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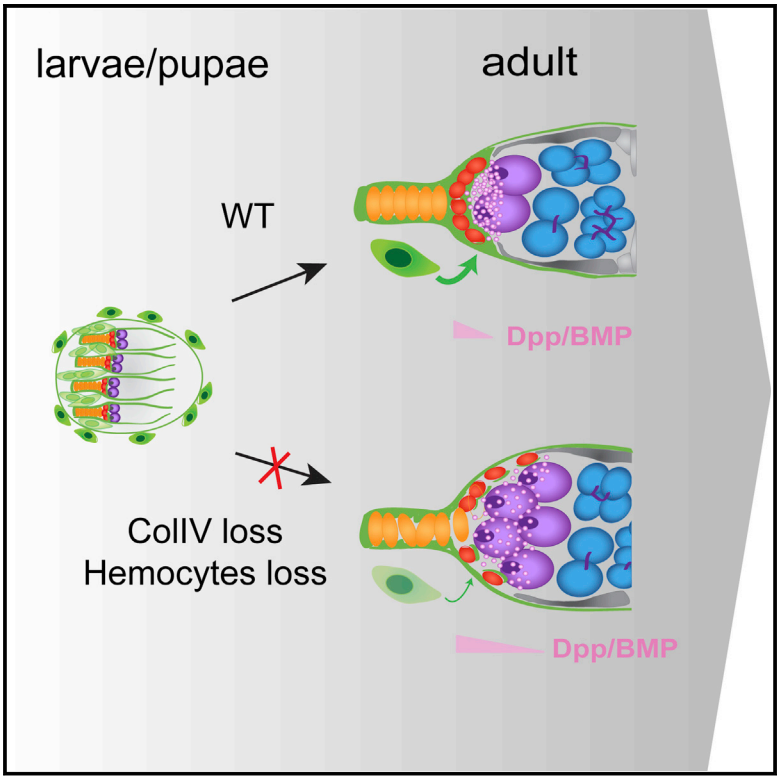
Companion Blood Cells Control Ovarian Stem Cell Niche Microenvironment and Homeostasis

Graphical Abstract



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In Brief

The ECM is important for stem cell niche development and function, but its origin is not well defined. Van de Bor et al. find that "companion" hemocytes associate with the *Drosophila* female gonad to secrete ColIIV present in the adult stem cell niche. Their results show that hemocyte-derived ColIIV is essential for stem cell niche organization and stem cell number.

Highlights

- "Companion" hemocytes associate with the female larval gonad
- Hemocytes produce functional ECM in the germline stem cell (GSC) niche
- Loss of hemocyte-derived ColIIV leads to abnormal stem cell niche with excess GSCs
- Hemocyte-derived ColIIV controls the extent of BMP signaling and niche homeostasis

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Companion Blood Cells Control Ovarian Stem Cell Niche Microenvironment and Homeostasis

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SUMMARY

The extracellular matrix plays an essential role for stem cell differentiation and niche homeostasis. Yet, the origin and mechanism of assembly of the stem cell niche microenvironment remain poorly characterized. Here, we uncover an association between the niche and blood cells, leading to the formation of the *Drosophila* ovarian germline stem cell niche basement membrane. We identify a distinct pool of plasmatocytes tightly associated with the developing ovaries from larval stages onward. Expressing tagged collagen IV tissue specifically, we show that the germline stem cell niche basement membrane is produced by these "companion plasmatocytes" in the larval gonad and persists throughout adulthood, including the reproductive period. Eliminating companion plasmatocytes or specifically blocking their collagen IV expression during larval stages results in abnormal adult niches with excess stem cells, a phenotype due to aberrant BMP signaling. Thus, local interactions between the niche and blood cells during gonad development are essential for adult germline stem cell niche microenvironment assembly and homeostasis.

INTRODUCTION

Stem cells provide organs with plasticity and regenerative capabilities essential for normal development and aging. Defective stem cell function leads to a number of pathologies, including severe congenital disorders, neurodegenerative diseases, and cancer (Bateman et al., 2009; Kim et al., 2011; Wong et al., 2012; Yurchenco, 2011). An important aspect of stem cell biology is the organization into a functional niche, which provides a specialized 3D microenvironment sustaining stem cells through the control of their proliferation and pluripotent states (Schofield, 1978; Spradling et al., 2001). Therefore, understanding the molecular mechanisms governing stem cell niche development, structure, and homeostasis is of prime interest. The extracellular matrix (ECM) is an essential component of the niche (reviewed in Daley et al., 2008), whose alteration can affect stem cell maintenance, proliferation, and differentiation (Gattazzo et al., 2014; Guo and Wang, 2009; Lu et al., 2012; Ricard-Blum and Ruggiero, 2005; Tanimura et al., 2011; Watt and Huck, 2013). Although progress has been made in elucidating stem cell niche function, it remains unclear how exactly the niche microenvironment assembles during development and what are its components as well as their dynamics and functions in vivo.

Drosophila ovaries represent a valuable, genetically tractable model to investigate stem cell niche development in vivo. Adult ovaries are composed of approximately 20 ovarioles containing egg chambers surrounded by a thin muscular sheath (Hudson et al., 2008). These egg-producing units arise from two pools of stem cells: the somatic and the germline stem cells (GSCs), located in the germarium at the apex of the ovariole (Figure 1A). The GSC niche itself is made of a group of five to seven cap cells positioned at the tip of the germarium, contacting the terminal filament cells anteriorly and anchoring GSCs posteriorly through DE-cadherin-β-catenin-mediated adhesion (Song et al., 2002). Cap cells produce the decapentaplegic (Dpp)/BMP ligand to maintain the GSC pool (Chen and McKearin, 2003; Guo and Wang, 2009; Harris and Ashe, 2011; Losick et al., 2011; Xie and Spradling, 1998).

The ECM in *Drosophila* essentially consists of basement membrane (BM), aka basal lamina (Fessler and Fessler, 1989). BMs provide mechanical stability to organs and are essential for migration, survival, proliferation, and differentiation (Khoshnoodi et al., 2008; LeBleu et al., 2007; Yurchenco, 2011). They are made of self-assembled collagen IV (ColIV) and laminin networks essential for BM stability. Nidogen/entactin and perlecan crosslink the laminin and ColIV networks, increasing their stability and controlling the structural integrity of the overall membrane. *Drosophila* ColIV consists of two α chains, α-1 (Cg25c) and α-2 (Vkg), which form heterotrimers (Blumberg et al., 1988; Lunstrum et al., 1988) that are post-translationally modified by lysyl and prolyl hydroxylases enzymes, ultimately forming a functional BM (Bunt et al., 2010; Lerner et al., 2013; Pastor-Pareja and Xu, 2011). In adult ovaries, somatic follicular cells produce