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Follicular renewal and stemness potency of follicular cells depended of telomerase activity and TERT expression – short review

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Abstract

Several hypotheses have been proposed, relating to the potential genesis of follicular cells in the ovarian niche. Reports using mice as an experimental model have suggested that the ovaries may contain stem cells that are likely involved in the formation of new follicles in adult reproductive life. Over recent years, various types of ovarian cells have been identified and described to confirm or disprove the existence of ovarian adult stem cells. Most research is focused on granulosa cells (GCs), which are essential for follicular development and maturation of female germ cells (oocytes). GCs exhibit the features of stem cells, such as expression of stem cell markers: OCT-4, Sox-2, Nanog as well as certain markers of mesenchymal stem cells, including CD29, CD44, CD90, CD105, CD117, and CD166. Another discovery in favor of the potential stemness of GCs is their ability to transdifferentiate towards other cell lines and high telomerase (TERT) activity in dividing compartments of the follicle during its maturation.

Running title: Follicular renewal and stemness potency

Keywords: follicular renewal, ovarian reserve, telomerase activity, TERT expression, stem cell niche

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Introduction

The central dogma of mammalian reproductive biology is that oogenesis starts in prenatal life and females are born with a limited, non-renewable pool of oocytes arrested in meiosis I surrounded by somatic cells. The theory of a limited number of oocytes was established in the 1960s and supported by numerous histological observations carried out on many species of mammals [1–3]. In most animal species all gametes – spermatozoa or oocytes derive from primordial germ cells (PGCs), which are a small primary undifferentiated population of stem cells [4]. It has been assumed that the number of potential germline cells capable of transforming into fertile oocytes during a female's life is determined early and does not change during maturation and adult life [5]. The depletion of the precursor germ cell reserve occurs around the age of fifty causing a menopausal state.

Drosophila melanogaster is the distinguish organism in which germline stem cells (GSCs) maintain the oocytes production in adult ovaries [6–8]. Prenatally in this species, a few primordial germ cells, characterized as polar cells, are segregated in a special germ cell niche. GSCs and unique qualities of oocytes have also been reported in other invertebrates – Japanese rice fish, also known as medaka (*Oryzias latipes*) [9] and zebrafish (*Danio rerio*) [10,11].The constant and extensive proliferation of germ cells and follicular cells in the ovaries after birth was also proven in certain mammals e.g. mice [1,2]. In 2004 [1] using the method of daily counting of arthritic follicles, researchers calculated that the ovary should be out of follicles within a month. However, the ovaries in mice remain functional for over a year. These research suggest the active follicular renewal. The aforementioned hypothesis is confirmed by immunohistochemical analysis of dividing active cells showed the expression of the Mouse Vasa homologue (MVH) suggesting the presence of germ cells [8]. Moreover, the proliferative potential of cells in the ovarian surface epithelium (OSE) in young and adult mice was confirmed by fluorescence labeling by bromodeoxyuridine (BrdU), which is a standard assay to detect the cells with active DNA synthesis [12]. Comparing the BrdU immunoreaction in MVH-positive cells with dividing follicular somatic (granulosa) cells outcomes of intensity were similar. The presence of germ cells in various stages of mitosis was confirmed by immunostaining for MVH counterstained with propidium iodide (PI) [1,13].

In the case of humans, some indications suggest the possibility of the constant presence of the primary germ cells in the ovaries. One of the clinical observations supporting the idea that a population of germ cells is the suggested cause of different types of ovarian cancer. [14–16]. The majority of ovarian types of cancers have endodermal origin from cortical zones (e.g. tunica albuginea) of the ovary, especially epithelial cells [15]. This may suggest that non-specialized primary cells are located in these areas and after genetic or molecular dysfunctions of regulatory and repair systems can resume proliferation and multiply clonally to convert into cancerous tumor tissues [3,17,18].

The theories that have emerged so far are interesting but often meet with sceptical opinions. However, the root cause of ovarian cancer, has not been officially confirmed because of the necessity to be verified and supported with more eligible data.

Follicular stem cell niche

In assisted reproductive technology programs (ART), the follicular fluid (FF) containing granulosa cells is routinely discarded after oocyte collection during the *in vitro* procedure providing an attractive source of cells. Researchers reported that several types of cells can be isolated and identified from the follicular fluid, such as granulosa cells (GCs), cumulus cells, theca cells, epithelial cells [19,20]. Numerous scientific studies have also confirmed that follicular fluid can be used as a potential source of cells with stemness characteristics [21–23].

Granulosa cells play an important role in folliculogenesis including hormonal activity, production of estradiol during follicular growth, and secretion of progesterone after ovulation. Recently GCs become the center of attention in reproductive biology due to the fact, that it has been shown that the subpopulation of GCs in the growing follicle is not terminally differentiated [24–26].

In 2009 and 2012, GCs have reviled stem cell properties, through the expression of stem cell markers, such as OCT-4, NANOG, and SOX-2 [25,27]. Moreover, GCs derived from human follicular fluid express luteinizing hormone receptors (LHR) and are capable of differentiation to several cell lineages e.g. osteogenic, chondrogenic, adipogenic, neurogenic under defined optimal *in vitro* cell culture conditions with Leukaemia Inhibitory Factor (LIF) [20,24,28,29]. Furthermore, the GCs in conditioned *in vitro* culture conditions express mesenchymal stem cell markers (MSCs); CD29, CD44, CD90, CD105, CD117 and CD166, without CD73 [21,30,31].

