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Review

Current approaches for the treatment of premature ovarian failure with stem cell therapy

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ABSTRACT

One of the common disorders found in women is premature ovarian failure (POF). Recently some studies have explained premature ovarian insufficiency (POI). The causes of it are unknown although various types of study have been done. The most common causes such as genetic and autoimmune conditions can have a role in POF and can lead to infertility. Some characterization of POF are hypo-oestrogenism (estrogen deficiency), increased gonadotropin level and most importantly amenorrhea. The main purpose of this review is to describe the cause and treatment of POF, especially stem cell therapy proposed in previous studies. Stem cells have self-renewal and regeneration potential, hence they can be very effective in the treatment of ovarian failure and consequently infertility. There are several kinds of stem cells such as, mesenchymal stem cells (MSCs), stem cells from extra-embryonic tissues, induced pluripotent stem cells (iPSCs), and ovarian stem cells that are used in POF stem cell therapy as observed in previous studies. This article reviews the latest studies on POF to summarize current understanding and future directions.

1. Introduction

Premature ovarian failure or Primary ovarian insufficiency and in other words, premature menopause, is a mysterious and complicated disease. The prevalence of POF is 1 in 250 women under the age of 35 years and 1 in 100 women under the age of 40 years [1–3]. The features of POF are hypooestrogenism, hypergonadotropinism, amenorrhea that contribute to female infertility and premenopausal syndrome [4]. In addition, POF have negative consequences such as increased risk of cardiovascular diseases, sexual dysfunction and osteoporosis [5]. Ovarian follicles contain 3 types of cell, oocyte, granulosa cell and theca cell. Granulosa and theca cells have receptor for follicle-stimulating hormone (FSH) and luteinizing hormone (LH), respectively that are essential for the growth and development of the follicles. In this cell, principal explained gene have a role in POF. Folliculogenesis is an organized and regulated process. In this process, primordial follicles turn into primary follicles then preantral and finally antral follicles and after this stage ovulation occurs (Fig. 1) [6]. This normal process is altered during POF. For premature ovarian failure, two histopathological types have been reported. In type 1, the ovarian follicles deplete completely while in type 2, there are follicular structures that are preserved in the ovary [7]. Probably, the most important mechanism in POF are follicle dysfunction and follicle depletion [8]. Although the cause of POF is not fully known, genetic, endocrine, paracrine, mitochondrial dysfunction and metabolic factors can affect the quality of the follicular pool and oocytes [9]. The routine diagnosis for this disease is module of serum FSH [10,11]. The age for natural menopause is about 50 years and this indicates the regular setting and conserved trait but due to environmental factors, the age of menarche is down over the past century [12]. POF has two pattern of inheritance, sporadic and familial. About 4–31% of POF are familial [13,14]; therefore, X-chromosome abnormality has the most important role in this disease [15].

