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Chromatin modifications regulate germ cell development and transgenerational information relay

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Germ cells transmit genetic, cytoplasmic and epigenetic information to the next generation. Recent reports describe the importance of chromatin modifiers and small RNAs for germ cells development in *Drosophila*. We also review exciting progress in our understanding of piRNAs functions, which demonstrate that this class of small RNAs is both an adaptive and inheritable epigenetic memory.

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Introduction

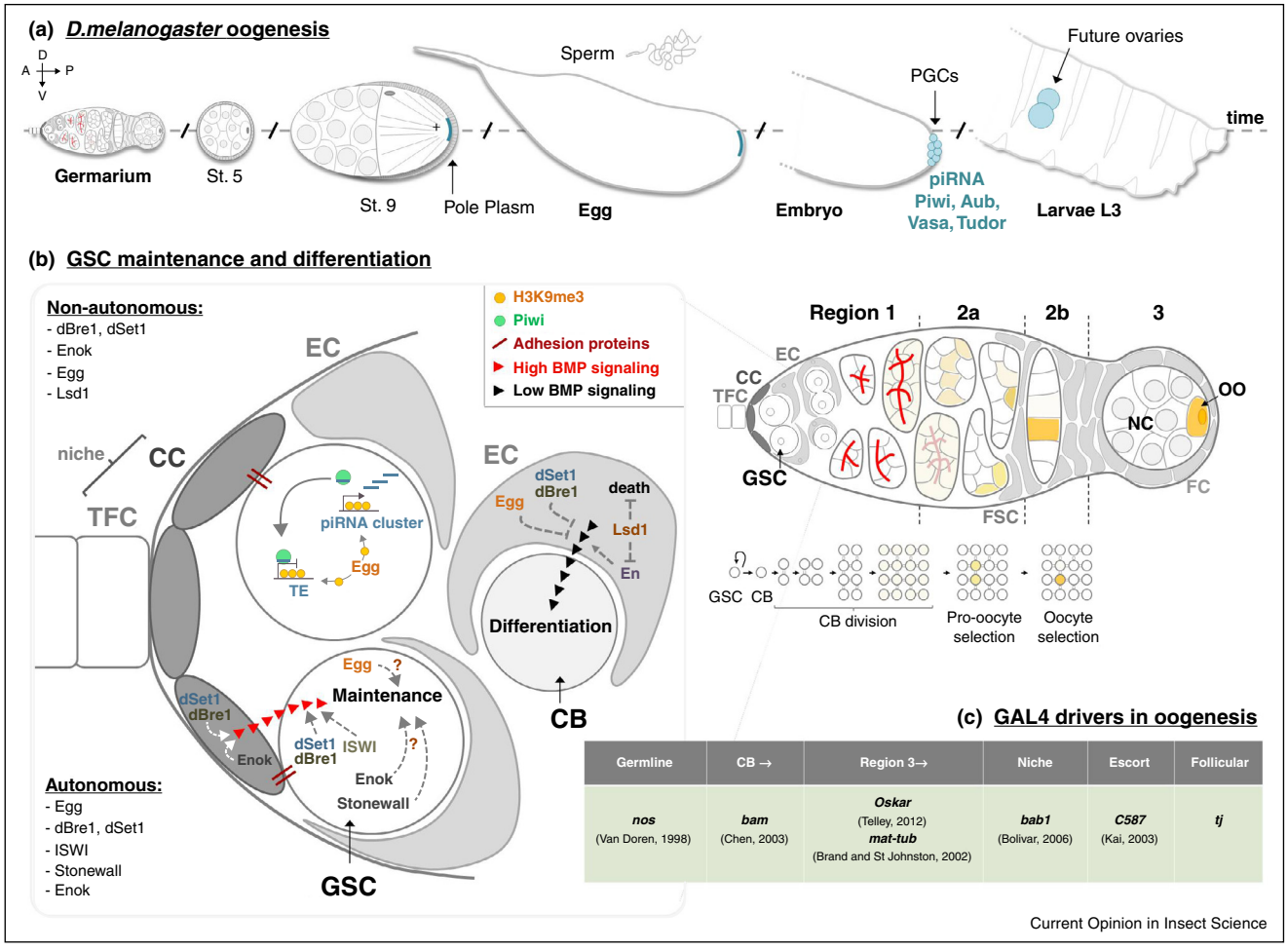
Germ cells are the only cells which are transmitted from one generation to the next, and can thus be considered immortal. Germ cells produce highly specialized cells called gametes, which have the unique capacity to convey all the information needed to build an entirely new organism. Understanding how this information is transferred from one generation to another is not only of utmost medical importance for reproductive medicine, but is also crucial to comprehend how animal shapes and forms evolve through generations. Germ cells can transmit at least three types of information: firstly, genetic information, which is the sequence of DNA corresponding to the maternal or paternal genome; secondly, cytoplasmic components, which are mainly mRNAs coding for proteins to be expressed before the zygotic genome becomes transcribed; and finally, epigenetic information, which is both nuclear and cytoplasmic, and which controls the expression of both the maternal and paternal genome. Here, we will focus on how epigenetic information is established and transmitted during the formation of the egg, the female gamete, in a process called oogenesis.

