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The effects of aging on stem cell behavior in *Drosophila*

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Abstract

Throughout life, adult stem cells play essential roles in maintaining tissue and organ function by providing a reservoir of cells for homeostasis and regeneration. A decline in stem cell number or activity may, therefore, lead to compromised organ and tissue function that is characteristic of aging. *Drosophila* has emerged as an ideal system for studying the relationship between stem cells and aging, as it has a short lifespan, tissues that are maintained by adult stem cells, and conserved pathways known to regulate aging. In this review, we highlight recent findings describing intrinsic and extrinsic age-related changes that affect the behavior of *Drosophila* germline and intestinal stem cells. We also discuss whether pathways affecting lifespan can act autonomously or non-autonomously in stem cells during aging.

Keywords

Aging; Stem cell; Niche; *Drosophila*; Germ line; Intestine

1. Introduction

In metazoans, adult tissue homeostasis is normally maintained by replacing spent cells with new ones that are generated from resident tissue stem cells. A decline in the ability of adult stem cells to produce newly differentiated tissue cells may, therefore, lead to decreased tissue regeneration and compromised tissue function that are characteristics of aging. The ability of stem cells to maintain tissue homeostasis is limited by the number of stem cells present and their frequency of division. Progressive decreases in adult stem cell number and activity have been observed in many systems during aging. In contrast, stem cell number increases in some tissues with age, but defects in differentiation potential compromise homeostasis (reviewed in Rando, 2006). However, the underlying mechanisms of such age-related changes in stem cell behavior remain poorly understood.

The age-related decline of the regenerative capacity of adult stem cells can be affected by both intrinsic and extrinsic factors. For instance, many studies have indicated that aged hematopoietic stem cells (HSCs) are compromised in their ability to respond to mobilization and homing cues and are skewed toward adopting a myeloid fate, suggesting cell-intrinsic aging with age changes (reviewed in Rossi et al., 2008). Consistent with these findings, molecular analysis of purified HSCs from young and old mice revealed different gene expression profiles. For example, p16^{INK4a}, an inhibitor of cell cycle progression, has been shown to accumulate with age in a number of stem cells, including HSC's. While loss of p16^{INK4a} suppressed the age-related decline in proliferation, overexpression of p16^{INK4a}

reduced HSC activity in an age-dependent manner, providing one possible mechanism for stem cell intrinsic aging (reviewed in Rando, 2006; Sharpless and DePinho, 2007).

Although cell intrinsic changes clearly affect stem cell function during aging, recent studies have demonstrated that extrinsic factors also impact on age-related changes in stem cell behavior. Stem cells reside in specialized microenvironments, or niches, that provide molecular and physical cues that are necessary for stem cell maintenance, self-renewal, and differentiation. A decline in niche function, such as decreased secretion of self-renewal factors, therefore may underlie some age-related changes of stem cell function (Morrison and Spradling, 2008; Voog and Jones, 2010). In addition to cell intrinsic changes and changes in the local microenvironment, a number of studies have demonstrated that circulating systemic factors also regulate stem cell function directly or indirectly during aging (Conboy et al., 2005; Hsu and Drummond-Barbosa, 2009; LaFever and Drummond-Barbosa, 2005). Elucidation of the mechanisms by which local, systemic, and cell intrinsic changes regulate stem cell function is integral to understanding the relationship between stem cells and aging and will be of critical importance in developing stem cell-based therapies to combat aging-related diseases.

Drosophila has emerged as an ideal system for studying aging, as it has a relatively short lifespan and conserved signaling pathways that regulate aging in mammalian systems (Helfand and Rogina, 2003). In addition, several discrete populations of adult stem cells have been identified in *Drosophila*, such as germline stem cells (GSCs) in the ovary and testis and the recently discovered intestinal stem cells (ISCs) in the midgut. These stem cells reside in defined niches and play active roles in maintaining local tissue homeostasis, resembling the behavior of mammalian stem cells. Due to a battery of sophisticated genetic tools, *Drosophila* provides a unique advantage in defining the relationship between stem cells and aging. In this review, we highlight recent findings describing intrinsic and extrinsic age-related changes that affect the behavior of *Drosophila* germline and intestinal stem cells. We also discuss whether systemic signals affecting lifespan can act autonomously or non-autonomously to regulate stem cell behavior during aging.

