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Commentary Open Access

Age Regulates *Drosophila* Ovarian Germline Stem Cells *via* Insulin-Dependent and Independent Mechanisms

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Commentary

Stem cells reside in a specialized microenvironment, called a niche that provides both physical contact and stemness factors that regulate stem cell identity, thus maintaining tissue homeostasis throughout adult life. Aging of the organism, however, decreases stem cell number and function through mechanisms that are not completely understood. Signaling of insulin/insulin-like growth factor (IGF), a systematic factor, controls cellular nutrient sensing and organismal aging. Although insulin/IGFs are known to mediate systemic effects on stem cells in many tissues, the link between insulin/IGFs and stem cell aging remains unclear. This commentary aims to briefly discuss the impact of insulin signaling on *Drosophila* ovarian germline stem cells (GSCs) during aging.

The insulin/IGF pathway is evolutionarily conserved and controls many essential processes linked to nutrient sensing, such as metabolism, reproduction, and cell growth and proliferation [1,2]. Insulin/IGF signalling is also necessary for division or maintenance of stem cells in diverse organisms, including *Caenorhabditis elegans*, *Drosophila*, and mouse [3-6]. However, insulin/IGF signalling is attenuated during aging [7,8]. *Drosophila* has seven *Drosophila* insulin-like peptide (dilp) genes but only one homolog for each component of the insulin/IGF pathway, including one receptor (*Drosophila* insulin receptor or dinr). Upon binding of Dilps to their receptors, the phosphoinositide-3 kinase pathway is activated to induce cell growth and proliferation [9,10].

To investigate the role of insulin/IGF signaling in the stem cell response to physiological aging, we use the *Drosophila* ovary as a model, as it carries well-characterized GSCs and their niche [11] (Figure 1A). In addition, the relatively short lifespan of *Drosophila* (approximately 2 months) is an advantage in studying stem cell aging. One *Drosophila* ovary is composed of 16-20 ovarioles, functional units that produce eggs [12]. In the anterior-most structure of each ovariole, the germarium, two to three GSCs reside at its anterior tip. GSCs directly attach to niche cap cells, a major niche component. Each GSC carries a unique organelle with a membranous-like structure, called a fusome, which is juxtaposed to the interface between the cap cell and the GSC. During the late G2/M, S, and early G2 phases of the GSC cell cycle, fusomes display a round, elongated, and exclamation point shape, respectively (Figure 1B) [13,14]. A single GSC division gives rise to a cystoblast, which undergoes four rounds of incomplete division to form a 16-cell cyst; the cells of the cyst are interconnected with a branched fusome [12]. The 16-cell cyst is then surrounded by a layer of follicle cells, and the entire structure buds off from the germarium and develops into a mature egg. As a result of detailed cell biology studies of the *Drosophila* ovary and the availability of genetic tools, GSC maintenance can be unambiguously identified by the number of GSCs that reside in the niche (recognized by their anteriorly anchored fusome facing the cap cells). GSC division can be analysed by the proportion of GSCs expressing specific cell cycle makers, or by fusome morphology.

In our recent study [14], we investigated how age affects GSCs. We found that both GSC self-renewal and division decrease with age. The number of GSCs was gradually reduced in both mating and non-mating females. None of the GSCs had positive results in the apoptotic assay during aging, suggesting that GSCs lose their attachment to the niche and undergo differentiation. On the other hand, GSCs of aged females were slow to divide and accompanied by a prolonged S phase, probably because of an accumulation of DNA damage induced by aging. Furthermore, aged germaria were filled with tumorous GSCs (Figure 1C), suggesting a link between aging and tumorogenesis. However, the possibility of age-induced dedifferentiation of germ cells into GSCs cannot be ruled out.

Insulin signaling controls GSC maintenance both cell autonomously and non-cell autonomously with age dinr mutant GSCs, generated by Flipase-Flipase recognition site system-mediated recombination [15], are still maintained properly in the niche two weeks after clone induction [7], although they leave the niche three weeks after clone induction [16]. Strikingly, overexpression of *Drosophila* Dilp2 in the aged niche using a p[switch]GAL4 delays age-dependent GSC loss (data not shown). Furthermore, age also reduces the number of niche cap cells, and disruption of insulin receptor expression in niche cap cells results in GSC loss [7]. Although we have not been able to examine insulin signaling levels in young versus aged GSCs and their niche, our results show that aging affects GSC maintenance, at least in part, via the insulin signaling pathway.

