Oogenesis in Women

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It is a well-known fact that the reproductive organs in women, especially oocytes, are exposed to numerous regulatory pathways and environmental stimuli. The maternal age is one cornerstone that influences the process of oocyte fertilization. More precisely, the longer a given oocyte is in the waiting-line to be ovulated from menarche to menopause, the longer the duration from oogenesis to fertilization, and therefore, the lower the chances of success to form a viable embryo. The age of menarche in girls ranges from 10 to 16 years, and the age of menopause in women ranges from approximately 45 to 55 years. Researchers are paying attention to the regulatory pathways that are impacting the oocyte at the very beginning during oogenesis in fetal life to discover genes and proteins that could be crucial for the oocyte's lifespan.

oocyte oogenesis women

1. Introduction

Sexual reproduction is a process during which many organisms ensure the continuity of the species by producing offspring [1]. It arises in connection with the fusion of haploid gametes from parental organisms, and as a consequence, a zygote is formed, from which an embryo develops [2][3]. The process of gamete formation to create a progeny organism is a highly complex process regulated by many intra- and extraovarian factors in the female embryo. Previous studies have provided knowledge with regard to aging and infertility.

2. Oogenesis, Oocyte Growth, and Oocyte Maturation

Oogenesis is the process during which the formation of the body's largest cell, the oocyte, takes place [4][5]. This multi-step process consists of many interactions between the developing oocyte and the granulosa cells and cumulus cells surrounding the oocyte [6]. Oogenesis begins in the fetal ovaries when oogonia are developed from primordial germ cells (PGC), as soon as the development of the embryo progresses, in approximately the 12th week of gestation in women [4][7]. They then undergo well-organized processes, such as the pairing of homologous chromosomes and the crossing-over process of chromosomes [8]. Genes that are important for chromosome segregation include *STAG3*, which encodes protein stromal antigen 3, or BUB1B, which encodes Mitotic Checkpoint Serine/Threonine Kinase B [9]. During the prophase of meiosis I, homologous chromosomes undergo recombination, during which DNA double-strand breaks (DSB) occur [10]. This is when the proliferation phase of the oogonia takes place. Following, these cells arrest at the end of prophase I, and remain dormant in this state until

the periovulatory phase [1][11]. It has been reported that the number of oocytes in newborn girls is about 1 million, and at the timepoint of reaching puberty, this number has already decreased to 400,000 [5].

To determine the reproductive potential of the ovaries, the so-called ovarian reserve is commonly used in human fertility clinics, reflecting the number of remaining follicles bearing the oocytes [11]. The reproductive machinery prepared in this way remains transcriptionally inactive from the start of follicle growth until fertilization; thereafter, activation of the zygotic genome takes place (ZGA) [11][12]. In some women, a sudden decrease of the ovarian follicles after puberty can occur, diminishing the ovarian reserve and symptoms of irregular cycles or an early onset of menopause might be present [5]. The process of oogenesis is regulated by the neurotrophin signaling pathway. Polypeptide growth factors, called neurotrophins (NT), and their receptors in cell membranes have been shown to control processes such as follicle formation and growth [13]. Oogenesis is also under the control of endocrine, paracrine, and autocrine factors. One of the factors influencing the process of oogenesis is adipokines, i.e., substances secreted by adipose tissue [14].

Leptin is one of the adipokines that is present both in mature follicles and in the earlier stages of follicle development, and its presence supports, among others, the development to the stage of primary follicles [15]. It has been confirmed that treatment with leptin administered in low doses provides a chance to accelerate the growth and maturation of ovarian follicles [16]. In addition, previous research has shown that mice showing a deficiency of leptin had a smaller number of follicles [17]. However, it has also been reported that an extrinsic apoptosis pathway can be induced via the upregulation of caspase 3 (CASP3) as a result of acute leptin treatment [18]. Another essential adipokine affecting the process of oogenesis is adiponectin. The deficiency of the latter-mentioned one reduces the number of ovulated oocytes [19]. Different expressions of resistin can be observed in human ovarian follicles at different stages of development, which provides evidence for the participation of this adipokine in the process of oogenesis [20].