2. Aging of male germline stem cells and their niche

In newly eclosed wild-type *Drosophila* males, 5–10 GSCs are located at the tip of the testis where they surround and directly contact a cluster of non-dividing somatic cells, known as the hub. The hub cells promote stem cell self-renewal by secreting the ligand Unpaired (Upd), which activates the JAK-STAT pathway in adjacent stem cells; therefore, hub cells are an integral component of the stem cell niche in the testis. GSCs in the testis divide asymmetrically, generating one daughter cell that maintains contact with the hub and retains stem cell identity, while another daughter cell is displaced away from the hub and initiates differentiation as a gonialblast. Gonialblasts undergo four rounds of mitotic divisions with incomplete cytokinesis to generate a cyst of 16 interconnected spermatogonia, which undergo meiosis and give rise to spermatocytes and, eventually, mature sperm.

Drosophila spermatogenesis markedly decreases with age, which is correlated with a progressive loss of GSCs (Boyle et al., 2007; Wallenfang et al., 2006). While the median lifespan of wild type *Drosophila* adults is approximately 40 days, a significant 25% decrease in the average number of GSCs was observed in 30-day-old males. This age-related decline in GSCs continues with age, such that there is an approximate 40% decrease in 50-day-old males, and the remaining GSCs in 50-day-old males divide much less frequently when compared to those in young males (Boyle et al., 2007; Wallenfang et al., 2006). Thus, fewer GSCs and less GSC divisions together could contribute to decreased spermatogenesis in aged males.

However, the most dramatic change we observed in testes from aged males was reduced expression of the key self-renewal signal *unpaired (upd)*. Forced expression of *upd* within hub cells suppressed the loss of GSCs in testes from aged males, indicating that molecular changes to the stem cell niche likely contribute to the decline in stem cell function in the *Drosophila* testis during aging (Boyle et al., 2007). However, forced expression of *upd* within hub cells did not lead to an increase in GSC proliferation rates in testes from aged males, suggesting that other factors, including cell-intrinsic changes, may also be involved in male GSC aging. Higher levels of cyclin E, a regulator of the transition from G1 to S phase during cell cycle, were observed in GSCs from aged testis, providing one possible explanation for reduced GSC dividing rates during aging (Boyle et al., 2007).

Despite a significant loss of GSCs in *Drosophila* testes during aging, the rate of decline in GSC number is less than one might predict. Based on lineage tracing experiments, the half-life of GSCs in *Drosophila* testis is estimated to be 14 days, while only a 35% decrease in the average number of GSCs was observed in 50-day-old males (Boyle et al., 2007; Wallenfang et al., 2006). This discrepancy strongly suggests the existence of replenishing mechanisms for lost GSCs during aging. One possibility for stem cell replacement would be symmetric division of a remaining stem cell (reviewed in Toledano and Jones, 2009; Xie and Spradling, 2000); however, examples of symmetric division of male GSCs in wild type testes are rare. In the *Drosophila* testis, male GSCs align centrosomes and the microtubule spindle perpendicular to the hub. This alignment ensures the production of one daughter cell that retains the stem cell fate and another daughter cell that goes on differentiating (Yamashita et al., 2003).

Previous studies indicated that both female and male GSCs can be replaced by partially differentiated germ cells through a process called dedifferentiation (Brawley and Matunis, 2004; Kai and Spradling, 2004). Indeed, a recent report demonstrated that GSCs are regularly replaced by dedifferentiation of spermatogonia in response to damage and over the normal course of aging. GSCs produced through dedifferentiation tend to have frequently misaligned centrosomes, which leads to a transient cell cycle arrest until the misalignment is corrected (Cheng et al., 2008). Therefore, an increase in the proportion of GSCs produced from dedifferentiation could provide one explanation for the decrease in the proliferation rate of GSCs in testes from aged males (Boyle et al., 2007; Wallenfang et al., 2006). Recent studies have indicated that successful dedifferentiation in the testis requires normal levels of JAK-STAT pathway activation (Sheng et al., 2009). Given the significant decrease in expression of *upd* in aged hub cells (Boyle et al., 2007), it would be interesting to determine whether dedifferentiation becomes less efficient during aging, thereby leading to the loss of GSCs.