Nonetheless, insulin signaling does not control the S phase progression of the GSC division cycle that is delayed in aged GSCs; rather, it controls the G2 phase, in agreement with our recent study and a previous report [13,14]. *dInr* mutant GSCs increase their population by expressing a G2 phase marker (e.g., exclamation point and round fusomes and cyclin B), and dividing at the rate that is one-third that of controls. In addition, tumorous GSCs are not present in the germaria of *dInr* mutant lies. These results suggest that aging impedes GSC division and induces GSC tumors independently of insulin signaling. We conclude that insulin signaling controls GSC maintenance with age, both cell autonomously and non-cell autonomously; insulin signaling predominately regulates the G2 phase, whereas aging delays the S phase progression of the GSC division cycle (Figure 1D).

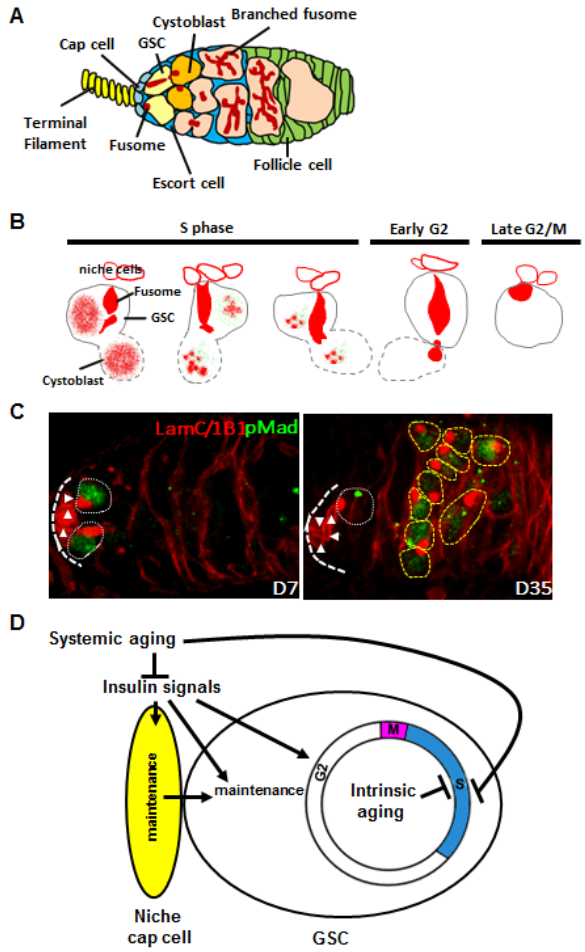

Figure 1: GSC fusome morphology corresponds to GSC cell cycle progression and a model of GSC aging. **(A)** The *Drosophila* germarium. The anterior tip of the germarium is the GSC niche comprising the terminal filament, cap cells (the major component), and anterior escort cells. The GSC niche houses two to three GSCs; each GSC contains a spectrosome (fusome). A single GSC division generates a cystoblast that develops into a germline cyst, which contains a branched fusome. The cyst is subsequently surrounded by somatic follicle cells. **(B)** Correlation between GSC fusome morphology during the S, G2, and M phases in GSCs. The G1 phase is omitted, as it is extremely short in the GSC division cycle [14]. **(C)** Age induces tumorous GSCs. Day (D)-7 and -35 day-old germaria with 1B1 (red, fusomes), Lam C (red, Terminal filament and cap cell nuclear envelopes), and phosphor (p)-Mad (green, GSC marker). **(D)** GSC aging *via* insulin-dependent and independent mechanisms. Systemic aging suppresses systemic insulin signals that promote GSC maintenance directly and indirectly *via* their niche. Systemic aging or GSC intrinsic aging suppresses the S phase of the GSC cell cycle; however, systemic insulin signals predominately control the G2 phase. Panels A-C adopted from Kao et al. [14].

Accumulating evidence has documented the role of insulin/IGF signaling in stem cell regulation. In *Drosophila*, neural-producing Dilps cell-autonomously regulate male GSC division at the G2 phase, as well as GSC and hematopoietic progenitor maintenance [17-19]. They also non-cell autonomously control midgut intestinal stem cell proliferation [20]. In mice, insulin/IGF signaling controls neural stem cell self-renewal and proliferation [5] and muscle stem cell activation under injury [21]. Despite the complexity of the aging process in tissue degeneration, on the basis of the conservation of the insulin/IGF signaling pathway, we propose that insulin/IGF signaling may be generally involved in stem cell aging to meet the needs of the organism.

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