Polycomb Group Gene *E(z)* Is Required for Spermatogonial Dedifferentiation in *Drosophila* Adult Testis

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Abstract

Dedifferentiation is an important process to replenish lost stem cells during aging or regeneration after injury to maintain tissue homeostasis. Here, we report that Enhancer of Zeste [E(z)], a component of the Polycomb repression complex 2 (PRC2), is required to maintain a stable pool of germline stem cells (GSCs) within the niche microenvironment. During aging, germ cells with reduced E(z) activity cannot meet that requirement, but the defect arises from neither increased GSC death nor premature differentiation. Instead, we found evidence that the decrease of GSCs upon the inactivation of *E(z)* in the germline could be attributed to defective dedifferentiation. During recovery from genetically manipulated GSC depletion, *E(z)* knockdown germ cells also fail to replenish lost GSCs. Taken together, our data suggest that E(z) acts intrinsically in germ cells to activate dedifferentiation and thus replenish lost GSCs during both aging and tissue regeneration.
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Introduction

Many tissues with short-lived cell types in the body are maintained by adult stem cells, either continuously or in response to physiological signals or injuries. In many adult stem cell lineages, progenitor cells derived from stem cells first undergo a proliferative stage to expand their population before commitment to terminal differentiation. The switch from proliferation to differentiation must be tightly regulated, and misregulation of this transition can lead to tumorigenesis or tissue dystrophy [1]. On the other hand, progenitor cells remain plastic and can undergo dedifferentiation in multiple stem cell lineages, a process that is critical to replenish lost stem cells during aging or tissue injury [2–14]. In order to properly differentiate adult stem cells or progenitor cells *in vitro* and/or to promote dedifferentiation *in vivo* for regenerative medicine, we need to better understand the molecular mechanisms underlying the dedifferentiation process in endogenous adult stem cell lineages *in vivo*.

Drosophila spermatogenesis is gaining attention as a model system for the study of mechanisms regulating the maintenance, proliferation, and proper differentiation of germline stem cells (GSCs) [6,15–18] (Fig. 1a). In adult testis of *Drosophila melanogaster*, GSCs can be located precisely by their proximity to a group of post-mitotic hub cells. Upon asymmetric cell division, a GSC gives rise to both a self-renewed stem cell and a gonialblast (GB), the daughter cell that initiates differentiation. GBs first go through a transit-amplifying stage, in which they undergo exactly four rounds of mitosis. Once spermatogonial mitosis is complete, germ cells enter the spermatocyte stage, in which each cell grows approximately 25-fold and initiates a robust gene expression program that enables meiotic division and spermatid differentiation (reviewed in Refs [19–22]). Lost GSCs could be replenished by dedifferentiation of the mitotic spermatogonial cells [2,4,6,7]. However, once the meiotic program is initiated in spermatocytes, dedifferentiation can no longer be detected [2,6,7], suggesting that mitotic