Recent studies have begun to illuminate the complex relationships between hub cells, somatic cyst stem cells (CySCs) and GSCs in the testis niche; therefore, it is of interest to understand how aging affects each of these cell types and the implications for signaling throughout the niche. GSCs mutant for *Stat92E* did not undergo self-renewal and were not maintained, supporting the model that JAK-STAT signaling was required autonomously for regulating the behavior of male GSCs (Kiger et al., 2001; Tulina and Matunis, 2001). However, activation of JAK-STAT signaling in somatic early cyst cells is sufficient to drive germ cell overproliferation in a non-autonomous manner, which is dependent on the putative *Stat92E* target *zfh-1* and the BMP pathway (Leatherman and Dinardo, 2008, 2010). According to this model, *upd* secretion from the hub would activate JAK-STAT signaling primarily to support CySC self-renewal and maintenance, which would then specify GSC proliferation. However, recent experiments suggested that the primary role for JAK-STAT signaling in GSCs is to support adhesion to hub cells (Leatherman and Dinardo, 2010). Hub cells in testes from aged flies displayed decreased expression of the cell adhesion molecule

DE-cadherin, which is required for maintenance of GSCs (Boyle et al., 2007; Voog et al., 2008). Therefore, one could speculate that an aging-related decline in expression of *upd* in hub cells could lead to a decline in the average number of GSCs, due to decreased JAK-STAT activation in GSCs and reduced cell–cell adhesion to the hub.

In addition, reduced JAK-STAT signaling in CySCs could lead to decreased levels of *zfh-1* and, subsequently, a disruption in the cyst cell-dependent GSC self-renewal signal, contributing to decreased GSC proliferation (Boyle et al., 2007; Wallenfang et al., 2006). Lastly, our lab has demonstrated that CySCs are multipotent and generate progeny that contribute to the apical hub as a mechanism to maintain this key population of niche support cells (Voog et al., 2008). Preliminary data indicate that Stat92E activity in hub cells is required for maintaining the hub (J. Voog and L. Jones, unpublished observations); therefore, an aging related decline in *upd* in hub cells could affect the ability of CySC progeny to adopt definitive hub cell fate, initiating a negative feedback loop that would lead to compromised niche function in testes from older males. Determining the degree to which decreased CySC activity leads to aging-related changes to the hub and GSCs presents an exciting direction for future experiments.

3. Aging of female GSCs and their niche

The *Drosophila* ovary contains approximately 16 ovarioles, each containing two to three GSCs at its most anterior tip in a specialized structure called the germarium. In each germarium, GSCs directly contact a distinct set of somatic cells, called the cap cells. The cap cells, along with another group of somatic cells called the escort cells, form the stem cell niche and produce the bone morphogenic protein (BMP) signals, including Dpp/BMP2–4 and Gbb/BMP5–8. These BMP signals act on GSCs directly and are essential for directing their self-renewal. GSCs divide asymmetrically, producing one daughter cell that remains in contact with the cap cell and retains stem cell fate, and another daughter cell, called the cystoblast, that undergoes four rounds of transit amplifying divisions before producing 15 nurse cells and an oocyte.

Drosophila oogenesis rapidly declines with age, which is correlated with a significant decrease in GSC number (Margolis and Spradling, 1995; Xie and Spradling, 2000). Although the total number of germaria remains the same in aged ovaries, a nearly 30% decrease in the number of GSCs in older germaria was observed when compared to germaria from young flies (Pan et al., 2007; Zhao et al., 2008). In addition, mitotic activity of GSCs also declines with age resulting in decreased production of germ cells, similar to what was observed in the testis (Pan et al., 2007; Zhao et al., 2008). The decreases in GSC maintenance and activity in aged ovaries were caused by changes intrinsic to the stem cells as well as changes in extrinsic factors. An age-dependent decrease in the number of cap cells was observed, which is accompanied by impaired *dpp* signaling activity in aged GSCs indicated by two pathway activation markers, pMad and *dad-lacZ* (Pan et al., 2007; Zhao et al., 2008). Furthermore, dampening BMP signals by elimination of one copy of *dpp* or *gbb* enhances age-related loss and functional decline of GSCs, whereas genetically increasing *gbb* or *dpp* expression in the niche or forced activation of BMP signaling in GSCs significantly suppressed the age-related decline in GSC number and activity (Pan et al., 2007; Zhao et al., 2008). Together, these results indicate that decreased production of self-renewal signals from the niche significantly contribute to age-related decline in GSC function. Interestingly, overexpression of superoxide dismutase (SOD) specifically in cap cells significantly attenuated the age-dependent loss of cap cells and GSCs and promoted proliferation of aged GSCs, suggesting that cellular oxidative damage contributes to aging of the niche (Pan et al., 2007). Overexpression of SOD exclusively in GSCs also promoted stem cell maintenance and proliferation in aged ovaries, indicating that GSCs age due to

changes in cell intrinsic parameters, as well as changes within the local niche (Pan et al., 2007).