2. Etiology of premature ovarian failure

2.1. Role of genetics in premature ovarian failure (POF)

Studies have shown that gene defects such as X and autosomes

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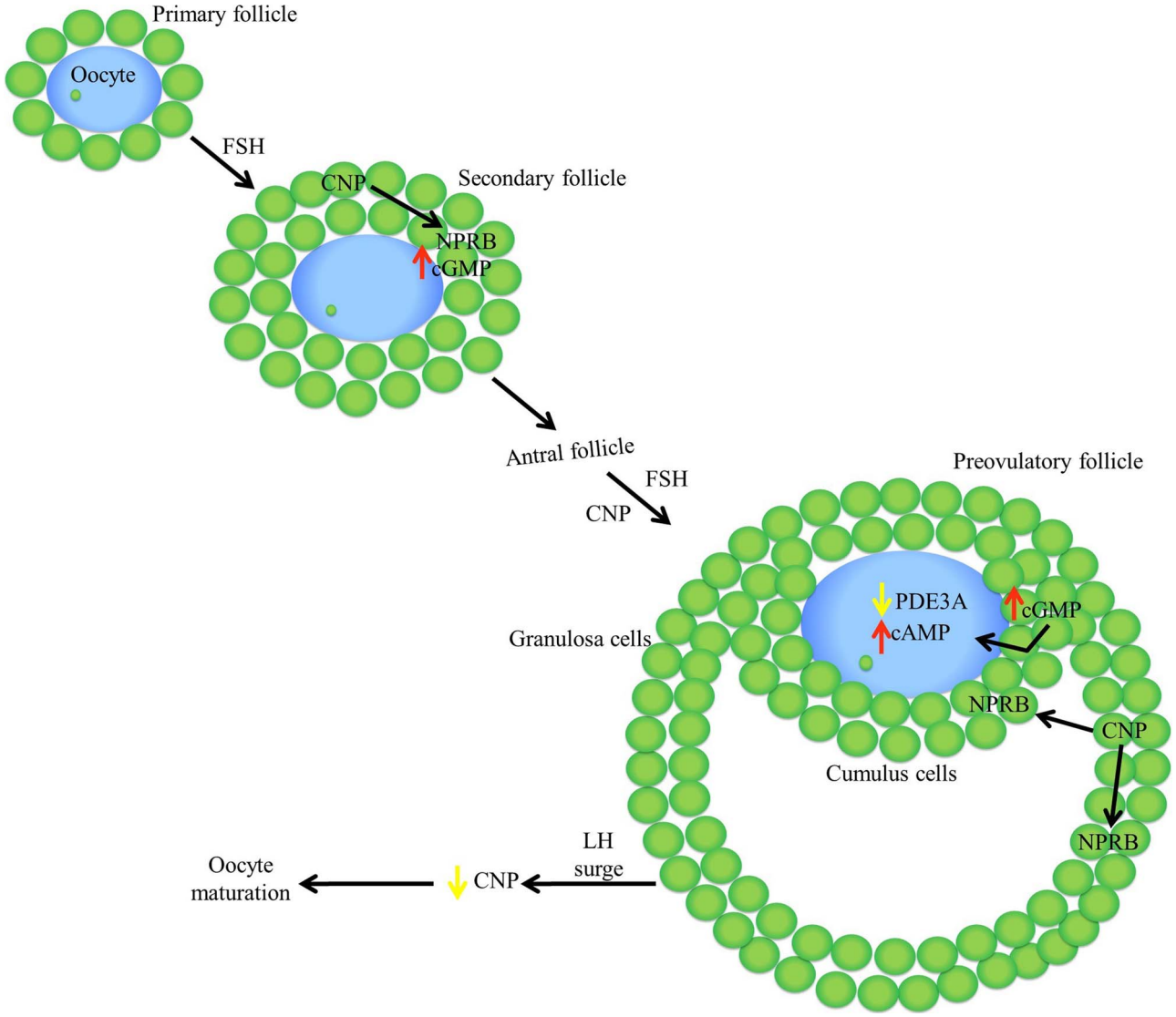

Fig. 1. Folliculogenesis: ovarian follicle include of somatic cells and an immature oocyte. Maturation of ovarian follicle describes the passage of a number of small primordial follicles into pre-ovulatory follicle and finally oocyte maturation. Abbreviation: C-type natriuretic peptide (CNP), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), natriuretic peptide receptor-B, phosphodiesterase 3A (PDE3A).

chromosome abnormalities have important role in POF [15–20]. Most especially, structural anomalies and translocation of X with autosomes in X chromosome [21–25]. Turner syndrome, trisomy X, mutations and pre-mutations of X linked gene and abnormalities of autosomal related genes have been observed in POF cases [26].

2.1.1. X chromosome disorder

Turner syndrome have been seen in 1 of 2500 females that are born. One of the characteristic features of turner syndrome is POF. After the third month of fetal life, apoptosis of oocytes is accelerated [27–29]. Therefore, just 10% of turner syndrome women achieve menarche. Likely undetected X chromosome mosaicism could result in some unexplained POF cases [30]. The deletion of small part of X chromosome gene in turner syndrome women causes oocyte depletion. Some X chromosome genes involved in ovarian function are Zinc finger X-chromosomal protein (ZFX), ubiquitin specific peptidase 9 X-linked (USP9X), and Bone Morphogenetic Protein 15 (BMP15). These genes are located on short arm of X-chromosome (XP) [11]. Other X-linked ovarian failure such as X chromosome deletions, duplications and inversions are the most common reasons for POF [11]. Trisomy X syndrome may also result in POF [31]. Also, studies reported missense mutation of heterozygote *BMP15* resulted in POI [32–34]. The location of this gene is on Xp11·2 and encode the BMP 15 protein. Exclusively the expression of *BMP15 gene is in ovaries and* involved in follicular development [35].

2.1.2. Fragile X pre-mutations

About 20% of women with fragile X pre-mutation will show symptom of fragile X-associated primary ovarian insufficiency(FXPOI) [36]. Fragile X syndrome is a triple repeated disease [37,38]. Fragile X mental retardation 1 (FMR1) gene mutations cause fragile X syndrome and carriers of Fragile X pre-mutation include 55–200 CGG repeats in the 5' untranslated FMR1 gene region [39]. Women with fragile X chromosome have increased FSH and decreased inhibin B levels proposing ovarian ageing [40].

2.1.3. Autosomal disorder

Other genetic causes of POF are single gene disorders that include mutation in the receptor of LH and FSH, galactosemia and inhibin mutation [41]. POF have been seen in 80% of galactosemia patient [42]. Several studies have demonstrated that the mutation of Forkhead Box protein L2 (FOXL2), Newborn ovary homeobox gene (NOBOX),