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Ovarian cells with differentiation potential

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SUMMARY

The adult ovarian surface epithelium has already been proposed as a source of stem cells and germinal cells. Present studies have confirmed the occurrence of stem cells in ovaries of adult mammals, including humans. This paper briefly describes ovarian stem cells, mesenchymal stem cells, putative stem cells and ovarian germ cells. With their differentiation potential, these cells constitute a very interesting research field as stem cells are used in a few medical disciplines and their application in fertility treatment is probably only a matter of time.

Key words: ovarian stem cells; mesenchymal stem cells; putative stem cells; ovarian germ stem cells; infertilityXSX

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INTRODUCTION

Stem cells (SCs), frequently termed totipotent, pluripotent, multipotent, oligopotent and unipotent, are responsible for maintaining tissue homeostasis. In adult tissues, stem cells can divide into offspring cells that maintain the continuity of stem cell populations and into different types of cells that replace damaged or dying cells [1,2].

SCs can be obtained from the embryo at cleavage or blastocyst stages (embryonic stem cells, ESC), but also from extra-embryonic tissues, such as the umbilical cord, placenta and the amniotic fluid [3–5]. Moreover, SCs can be obtained from specific niches in adult mammals. These somatic SCs reside in a wide range of tissues including bone marrow, blood, fat, skin and testis [6–10]. This paper is focused on a few types of stem cells that can be found in the human ovary.

OVARIAN STEM CELLS (OSCs)

Ovarian stem cells (OSCs) originate from the human ovarian surface epithelium (OSE) [11]. The OSE stem cells are always present in mid-pregnancy fetal ovaries and can be sporadically found in normal adult ovaries. The so-called mesenchymal-epithelial transition of mesenchymal cells isolated from the tunica albuginea indicate their capability of proliferation [2,12]. Bhartiya et al. believe that OSCs harbor two distinct cell populations: very small embryonic-like stem cells (VSELs) and larger ovarian germ stem cells (OGSCs) with progenitor features [13].

Human OSE stem cells are bipotent progenitors of oocytes and granulosa cells [2,14]. Granulosa and theca cells support germ cells within the developing follicle [15]. During the fetal period, which is the primary stage of reproductive system development, oocytes and primary follicles formed as new structures serve as a source of follicular renewal [2].

Unlike most epithelia, the OSE expresses epithelial and mesenchymal markers. In a functional ovary, this special epithelium covers only a certain area, but in a resting ovary the epithelial layer is spread over the entire surface of the female gonad. This is observed during menopause, in PCOS or sclerotic ovaries and also when ovulation is not occurring [16].

The periodical follicular renewal decreases between 35 and 40 years of age, and the remaining primary follicles are utilized during the premenopausal period until the pool is exhausted [2].

The normal human OSE is single-layered squamous-to-cuboid epithelium [17]. The ovarian surface epithelium of adult human females has been reported to be a source of germ cells in the mechanism of asymmetric division of OSE cells [2,14].

The possible regenerative properties of SCs in the OSE, i.e differentiation into different cell types (including mesenchymal, epithelial, granulose, neural cells) and oogenesis in *in vitro* settings, make them interesting targets for further investigation in the context of individualized patient treatment (especially in infertility and ovarian epithelial cancers) [2,18,19].

Gene expression profiling has supported the hypothesis that human ovarian surface epithelial cells are multipotent and capable of serving as ovarian cancer-initiating cells. However, as shown by Bowen et al., genes associated with the maintenance of adult stem cells with a multipotent capacity are not expressed or expressed at very low levels in adenocarcinoma [20].

MESENCHYMAL STEM CELLS (MSCs)

Mesenchymal stem cells (being somatic stem cells) reside postnatally in many organs and connective tissue [21]. Their perivascular location close to small vessels allows their migration [22]. Mesenchymal stem cells are present in the ovarian tunica albuginea (TA) [23,24]. Stimpfel et al. reported that, in *in vitro* conditions, healthy adult ovaries can also serve as a source of cells showing MSCs characteristics [25]. Moreover multipotent MSCs can be generated from human embryonic stem cells (hpESCs) [26].

Adult mesenchymal stem cells (MSCs), with their capacity for extensive self-renewal and high potential to differentiate into a variety of tissue lineages, may leave their niches to migrate and participate in wound repair and tissue regeneration [27,28].

Mesenchymal cells present in the ovarian tunica albuginea (TA) can also differentiate into the surface epithelium which participates in follicular renewal in human adult females [23,24]. Moreover, it was observed that cytokeratin-positive mesenchymal progenitor cells of the tunica albuginea can differentiate into the components for the primary follicle (primitive granulose and germ cells) [14]. Components for the new primary follicle, primitive granulosa and germ cells, differentiate sequentially and are produced *de novo* from mesenchymal progenitor cells residing in the ovarian TA. It appears that mesenchymal progenitor cells first contribute to the development of epithelial cells similar to granulosa cells, and subsequently these cells form epithelial nests descending into the deeper ovarian cortex. Oogenesis progresses. During this period, mesenchymal progenitor cells differentiate into OSE cells with an embryonic character, lining either the ovarian surface or invaginated epithelial crypts. These cells are a source of germ cells, which assemble with nests of primitive granulosa cells to form primary follicles [24].

