaling to specify polar and stalk cell fates (Figure 4). Notch signaling is not required for FSC self-renewal [14,34] but provides the earliest-known differentiation signal in pFCs [20**,37,38], and constitutive activation of Notch causes an increased rate of FSC loss from the niche [34], presumably due to premature differentiation. A subset of newly produced pFCs with low levels of Wnt signaling and high levels of fringe expression receive a Delta signal from the anterior surface of a germ cell cyst that is moving into Region 2b [14,20**,38–41]. This initiates a program of differentiation toward the polar cell fate in which 2 polar cells are selected from a cluster of 4–6 'polar-fated' cells. As the cyst begins to bud from the gerarium, the polar-fated cells secrete a JAK-STAT signal to induce nearby pFCs to differentiate into stalk cells, which then contribute to the establishment of the polar cells on the posterior surface of the next younger cyst [42–44]. Within the cluster of polar-fated cells, one cell becomes refractory to Notch signaling, resistant to apoptosis, and upregulates Delta. This activates high levels of Notch in a neighboring polar-fated cell, while the remaining cells are eliminated by apoptosis, leaving a single pair of polar cells on the anterior surface of the cyst by Stage 5 [45,46]. In this way, Notch signaling initiates a stepwise chain reaction of events that ensures the polar and stalk cells are formed in the correct time and place on two adjacent follicles. Cells that do not adopt either fate differentiate into main body follicle cells.

No inductive cues of main body follicle cell fate have been identified thus far, suggesting that it may be a default fate for pFCs that are not directed toward the polar or stalk cell fates. Notch signaling antagonizes JAK-STAT signaling in the follicle epithelium and Notch mutant main body cells exhibit nuclear accumulation of Stat, so Notch signaling may help to maintain this default fate by inhibiting JAK-STAT signaling [43]. However, the levels of Notch signaling in main body cells are not high enough to activate Notch reporters such as Su(H)-LacZ or m7-LacZ. [18*,20**,43]. Indeed, even overexpression of the constitutively active Notch intracellular domain is not sufficient to activate Su(H)-LacZ in all main body and stalk cells [18*,20**]. Thus, it may be
Notch and JAK-STAT signaling.
(a) Notch signaling provides the earliest-known differentiation signal in pFCs but is inactive in FSCs. A subset of pFCs receive Delta (Dl) signal from neighboring germ line cells. Dl interaction with Notch (N) is enhanced by high levels of the glycosyltransferase Fringe (Fng). Dl binding to N leads to proteolytic cleavage release of the Notch intracellular domain (NICD) by the gamma secretase complex subunits, including Preslin (Psn) and Nicastrin (Nct). NICD enters the nucleus and triggers the release of Suppressor of Hairless (Su(H)) from its co-repressor Hairless (H). Together with Su(H) NICD induces the expression of target genes, including Enhancer of split (E(spl)) genes.
(b) JAK-STAT signaling functions in FSCs as well as in pFC differentiation. The ligand Unpaired (Upd) is produced by polar fated cells and binds to the receptor Dome. Upon unpaired binding, bound Hopscotch (Hop, Drosophila JAK) is autophosphorylated and phosphorylates Dome, allowing binding of STAT92E. STAT92E is then phosphorylated, dimerizes and transfers to the nucleus to induce gene expression.

that these Notch pathway reporters are not effective in main body follicle cells or that additional mechanisms, such as regulation at the level of endocytic trafficking of the Notch ligand [46,47] or through interactions with Gro [18*] attenuate Notch signaling in these cells.

Proliferation in the FSC lineage
FSC proliferation must be tightly controlled so that the production of new follicle cells matches the rate of new cysts entering the follicle epithelium. This coordination between the germ cell and follicle cell lineages was revealed by studies of insulin signaling, which found that loss of the insulin receptor from GSCs causes a decrease in GSC proliferation, and that this induces a non-autonomous decrease in FSC proliferation [48]. Within the FSC lineage, there are distinct modes of regulation in the FSC, pFC, and main body follicle cell populations. Specifically, proliferation in FSCs is regulated by the Wnt-EGFR and Hh-Hippo signaling networks described above as well as by BMP and TOR signaling [49,50], whereas the pFCs do not appear to require Wnt, EGFR, or TOR signaling for proliferation. Indeed Wnt and EGFR signaling are not active in early pFCs, though EGFR signaling becomes detectable again starting in Region 3. However, the Endosomal Sorting Complex Required for Transport (ESCRT) machinery has been shown to regulate the proliferation of pFCs but not main body follicle cells outside of the germarium [51**].
Understanding why follicle cells rely on distinct modes of regulation as they progress through differentiation will be an interesting area for future study.

**Regulation of FSC self-renewal and competition for the niche**

Adult stem cells are defined by their ability to undergo self-renewing divisions in which one daughter retains the stem cell fate and the other daughter differentiates. In some stem cell lineages, such as the GSCs, this segregation of cell fate occurs during mitosis, producing two unequal daughter cells. In contrast, in most epithelial tissues, stem cell divisions are not inherently asymmetric but instead produce two daughter cells that appear to have an equal potential to acquire either the stem cell or daughter cell fate [52–54]. The ultimate fate of each cell is determined by stochastic events, such as the position of each cell relative to the niche and the behavior of cells produced by neighboring stem cell lineages. The size of the niche limits how many cells can have the stem cell identity at any moment in time, but which cells have this identity is relatively fluid. This mode of self-renewal is referred to as population asymmetry because the mechanisms that govern the segregation of cell fate do not act at the level of each stem cell division but instead on the population of cells produced by multiple stem cells dividing in close proximity to one another [55–57]. The patterns of this type of stem cell loss and replacement can be described with statistical models of neutral competition that have been adapted from those used in population genetics [58–60].

