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Review

Genetics and mechanisms of ovarian cancer: Parallels between *Drosophila* and humans

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ABSTRACT

Considering the degree of detail available at the genetic and cellular levels, the *Drosophila* ovary stands out as a powerful system to identify new players in the regulation of key aspects of cancer progression. In this review, we will comment on how the use of the *Drosophila* ovary has helped to elucidate some of the molecular bases of ovarian malignancies and to identify and characterize critical tumour suppressor genes and oncogenes with an impact in human pathologies.

Contents

1. The mammalian system

Ovarian cancers are the most deadly gynaecological malignancies. The events that turn on ovarian carcinogenesis are still poorly understood and they are usually diagnosed when the tumour has spread to other places in the body. Thus, understanding the mechanisms that control tumour initiation, progression and dispersion in the female reproductive tissues is critical in the race against ovarian cancer. The human female gonad is a complex tissue of different embryological origin that includes, among other components, the ovaries — where germ cells or oocytes develop —, the ovarian surface epithelium (OSE), the fallopian tubes, the uterus and connective tissues (Fig. 1).

The adult human ovary is walled internally by the OSE, which is formed by an inconspicuous monolayer of flat-to-cuboidal epithelial cells adhered to each other by simple desmosomes, incomplete tight junctions and largely N-cadherin, and to the surrounding extracellular matrix by a number of integrins [1]. For a long time, the biology of the OSE remain neglected because of its seemingly purposeless histological appearance and due to the difficulty to culture OSE cells *in vitro*. However, the most deadly forms of ovarian cancers are carcinomas of OSE origin, which account for 85–90% of all ovarian cancer cases. The spreading of ovarian carcinoma cells into adjacent organs is facilitated by the normal flow of the peritoneal fluid. Exfoliated carcinoma cells travel inside the peritoneal cavity and seed onto internal organs, while dissemination of malignant cells through the vasculature

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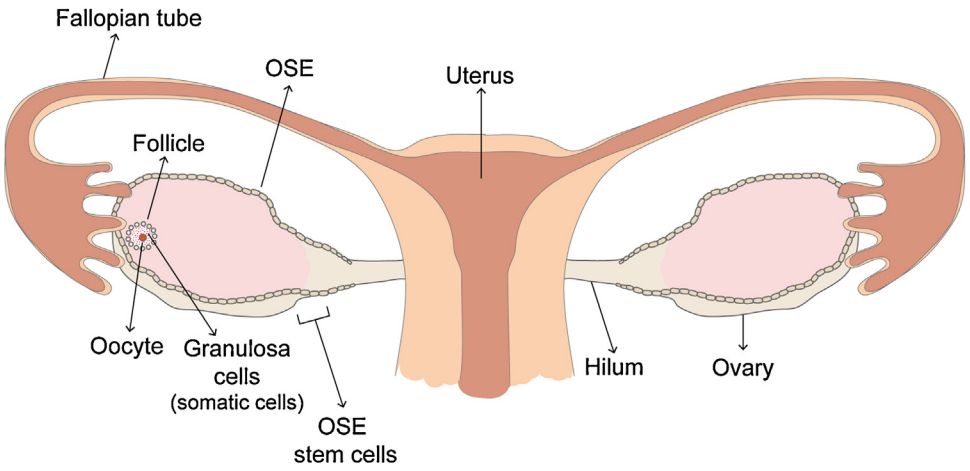

Fig. 1. Structure of the human female reproductive system. The figure depicts the main components of the adult female gonad relevant to this review: the two ovaries, the uterus and the fallopian tubes. Ovaries are covered by a monolayer of epithelial cells called ovarian surface epithelium (OSE), originated from the OSE stem cells in the hilum region.

is infrequent. The aetiology of epithelial ovarian cancer (EOC) has been the subject of a long debate, but recent work in mice has identified a niche that hosts the stem cells responsible for the replenishment of the OSE. Importantly, the transformation potential of these stem cells in transplantation experiments upon inactivation of the tumour-suppressor genes Trp53 and Rb1 — mutated in 96% and 67%, respectively, of high-grade serous adenocarcinoma, the most common and aggressive human EOC — showed that the OSE stem cells may be the cell-of-origin of EOC [2].