The phenomenon of the mesenchymal–epithelial transition enables mesenchymal cells of the tunica albuginea to be transformed back into the OSE during adulthood under certain conditions but not prior to puberty or around menarche [2].

Similarly to ovarian stem cells, these cells, which are easy to isolate and culture, may become a promising tool in tissue engineering and regeneration because of their multipotency, expansive potential and immunosuppression properties [27].

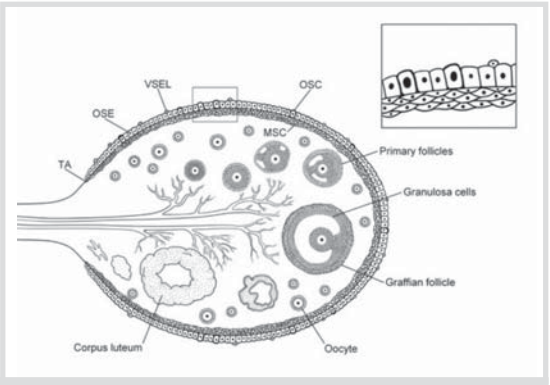

Fig. 1. Elements of the primordial follicle: primordial granulosa and ovarian germ cells. Based on [24]

PUTATIVE STEM CELLS (PSCs)

Several reviews have elegantly discussed the available data on the presence of putative stem cells (PSCs) in the adult mammalian ovary [29–33]. It has been stated that PSCs can directly participate in postanal oogenesis. The studies of Parte et.al. showed that stem cells can increase in size and differentiate spontaneously into small oocyte-like structures being surrounded by distinct zona pellucida-like structure [34]. Similar development of putative ovarian stem cells into oocyte-like cells in *in vitro* conditions has been reported by Virant-Klun et al. [11,35]. Furthermore, the adult OSE in women with non-functional ovaries may also be an important source of putative stem cells [36].

PSCs vary in size: one being smaller and other being the size of a red blood cell. The smaller cells that are pluripotent in nature, measure 1–3 ìm, and are called very small embryonic-like PSCs (VSELs) have been detected in the ovarian surface epithelium [37].

VSELs are smaller than red blood cells, have high nucleocytoplasmic ratio, their nucleus is abundant in euchromatin, with open chromatin for OCT-4 and Nano promoter, cell surface SSEA-4 and other pluripotency markers [34,38]. VSELs are quiescent stem cells, and they probably undergo asymmetric cell division to give rise to progenitor stem cells which divide rapidly and maintain tissue homeostasis [13,39].

De Felici stated that VSELs are primordial germ cells that migrate to the gonadal ridge during early embryonic development and persist into adulthood [31]. These cells express several genes related to pluripotency, embryonic development and germinal lineage [37]. VSELs can differentiate into any kind of differentiated progeny depending on the body's needs, i.e. into: oocyte-like structures, parthenote-like structures, embryoid body-like structures, cells with neuronal-like phenotype, and embryonic stem cell-like colonies [40]. On this basis, the authors postulate that VSELs are the most primitive, pluripotent stem cells in the ovary and give rise to OSCs-specific progenitors. VSELs exist in aged and non-functional ovary. Their retrieval from a healthy niche may support ovarian tissue renewal and enable the application of these properties in infertility treatment [41].

OVARIAN GERM STEM CELLS (OGSCs)

Primordial germ cells (PGCs) colonize the gonadal ridge in the epiblast stage. These PGCs possibly persist as VSELs in adult (female or male) gonads where they undergo asymmetric cell divisions for self-renewal and give rise to gonadal stem cells, namely ovarian germ stem cells (OGSCs) [40]. Additionaly, PGCs or VSELs give rise to OGSCs sized 5–7 μm [31,34,42].

OGSCs are progenitor stem cells, which proliferate and form germ cell nests that subsequently differentiate into oocytes surrounded by somatic cells and assemble into primordial follicles [39]. Progenitor stem cells then differentiate and undergo subsequent meiosis to give rise to haploid female gametes [13]. Ovarian GSCs are located in the ovarian surface epithelium and express markers of undifferentiated GSCs [43].

CONCLUSION

The prevailing view that there is no oogenesis in the postnatal mammalian ovaries had not been challenged until recently, when the putative GSCs were discovered [44]. Studies of human ovarian stem cells are not numerous. For that reason, there is a vast area to investigate, particularly with respect to fertility restoration (including anticancer therapy), infertility treatment and delaying menopause. Stem cells have an immense potential for therapeutic use in regenerative medicine and for developing anticancer therapies that specifically eliminate cancer stem cells as it is known that tumors may originate from a few altered stem cells [2,45].

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