Organizing stem cell units in the Drosophila ovary
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Organogenesis utilizes processes fundamental to development: cell proliferation, cell differentiation and morphogenesis. Each of these processes is complex in itself; the challenge of studying organogenesis is to determine how all of them integrate to shape organs with recurring precision. This review focuses on the emerging understanding of how synchronized proliferation and differentiation of both somatic and germ cell lineages form 16–20 germ line stem cell (GSC) units in the ovary of Drosophila melanogaster. Recent work demonstrates that the Insulin, ecdysone, Epidermal Growth Factor, Decapentaplegic and Activin signaling pathways are used reiteratively for proliferation and differentiation in both somatic and germ cell lineages. This linkage underlies ovarian coordinated development and provides opportunity for correction mechanisms for stem cell unit numbers.

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Introduction
The adult Drosophila ovary is divided into 16–20 ovarioles that continually produce eggs [1]. Egg production relies on the synchronized function of germ line stem cells (GSCs) and the somatic support cells that direct their self-renewal (terminal filament, cap cells, and anterior escort cells) and differentiation (escort cells) [2–4]. These cells are located at the anterior of each ovariole and together they make a functional stem cell unit (Figure 1). The Drosophila ovary forms during embryogenesis by association of somatic gonadal precursors and primordial germ cells (PGCs) [5–8]. During larval development, these two lineages proliferate and differentiate [9**,10**,11,12*]. In the first two days of larval development, proliferation is the primary force, although some differentiation must also occur [13]. Within the next 24 hours, some anterior cells (swarm cells) migrate to form part of the posterior of the ovary [14]. Throughout these stages, PGCs are in close contact with intermingled cells (ICs), a group of interstitial cells that enwrap the germ cells throughout their development [10**,15].

The terminal filament (TF) lineage is the first somatic niche component to form (Figure 1). TF specification begins prior to third instar [11,16**]. However, the adult lens-shaped cells only appear at ~96 hours after egg laying (AEL), and their development depends on transcription factors such as Bric-a-brac, Engrailed, and other Tramtrack-group nuclear factors [17,18,19**,20]. During the last 24 hours of larval development, TF cells accumulate rapidly and stack to form 16–20 TFs [17]. Importantly, TF cells are post-mitotic. During the larval/pupal transition, TFs recruit ICs via Notch signaling to form cap cells [21**], which recruit the anterior-most PGCs to become adult GSCs. The process involves attachment of GSCs to cap cells by a prominent ‘patch’ of E-Cadherin [22]. PGCs that are not in close proximity to TF/Cap cells differentiate during late third instar (~112 hours AEL), and the first cysts can be observed during prepupal stages [12**,23**,24**].

In the last stage of ovarian morphogenesis, a group of apical cells migrates posteriorly between TFs, laying a basement membrane in their path. This separates of the gonad into the adult ovarioles [25,26].

The ovary as a model for lineage coordination during organogenesis
In its essence, gonadogenesis in females creates 16–20 stem cell units. To make these units, somatic cell proliferation, PGC proliferation, niche differentiation and PGC differentiation must be coordinated in three different ways (Figure 2): first, somatic and germ cell proliferation should be synchronized to create sufficient precursors for 16–20 units without excess or shortage in either lineage. In particular, enough PGCs should be available to fill the newly formed niches prior to their separation to ovarioles, since TFs that are separated without underlying PGCs will remain empty, sterile units. Second, somatic proliferation and differentiation should be correlated. This is particularly important when TFs form. TF cells are post mitotic, and are recruited from a group of proliferating precursor cells. The extent of recruitment and its timing will determine both TF numbers (and hence niche numbers) and the number of precursor cells that are available to give rise to other somatic lineages [14,24**,27**]. Third, PGC differentiation should be temporally adjusted to niche differentiation. The natural tendency of PGCs to differentiate is repressed during larval development until
Larval ovary development. Larval ovaries are depicted from the initiation of larval development (24 hours after egg laying) until the end of larval development (120 hours after egg laying). The different cell types are described in the legend and text. The anterior part of the adult germarium is also depicted, to indicate adult fate of the larval cells.

Coordination between cell proliferation and differentiation in larval ovaries. The four axes of ovarian development are depicted in ellipses. Signaling pathways that affect more than one process are indicated on double-headed arrows between them. Together, these signaling pathways form a control network that underlies the coordinated formation of the gonad.