Other types of solid cancers present in human female gonads are derived from additional cell types present in the organ, such as teratomas and yolk sac tumours, originated in the germ cells, or granulosa cell tumours, developed from somatic cells [3]. In summary, malignant growth in human ovaries affects both somatic cells and the germline, being the epithelial turmours originated in the OSE the most aggressive and detrimental for the patient.

2. What can *Drosophila* offer?

Although mouse models have been developed to investigate the effect of targeted disruption of possible cancer tumour suppressors or the expression of candidate oncogenes in the OSE [4], the mammalian ovary is not suitable for large-scale forward genetic studies. The use of genetically tractable models such as the fruitfly *Drosophila melanogaster* overcomes this limitation and allows the systematic screening of genes involved in cancer initiation and progression in different organs. In this context, the *Drosophila* ovary has emerged as a valuable system to implement research strategies aimed at the understanding of the genetic, developmental and molecular mechanisms behind ovarian cancer (see for instance [5]). Despite the obvious differences between the mammalian female reproductive system and the one in flies, *Drosophila* offers several advantages: its ovaries display a simple organization, a wealth of genetic markers and tools are available, and live analyses and the study of systemic signals in the control of cell migration can be easily performed. Genetic screenings on the *Drosophila* ovary have yielded important discoveries, including the identification of a number of tumour-suppressor genes required to control the abnormal proliferation of germline cells or somatic follicle cells [6–8], the deciphering of the genetic and cell biological steps behind hyperplastic growth of epithelial cells [5,9–11], the process of cell migration and its hormonal control [12–14], and the signalling events necessary to maintain a functional population of epithelial and germline stem cells [15–18]. Impaired functioning of these stem cell types could result in massive overgrowths of germ cells and follicle cells [19].

2.1. The Drosophila ovary

Each *Drosophila* ovary is composed of 16–18 tubes termed ovarioles in which developing egg-chambers or follicles are found (Fig. 2). At the most anterior part of each ovariole, a conical structure called germarium hosts both the female Germline Stem Cells (GSCs; each germarium contains between 2 and 4 GSCs) and two follicle stem cells (FSCs), responsible for the generation of new germline cysts and follicle cells throughout the female lifespan. The niche where GSCs reside is located at the anterior tip of the germarium and it includes as well three differentiated somatic cell types: ~10 terminal filament cells (TFCs) that adopt a columnar shape to form the so called Terminal Filament (TF); 8–10 cap cells (CpCs) organized into a rosette at the base of the TF, in close contact with the GSCs underneath; and escort cells (ECs), which enfold almost entirely the GSCs with thin cellular extensions to avoid GSC-GSC contact [20].

The niche provides physical support and signalling molecules to ensure that the pool of GSCs is maintained within. GSCs normally undergo asymmetric division to give rise to a linage-renewing GSC and to a differentiating cystoblast. Cystoblasts divide four times with incomplete cytokinesis to produce 16-cell-cysts in which all cystocytes are interconnected by cellular bridges called ring canals. One of these 16 cystocytes is selected as the oocyte whereas the other 15 become polyploid nurse cells. At the end of this process, the 16-cell cyst adopts a spherical shape and it eventually leaves the germarium surrounded by a layer of follicle cells, generated from the two FSCs present in the germarium. This layer of follicle cells develops into a proper epithelium that forms a three dimensional, stereotyped monolayer that surrounds the germline cysts [21]. Oogenesis in *Drosophila* is subdivided into 14 different stages, but follicle cells remain mitotically active only until stage 6. They orient their division roughly parallel to the germline so that both daughter cells end up within the same plane of the epithelial monolayer.

During the first stages of oogenesis, the follicular epithelium is subdivided into genetically distinct regions. As egg chambers mature, pairs of specialized cells called “polar cells” are determined at each pole and remain quiescent for the rest of oogenesis. The polar cells act as signalling sources to pattern the epithelium later in oogenesis. As a consequence of polar cell signalling, the epithelium