The second interesting structure of the ovary is the ovarian surface epithelium (OSE). According to some reports, the OSE contains two stem cell populations: very small, embryonic-like stem cells (VSELs) and ovarian stem cells (OSCs) [32–34]. OSCs isolated from patients with severe ovarian infertility revealed the expression of pluripotent markers such as SOX-2 or SSEA-4 [35]. The presence of VSELs has been detected in adult mice, rabbits, sheep, marmoset monkeys [32,36,37] including humans - postmenopausal women and women with premature ovarian insufficiency [38].

Among the cells present in the follicular fluid, the greatest stem cell potential is shown by granulosa cells. In recent years, stem cells have gained much interest in the area of regenerative medicine. There are hopes of using GCs in the future in clinical practice forfertility preservation, *in vitro* feralization (IVF), and for cell-based therapies in the future [39,40].

Ovarian reserve

Women are born with a defined pool of ovarian follicles that decreases dramatically during prenatal life from about 7-9 million to 1 million at birth. While the decline of follicle pool with age, a sequence of reproductive natural events occurs, beginning with reduced fertility ending at natural sterility state – menopause. However, these processes can be accelerated and may occur at a younger age [41].

Ovarian reserve is defined as the number of oocytes remaining in the ovary. In humans, oocyte number can be indirectly measured using the level check of crucial hormones, such as Anti-Mullerian Hormone (AMH) and follicle-stimulating hormone (FSH) or ultrasonography of the ovaries [42]. The aim of ovarian reserve tests (ORT) is to identify the risk of hypo or hyper response to ovarian stimulation, detect reproductive lifespan and approximate menopausal timing, consult the plans for offspring and optimize the individual ovarian response while minimizing risks [43].

Indicators of the stemness potency of cells isolated from follicular fluid

Telomerase activity and TERT expression in cells derived from follicular fluid

Telomerase is a ribonucleoprotein (RNP) responsible for maintaining telomere length, the integrity of 3' chromosome ends, using telomerase reverse transcriptase (TERT) and matrix-containing integral telomerase RNA (TERC) [44,45]. The activity of telomerase is a determinant factor to differ the types and stages of cells. The telomerase is active in embryonic germinal cells and stem cells [46,47] whereas most somatic cells [48] do not exhibit telomerase activity except for rare cell types with the opportunity to divide continuously. The adult stem cells are known for a relatively slower rate of telomere shortening and high telomerase activity compared to adult non-stem somatic cells [46]. The expression of TERT can be detected only in telomerase-positive cells [49].

Granulosa cells undergo many mitotic divisions and either granulosa cells or oocytes are exposed to a variety of genotoxic factors during the maturation and development of the follicles. The telomerase activity and telomere length of ovarian cells are significant [50].

The high telomerase activity was observed in developing bovine follicles, suggesting other multipotent stem cell features of granulosa cells. The telomerase activity decreased as the follicles enlarged [51]. Interestingly, the results of the Fluorescent In Situ Hybridization (FISH) indicate the existence of a correlation between TERT expression and telomere length in follicles. The longer telomeres were observed in preantral follicles compared to matured antral follicles. The longer telomeres were documented as well in the cells of the cumulus oophora and the antral layer – the layers with a higher proliferation rate than in the basal lamina [52]. Importantly, the epidermal growth factor (EGF) stimulates telomerase activity in granulosa cells isolated from small follicles [53] suggesting that telomerase activity and telomere elongation are essential for the right proliferation of granulosa cells, especially in small, rapidly growing porcine follicles. It is possible that the high proliferative activity of granulosa cells can be partially connected to telomerase activity [54].

Significantly reduced telomerase activity was observed in large and atretic follicles compared to telomerase robustly expressed in small and healthy preantral follicles in mice. Therefore, it appears that telomerase in GCs may have an important role in the development of a healthy follicle and that its loss of activity may be related to follicular atresia [55].

Correlation between telomere length and telomerase activity and potential ovarian insufficiency or infertility

Over the past few years the scope of research of telomerase activity and telomeres shortening in human follicular cells is expanding. It has been shown that the relative length of telomere is longer in cells isolated from mature oocytes compared to immature oocytes. The researchers proposed the relative length of telomeres as a new biomarker for selecting good-quality oocytes and good-quality embryos [56]. It has been confirmed that abnormal telomere lengths in GCs are associated with female infertility and reduced ovarian reserve [57].

Another important issue is, that in the field of assisted reproduction the human luteinized GCs have a defined proliferation level, which correlates with the activity of telomerase in these cells. This may be of clinical importance in predicting the possible outcome of *in vitro* fertilization [58].

In vitro studies on GCs in mice suggest that telomerase activity in follicular cells may be strongly related to estrogen metabolism. The estrogen stimulates the GCs proliferation through enhanced expression of the TERT gene, as well as ovarian tissue growth. It was also shown that no telomerase activity was detected in human ovarian epithelial cells cultured in the absence of 17beta-estradiol (E2), but after adding the E2 the activity of the enzyme was induced within 3 hours of treatment. This novel finding suggests hTERT as a target of estrogens and further research on telomerase regulation in hormone-dependent cells is crucial for understand-

ing the role hormones in cycle of the certain cells. In clinical practice, this may suggest that infertility women with estrogen deficiency are ineligible for an area of granulosa and epithelial stem cell studies [59,60].

Conclusions

Over the years a lot of research studies were conducted to investigate the cells present in an ovarian niche. Since follicular cells have been suggested to show the characteristic of stem cells and mesenchymal stem cells, such as multipotency, telomerase activity, high proliferation rate, their potential use of them in medicine has been implied. The follicular fluid is a simple source of such biological material. The cells isolated from FF are ideal for *in vitro* cultivation and complex tests. While the available data is still limited, ovarian stem cells are successfully used for *in vitro* maturation, prediction of oocyte and embryo quality, or in tissue engineering. However, more research is needed to fully behold the potential of these cells in regenerative and experimental medicine.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare they have no conflicts of interest.

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