Several mutations have been identified that cause non-neutral competition, in which mutant lineages displace wildtype lineages at disproportionately low or high rates (referred to as hypocompetition or hypercompetition, respectively) [18*,22*,23,24,57,58,61–63]. The identification of hypercompetition mutations is particularly interesting as it indicates that stem cells can exert non-cell autonomous effects on their neighbors, in which the presence of a fitter (mutant) lineage increases the chance that a neighboring less-fit (wildtype) lineage will be lost prematurely. This form of stem cell replacement has been observed in many different types of *Drosophila* and mammalian tissues [58–60,64–68], and attention in the field is now turning to the question of whether niche competition provides a useful function for the tissue and what the bases are for the selection of one lineage over another. The most likely function for niche competition would be to eliminate unhealthy stem cells from the niche, just as cell competition eliminates unhealthy cells from tissues [69,70]. Consistent with this possibility, several forward genetic screens have revealed that a wide range of mutations are selected against by the niche competition process [58,61,62]. These include mutations in components of the major signaling pathways, as might be expected, but also in cell adhesion components, mitochondrial genes, vesicle trafficking components, and many other types of genes. Studies of mutations that cause hypercompetition suggest that proliferation rate is positively selected for by the niche competition process [57,71]. Consistent with this, overexpression of *Cyclin E* or *string* is sufficient to cause hypercompetition and can suppress some hypocompetition phenotypes [36**,57]. However, Hh pathway mutants that cause a sustained increase in the rate of egg production in young flies also cause an increase in the rate of FSC loss in older flies, suggesting that hyperactivity of FSCs also leads to early stem cell exhaustion-like behavior [36**]. Taken together these observations suggest that, proliferation may need to be tightly regulated and that both increased and decreased proliferation rates can impair FSC self-renewal. Other hypercompetition mutations do not increase proliferation but instead impair pFC differentiation [18*,58], suggesting that there are multiple independent causes of hypercompetition. However, additional studies are needed to confirm that impaired differentiation is sufficient to cause hypercompetition and to determine how the biased selection occurs in these cases.

**Concluding remarks**

Collectively, research over the past 30 years has found that every major developmental signaling pathway is utilized at some point in the early FSC lineage. These studies have demonstrated that the spatial and temporal patterns of cell fate specification in the early FSC lineage are established by signaling pathways that intersect in complex ways to produce precise yet flexible outcomes. A particularly elegant example of this is the coordinated action of Hh signaling, low levels of Wnt signaling, and the perdurance of phosphorylated Gro to specify a narrow window of time and space for the specification of polar cell differentiation. In addition to providing insights into the signaling pathways themselves, the careful description of where and when each pathway operates in the FSC lineage have provided a foundation for investigations into new and understudied aspects of epithelial cell behavior, such as a unique form of parasitic bacterial tropism specifically to the stem cell niche region [72,73], plasticity in the sexual identity of somatic cells in the gonad [74], and the role of intracellular pH dynamics in the specification of cell fate [29,75]. Continued study of the FSC lineage is sure to provide many more insights into epithelial stem cell biology.

**Declarations of interest**

None.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This study uses a combination of single-cell RNA-sequencing, in vivo validation, and lineage tracing to provide new insights into cell identity and behavior in the adult Drosophila ovary. The authors identify new subtypes of IGS cells, a marker that can be used to identify FSCs, and several Gal4 lines with specific expression patterns in the ovary. The authors also discover an unexpected form of plasticity, in which IGS cells convert into follicle stem cells as part of a natural physiological response to starvation.


12. Fadiga J, Nyström TG: The follicle epithelium in the Drosophila ovary is maintained by a small number of stem cells. Elife 2019, 8.


Wingless is an essential FSC niche factor and, though wingless is produced by multiple cell types in the gerarium, the authors demonstrate that a short-range wingless signal produced by neighboring IGS cells is sufficient. In addition, they demonstrate that Wnt signaling operates genetically upstream of EGFR signaling in FSCs by inducing the expression of the EGFR ligand, spitz.


The authors identify two proteins, groucho and Six4, that are required for Notch signaling and polar cell differentiation. Groucho is inhibited by EGFR signaling, and they provide evidence that perdurance of the inhibited form of Groucho provides a ‘memory’ of the EGFR niche signal in newly produced pFCS.


The authors used careful quantitative imaging of pathway reporters in the gerarium to investigate the interactions between Wnt, Hh, and Notch signaling. They show that Wnt and Hh signaling operate independently and that low levels of Wnt signaling bias pFCS to adopt a polar cell fate by transiently inhibiting eyes absent.


The authors demonstrate that two glypicans, Dally and Dip have opposite roles in FSC self-renewal, with Dally mutations causing an increase in the rate of FSC loss from the niche and Dip mutations causing a niche hypercompetition phenotype. In addition, they show that Dally and Dip contribute to the regulation of JAK-STAT, Wnt, and Hedgehog signaling in the FSC lineage.


The authors demonstrate that the mir-310 family of miRNAs regulate the release of Hh from the cap and terminal filament cells in response to dietary cues. They show that mir-310 miRNAs act by repressing the expression of multiple targets that promote Hh release, including Rab23, Hr96, and tramtrack.


43. Asea-Kunik E, Torres I, Schejter E, Johnston D, Shilo B: Drosophila follicle cells are patterned by multiple levels of Notch signaling and antagonism between the Notch and JAK/STAT pathways. Development 2007, 134:1161-1169.


The authors demonstrate that the ESCRT machinery is required for proliferation of PFC outside of the stem cell niche but not for more differentiated follicle cells. The conclusion that the distinct niche domains in the early follicle cell lineage with distinct regulation of proliferation and suggest that the regulation of proliferation changes as the stem cell potential decreases.