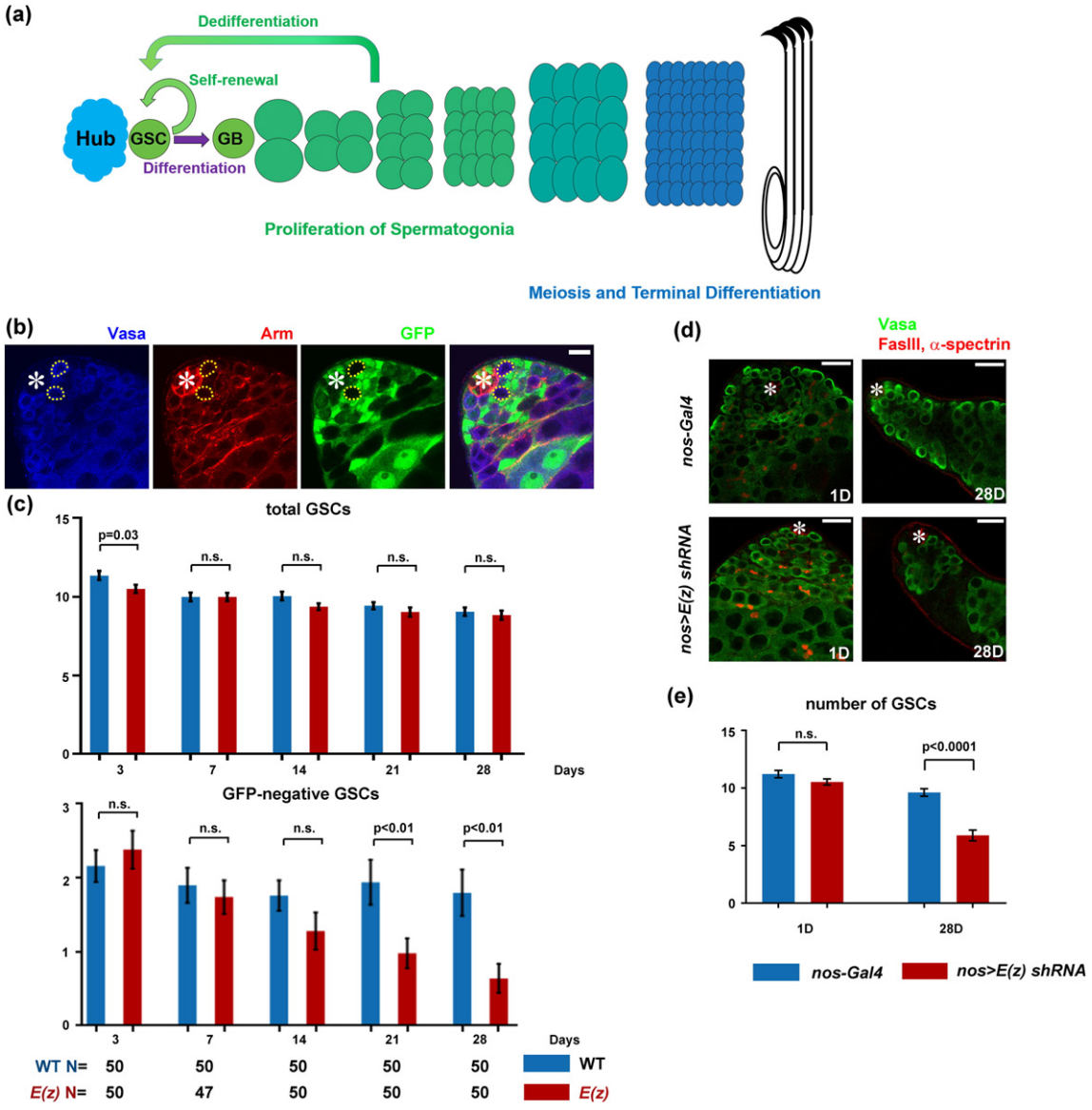

Fig. 1. E(z) is required for GSC maintenance. (a) A schematic diagram of *Drosophila* adult testis. (b) Apical region of testes 2 days ACI. Immunostaining with antibodies against Vasa (germ cell marker), Arm (hub and cyst cell marker), and GFP. GFP-negative cells (yellow outline) indicate $E(z)^{731}$ mutant GSCs. Scale bar represents 10 μm. (c) Quantification of total GSC number and GFP-negative GSC number in control testes with GFP-negative WT GSCs *versus* testes with GFP-negative $E(z)^{731}$ mutant GSCs (average ± S.E.M.). (d) Apical region of *nos-Gal4* control and *nos > E(z) shRNA* testis at 1 day (1D) and 28 days (28D) after eclosion. Immunostaining with antibodies against Vasa, FasIII (hub marker), and α-spectrin (marker of spectrosome and fusome, a germ cell-specific organelle [74]). Scale bar represents 20 μm. Asterisk: hub. (e) Quantification of GSC number of *nos-Gal4* control and *nos > E(z) shRNA* testis at 1 day (1D) and 28 days (28D) after eclosion. *P*-value calculated using two-tailed Student's *t*-test. Data presented using the GraphPad Prism software.

spermatogonial cells have unique characteristics that allow for it. In parallel with GSC asymmetric cell division, the two cyst stem cells (CySCs) surrounding each GSC also divide asymmetrically. Each division results in one daughter cell retaining CySC identity, while another becomes a cyst cell [23,24]. Two cyst cells encapsulate differentiating germ cells and never divide again. It has been demonstrated that CySCs and cyst cells communicate with accompanying germ cells *via* multiple signaling pathways for critical decisions, such as cell fate maintenance and proliferation *versus* differentiation throughout spermatogenesis [25–33]. The dramatic cellular differentiation during *Drosophila*

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