There is no doubt that oocyte development is a very energy-intensive process. The energy provided by the oocyte is especially important in the first stages of embryo development [21]. The main sources of energy are fatty acids and glucose. However, research has shown that fatty acids are the primary source of energy for oocytes, and not glucose. Oocytes secrete various paracrine factors, such as bone morphogenic protein 15 (BMP15) and growth differentiation factor 9 (GDF9) [22]. Paracrine factors secreted by fully developed oocytes have the ability to upregulate the process of glycolysis. It has been reported that the removal of oocytes from the COCs (cumulus-oocyte complexes) led to a decrease in the level of transcripts encoding for the enzymes Pfkp—phosphofructokinase and Ldha—Lactate dehydrogenase A, which are both glycolytic enzymes [23].

Transcriptional activity and gene expression regulation are topics of particular interest for reproductive biologists and reproductive medicine specialists [2][24]. Many factors affect transcriptional activity, including DNA methylation, histone modification, or changes in the histone composition of the nucleosome [25]. DNA methylation, which is a mechanism of epigenetic regulation, is observed during the transition of follicles to the antral stage, at the end of the growth phase, which corresponds to the time of their transcriptional silence [26][27].

There are several studies on proteins that have been shown to be indicators for oocyte growth. In cattle, a protein called connexin 43 (Cx43) has been recognized as a marker of oocyte developmental competence, and connexin 45 (Cx45) and connexin 60 (Cx60) are the main connexins expressed during folliculogenesis in pigs [28]. Apelin plays a very important role in the growth of the ovarian follicle, affects angiogenesis, and the formation of the corpus luteum, and may affect the proliferation of granulosa cells [29]. At the start of folliculogenesis, there is an increase in the expression of the gene encoding tyrosine kinase receptor—KiT in the oocyte [22]. A downstream effector of KiT is phosphatidylinositol 3-kinase (Pi3K), which, once it is activated, phosphorylates serine/threonine kinases. The latter-mentioned enzymes are involved in oocyte survival and proliferation [30]. As previously mentioned, BMP15 and GDF9 expressed in oocytes promote follicle differentiation [31].

It has been reported that an increase in the H3K4me3 modification, which is considered as a marker of active transcription, indicates histone methylation during oocyte growth. Recent studies indicate that it reaches its maximum level at the time point of silencing transcriptional activity, i.e., at the end of the growth phase [32][33]. Down-regulation of promoters of polymerase II (responsible, among others, for the production of pre-mRNA) is also indicated to be a result of global transcription silencing at the end of oocyte growth. The end of this phase will be dominated by processes of transcriptional silencing and degradation of some mRNAs [34]. Notably, oocyte maturation is a consequence of the interaction between the oocyte and the granulosa cells [22]. Most of the mechanisms discussed in this research are more of a sequence of events than a single event. In vitro maturation of human oocytes is one of the most difficult hurdles when performing an IVF procedure [4][35]. The time at which the egg reaches nuclear maturity and acquires meiotic competence occurs at the same time as the antrum is formed, which is specific to mammal species [36]. This occurs when the oocyte has grown to 80% of its final size [34]. It has been estimated that mouse oocytes that have reached meiotic competence contain approximately 200 times more RNA than a somatic cell, of which 10–15% will be pre-mRNA. What happens to this mRNA in the oocyte depends mainly on regulatory proteins and ribosomes, while after transcription, the poly-A tail will be added [34]. It is observed that polyadenylation is evolutionarily conserved in many species, i.e., insects (Drosophila), amphibians (Xenopus), fishes, and mammals [2]. The key proteins in this process are CPEB and CPEB1, the most present ones in the mouse and human oocytes, responsible for the control of polyadenylation and translation, as well as for the activation of translation. Furthermore, CDK1 (cyclin-dependent kinase 1) and Mos activate the MAPK cascade (mitogen-activated protein kinase) [32][37]. Interestingly, the maturation-promoting factor (MPF) is produced in oocytes with the association of Mos and CDK1 [11][25]. In mammals, meiotic resumption under the influence of LH (luteinizing hormone) and FSH (follicle stimulating hormone) meditates the activation of MAPK, which leads to the increased production of cAMP (cyclic adenosine monophosphate) [38][39].

During the entire oocyte maturation process, changes in the genome and expression are based on translation and degradation, rather than on transcription [37]. The occurrence of degradation of translated transcripts results in only half of the mRNA remaining after degradation until the oocyte reaches metaphase II, and only 30% will remain immediately before fertilization [11]. In mouse oocyte studies, downregulation of GPR3 has been shown to

contribute to oocyte maturation [40]. Mural granulosa cells and granulosa-derived cumulus cells play a crucial role in oocyte development by supporting the cell with metabolites and regulatory signals [41][42].

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