In addition to cell-intrinsic changes and changes in the local niche, changes in the physical interaction between GSCs and their niche also seems to play an important role in the age-related decline of GSC function. GSCs directly contact cap cells in the germarium through adherens junctions that are rich in the *Drosophila* homolog of E-cadherin (DE-cadherin). DE-cadherin-mediated anchorage between GSCs and cap cells has been shown to be critical for keeping GSCs in the niche and their long-term self-renewal, which may become weakened during aging (Song et al., 2002). Expression of DE-cadherin decreases at the stem cell–niche junction with age; however, increased expression of DE-cadherin specifically in the germ line ameliorated the decline in GSC number and activity in aged ovaries, demonstrating that weakened physical interactions between stem cell and supporting niche cells contribute to stem cell aging (Pan et al., 2007). Thus, decreased cell–cell adhesion between stem cells and niche support cells could contribute significantly to GSC loss with age in both males and females.

4. Aging of intestinal stem cells

In the *Drosophila* adult midgut, the entire epithelium undergoes fast turnover in a way that is strikingly similar to mammalian intestinal epithelium (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006; Radtke and Clevers, 2005). Tissue homeostasis in the midgut is maintained by pluripotent intestinal stem cells (ISCs), which are distributed along the basement membrane (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). Division of an ISC gives rise to one daughter cell that retains stem cell fate and another daughter cell that becomes an enteroblast (EB), both expressing a transcription factor called *escargot* (*esg*). Thus, expression of *Esg* is often used as a surrogate marker for ISCs and EBs. Daughter enteroblasts do not divide again and differentiate into either small, diploid enteroendocrine cells or large, polyploid enterocytes that constitute the majority of the gut epithelium (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). Cell cycle arrest and differentiation of enteroblasts are controlled by Delta-Notch signaling. While the ligand Delta (*DI*) specifically accumulates in ISCs, it is quickly lost in newly formed enteroblasts, which is accompanied by an activation of Notch (*N*) signaling (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). One component of the intestinal stem cell niche has been proposed to be the underlying circular muscles, which produce the ligand Wingless (*Wg*) to activate Wnt signaling pathway in the ISCs (Lin et al., 2008).

In contrast to the age-related loss of stem cells in the *Drosophila* germline, a dramatic age-dependent increase in *Esg*⁺/*DI*⁺ progenitor cells has been observed in *Drosophila* midgut, which is accompanied by a proportional decrease in differentiated enterocytes (Biteau et al., 2008; Choi et al., 2008). This leads to a loss of normal tissue homeostasis and severe deterioration of the midgut epithelium in aged flies (Biteau et al., 2008). However, it is somewhat controversial whether the increase in *Esg*⁺/*DI*⁺ cells includes an increase in true ISCs. A large proportion of the *Esg*⁺/*DI*⁺ appears to be polyploid; thus, this population is likely comprised of enteroblast-like cells that are blocked in the ability to terminally differentiate into functional enterocytes (Biteau et al., 2008; Choi et al., 2008; Park et al., 2009).

Recent studies have shown that disruption of the *Drosophila* gut epithelium by oxidative stress, tissue-damaging agents, enteric bacterial infections or direct ablation of enterocytes through apoptosis, all promote compensatory ISC division (Amcheslavsky et al., 2009; Biteau et al., 2008; Choi et al., 2008; Jiang et al., 2009) and a phenotype closely resembling what occurs during aging. Therefore, chronic exposure to these detrimental stresses could

contribute to an increase in ISC number and/or activity in guts from aged flies. For example, when flies are treated with paraquat, an oxidative stress-inducing agent, their guts display cellular phenotypes similar to those observed in aged flies within 1–2 days (Biteau et al., 2008).