Drosophila ovaries are one of the best model systems to study germ cell development, and to date, there is no cell line which can recapitulate oogenesis *in vitro*. Female flies produce eggs throughout their life, and all the different stages of oogenesis are present in their gonads at any one time (Figure 1a) (reviewed in [1]). This continuous production of eggs is supplied by two types of stem cells, each generating either germ cells (GSCs), or somatic follicle cells (FSCs) surrounding germline cells (Figure 1b). Both types of stem cells are located at the tip of each ovary in a specialized structure called the germarium, where the early steps of oogenesis take place. Each GSC divides asymmetrically to produce two daughter cells, one remains a GSC, while the other differentiates as a cystoblast. This cystoblast then undergoes a series of four divisions to form a germline cyst of 16 cells. These divisions are incomplete leaving all 16 cells linked by cytoplasmic bridges. However, only one sister cell becomes the oocyte, the future egg, while the 15 other cells become nurse cells and provide the oocyte with cytoplasmic components. Nurse cells endoreplicate their DNA, become polyploid and transcribe actively their genome. In contrast, the oocyte enters meiosis, compacts its DNA into a karyosome, and is mostly silent transcriptionally. The chromatin states of nurse cells and oocytes are thus very different. Recent findings have demonstrated that chromatin marks play a very important role during the differentiation of both cell types. In addition, germ cells themselves were shown to produce small RNAs able to induce the formation of heterochromatin. These novel and exciting results made use of the exquisite genetic tools available in *Drosophila*, which allow disrupting gene function in specific cell types at precise times of development.

Chromatin dynamics during early oogenesis

Genetic information encoded in the DNA sequence is packaged by histones into nucleosomes and chromatin (also see Mteirek *et al.*, in this issue). Access to DNA sequence is crucial for RNA transcription, DNA repair or DNA recombination, to name a few key processes. The accessibility to DNA is mainly modulated by post-translational modifications of histone tails such as methylation, acetylation, phosphorylation or ubiquitination, as there is no DNA methylation in *Drosophila* [2]. These histone

Figure 1



Germline	CB →	Region 3→	Niche	Escort	Follicular
nos (Van Doren, 1998)	***bam*** (Chen, 2003)	***Oskar*** (Telley, 2012) ***mat-tub*** (Brand and St Johnston, 2002)	***bab1*** (Bolivar, 2006)	***C587*** (Kai, 2003)	***tj***

Drosophila melanogaster oogenesis: **(a)** Each ovary is formed by 15–20 ovarioles, which are strings of progressively mature egg chambers. Egg chambers bud from the germarium, the most anterior region of the ovaries. Each egg chamber has 16 germline cells (15 nurse cells and one oocyte), surrounded by follicular somatic cells. By stage 9, several factors like Piwi, Aub, Vasa, Tudor proteins, and piRNAs accumulate in the posterior of the oocyte, forming the pole plasm (blue), which will form the primordial germ cells (PGCs) in the embryo. PGCs will give rise to the adult ovaries (light blue). Antero-posterior and dorso-ventral axis are shown. The dotted gray line shows time scale and only chosen stages of the ovarioles are shown. **(b-right)** In region 1 of the germarium, germline stem cells (GSCs) divide asymmetrically giving rise to another GSC and to a cystoblast (CB). The CB divides 4 times forming a cyst of 16 cells interconnected by the fusome (red), all surrounded by a mono-layer of follicular cells (FC). Terminal filament cells (TFCs) and cap cells (CC) are somatic cells that make the GSCs niche. Escort cells (EC) are somatic cells that interact with the germline in region 1. In region 2a only two cells out of the 16 cells cyst become pro-oocytes (light yellow) and, by region 2b, only one is selected as the oocyte (yellow). The other 15 cells become nurse cells (NC). **(b-left)** Autonomous and non-autonomous factors required for GSC maintenance and differentiation. CCs are connected to the GSCs by adhesion proteins and are responsible for maintaining their stemness. Differentiation of the CB is regulated by the ECs. Both processes are controlled by a balance in BMP signaling: high BMP is important for GSC maintenance whereas low BMP is required for CB differentiation. ISWI (chromatin remodeling factor), dSet1 (H3K4 trimethyltransferase) and dBre1 (E3 ubiquitin ligase) control GSC maintenance autonomously, through BMP signaling activation [5,7•]. Stonewall (chromatin remodeling factor), Enok (histone acetyltransferase) and egg (dSetDB1, H3K9 methyltransferase) act cell autonomously to maintain the stem cell [4,6•,10••], independently of BMP. In the niche, dSet1, dBre1 and Enok extrinsically regulate GSC maintenance, through BMP signaling activation. In Escort cells, dSet1, dBre1, Lsd1 (histone lysine demethylase) (through the transcription factor engrailed) and egg regulate CB differentiation by decreasing BMP signaling [10••,11,52,53]. Egg could also regulate piRNA transcription activation and transposable elements (TEs) silencing as recently suggested [12••,32••] in GSC and follicular cells. Dotted lines represent regulation by unknown targets. **(c)** GAL4 drivers in oogenesis. *nos*-GAL4 is expressed in germline cells; *bam*-GAL4 starts being expressed in the CB; oskar-GAL4 is expressed from stage 1 (region 3) onwards; mat-tub-GAL4 is expressed from region 2 onwards. *bab1*-GAL4 is expressed in the niche in adult flies; *c587*-GAL4 is specific for EC and is weakly expressed in early FC; *tj*-GAL4 is expressed in all FC.

marks constitute an important code which regulates gene expression, chromosome structure and even nuclear architecture, and which can be transmitted through cell divisions. However, in contrast to DNA sequences, the epigenetic landscape can be changed by environmental cues that can erase or write histone modifications [3]. In the case of germ cells, it opens the fascinating prospect that acquired epigenetic modifications could be transmitted not