When exposed to stress, cells often activate Jun-N-terminal kinase (JNK) signaling as a cytoprotective response. Consistent with this, enteroendocrine cells and enterocytes in aged *Drosophila* midguts exhibit strong levels of JNK activity (Biteau et al., 2008). Furthermore, activation of JNK signaling specifically in enterocytes caused a rapid increase in ISC mitotic activity (Jiang et al., 2009). Conversely, global, as well as ISC/EB-specific, downregulation of JNK activity prevented the accumulation of ISCs and enteroblasts in aged guts, indicating a significant contribution of JNK activation in age-related disruption of gut homeostasis.

How might a JNK-mediated stress response in differentiated gut epithelial cells lead to increased proliferation of ISCs? A recent study has indicated that the JAK/STAT cytokine signaling pathway coordinates the two responses (Jiang et al., 2009). Overexpression of the ligand *upd* in either enterocytes or ISCs/enteroblasts resulted in overproliferation of ISCs and gut hyperplasia. In addition, *upd* expression in the gut appeared to increase following JNK activation in enterocytes. In contrast, reduction of JAK/STAT activity blocked ISC proliferation induced by JNK activation, despite maintenance of normal numbers of ISCs and enteroblasts, (Jiang et al., 2009). Downregulation of the JNK pathway in ISCs/EBs was sufficient to block the increase in ISCs in response to bacterial infection or oxidative stress, indicating that the JNK pathway may play a more direct role in regulating ISC proliferation (Biteau et al., 2008; Buchon et al., 2009). Together, these results indicate that Upd family members can act as potent ISC mitogens and suggest that JAK/STAT signaling may play a critical role in the age-related deterioration of the *Drosophila* midgut.

As discussed earlier, the loss of tissue homeostasis in aged *Drosophila* midguts is marked by the reduction in differentiated enterocytes, which is likely due to differentiation defects in progenitor cells caused by aberrant Delta/Notch signaling. In aged guts, clusters of large, polyploid cells accumulate that do not express other markers of enterocytes, but they are *Esg*⁺. Furthermore, high levels of DI and widespread N activation were observed among *esg*-expressing cells in aged guts, and occasionally some cells exhibited both DI expression and N activity, indicating defects in differentiation (Biteau et al., 2008). Widespread activation of Notch can also be induced by JNK activation or *upd* expression in enterocytes, indicating that increased DI/N signaling is part of the gut stress response (Jiang et al., 2009). DI/N signaling restricts the proliferation potential of ISCs under both normal and stressed conditions (Biteau et al., 2008); however, it has been speculated that high levels of DI/N activity, while preventing overproliferation of ISCs, also prevents proper differentiation of ISCs and enteroblasts. In support of this, partial reduction of *Delta* expression appears to prevent the age-related deterioration of gut epithelium and the accumulation of mis-differentiated progenitor cells (Biteau et al., 2008). However, the pathways that act downstream of DI/N activity to regulate differentiation have not yet been identified. Characterization of these inputs and the integration with the N signaling pathway will shed light on the aging and stress-related differentiation defects observed in the *Drosophila* midgut.

In summary, the age-related changes in *Drosophila* midgut are likely caused by a variety of stress-induced damage to gut epithelial cells, which activate JNK signaling and stimulate ISC proliferation via JAK/STAT cytokine signaling. Interestingly, enteric bacterial infection or enterocyte apoptosis does not require JNK signaling to stimulate JAK/STAT-mediated ISC proliferation, suggesting that different stresses may induce JAK/STAT signaling via distinct mechanisms (Jiang et al., 2009). Additionally, other stem cell-intrinsic changes have

also been reported, such as the age-related increase in the expression of PVF2, a PDGF/VEGF-like growth factor (Choi et al., 2008) and activation of the p38/MAPK pathway (Park et al., 2009). In contrast, changes to the ISC niche have not been well characterized during aging. Given that Wingless (Wg) signaling from the adjacent circular muscle has been reported to regulate both ISC self-renewal and Notch-mediated differentiation, it will be interesting to determine whether age-related changes in Wg signaling also contribute to the aging of *Drosophila* midgut (Lin et al., 2008).

5. Insulin signaling and stem cell aging

The insulin/insulin-like growth factor (IIS) signaling pathway has been shown to be a conserved longevity regulator. For instance, lifespan can be increased by systemically reducing the IIS signaling in many organisms, including *Drosophila* (reviewed in Kenyon, 2010). Interestingly, IIS activity also regulates somatic and germline stem cell behavior in *Drosophila* and mammals, providing a provocative link between pathways regulating aging and tissue homeostasis (Jasper and Jones, in press). For example, ablation of cells in the brain that express insulin-like peptides (Dilps) or cell-autonomous loss of the sole insulin receptor (InR) in ovarian GSCs resulted in a significant decrease in their division rate, indicating that insulin signaling can directly control stem cell activity (LaFever and Drummond-Barbosa, 2005). IIS can also regulate GSC behavior in a non-autonomous manner by regulating the number of niche support cells, as well as adhesion to the niche (Hsu and Drummond-Barbosa, 2009). Similar results have also been found in the *Drosophila* midgut, where insulin signaling is autonomously required by ISCs for their proliferation (Amcheslavsky et al., 2009; Biteau et al., 2010). Recent results have indicated that insulin signaling is required for germ cell proliferation and spermatocyte growth in the testis (Ueishi et al., 2009). Consistent with these data, we have demonstrated that insulin signaling is required autonomously for male GSC maintenance and proliferation and that Dilps are expressed within the testis in subsets of somatic cells, which could act to regulate spermatocyte growth in a non-autonomous manner (McLeod et al. (in press)).

Although existing data indicate that insulin signaling is an important regulator of stem cell behavior, it remains largely unknown whether IIS activity coordinates stem cell function with organismal aging. A recent study utilizing dietary restriction (DR) to extend lifespan has provided some clues to answer this question. DR, reduced food intake without malnutrition, has been shown to increase lifespan in a variety of organisms ranging from yeast to primates (reviewed in Mair and Dillin, 2008). DR exerts its effects, at least in part, through reducing IIS activity (Fontana et al., 2010). Our results demonstrated that DR not only extends lifespan but simultaneously attenuates the age-related decline in the number of GSCs in *Drosophila* testis, suggesting enhanced maintenance of stem cells in long-lived flies (Mair et al., 2010). Whether reduced insulin signaling contributes directly to such enhanced stem cell maintenance remains to be determined. However, given the fact that removal of *dInR* activity in male GSCs also leads to GSC loss, it is more likely that an intermediate level of insulin signaling that is optimal for regulating stem cell behavior: either too much or too little is detrimental (Jasper and Jones, in press). Furthermore, it is likely that various tissue stem cells will require different levels of insulin signaling for proper regulation of tissue homeostasis. Fluctuations in insulin signaling not only can affect stem cells directly, but may also influence the stem cell niche. In fact, recent studies have indicated that aging-related changes to the niche, in some cases, may be due to altered IIS activity (Hsu and Drummond-Barbosa, 2009; McLeod et al., in press; Pan et al., 2007). Thus, we predict that targeted rejuvenation of stem cell niches will eventually accompany stem cell replacement and regenerative medicine techniques.

6. Future directions

In this review, we have highlighted age-related cell-intrinsic, local and systemic environmental changes that affect the function of *Drosophila* adult stem cells. In the germ line, a decline in stem cell number and proliferation rate is coupled to changes within the local niche, leading to a decrease in gametogenesis in both males and females. Conversely, aging results in increased proliferation of stem cells in the gut, which leads to an accumulation of progenitor cells that are impaired in terminal differentiation pathways. Improved tools for recognizing and manipulating stem cells exclusively, in an inducible manner, will greatly enhance the characterization of cell autonomous mechanisms that regulate stem cell aging. Furthermore, a more thorough characterization of niche components will provide a necessary link to clarifying how systemic changes can be relayed to the local niche, which will ultimately coordinate stem cell behavior with the metabolic status of the animal. Lastly, defining the tissue-specific requirements and effects of insulin and hormonal signaling pathways will facilitate understanding the contribution of systemic changes to the aging-related decline in stem cell function and tissue homeostasis. Examples of both extremes, decreases and increases in stem cell number and activity, have recently been documented in mammalian stem cell systems. Therefore, it is clear that understanding the molecular mechanisms underlying aging-related changes to stem cells in *Drosophila* will continue to have significant implications for similar studies in mammalian systems.

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