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Research Progress on the Pathogenesis of Premature Ovarian Failure: A Review

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Abstract: *Premature ovarian failure (POF) causes tremendous physical and psychological health problems in women worldwide. Many important scientific studies have shown that the pathogenesis of POF may be related to reproductive endocrine hormone levels, granulosa cell apoptosis, mitochondrial dysfunction, immune function, related signalling pathways, genes, and enzyme deficiencies. The modern treatment for POF is hormone replacement therapy, but this method has limitations and cannot meet the needs of patients with POF. Therefore, this paper reviews the research on POF in recent years, and by summarizing its mechanism, we search for a multiway and multimans treatment for POF to explore the optimal treatment plan.*

Keywords: *premature ovarian failure; pathogenesis; research progress*

1. Introduction

POF can be caused by follicular depletion or follicular dysfunction before the age of 40 years and is characterized by elevated serum concentrations of gonadotropins, such as follicle stimulating hormone (FSH) and luteinizing hormone (LH), and decreased concentrations of estradiol (E2) [1]. In clinical practice, reproductive endocrine disorders may occur, such as prolonged or even amenorrhea of the menstrual cycle, decreased reproductive ability, and even infertility. Some patients may experience menopausal symptoms such as hot flashes, night sweats, vaginal dryness, and decreased libido. According to the results of epidemiological surveys, the prevalence of POF in women is 3.5% globally, and patients with POF tend to be younger, which is a serious threat to women's reproductive health [2]. Currently, POF is widely believed to be a disease caused by multiple factors, but its pathogenic mechanism has not yet been elucidated. In modern medicine, hormone replacement therapy is used mainly to treat POF. Although this method can alleviate clinical symptoms related to POF in women, long-term acceptance of this therapy has a significant negative impact on the body [3]. Therefore, this article comprehensively discusses the pathogenesis of POF from the aspects of reproductive endocrine hormone levels, granulosa cell apoptosis, mitochondrial dysfunction, immune function, related signal transduction pathways, genes, and enzyme deficiency, providing a reference for further research on the treatment of this disease.

2. The mechanism of premature ovarian failure

The pathogenesis of POF is very complex, but ultimately, POF is related to three basic mechanisms, namely, accelerated follicular apoptosis, follicular maturation atresia, and follicular overactivation. According to the latest research, the levels of reproductive endocrine hormones, granulosa cell apoptosis, mitochondrial dysfunction, immune function, related signal transduction pathways, and gene and enzyme deficiencies can directly or indirectly lead to these conditions, which in turn can cause POF [5] (Figure 1).

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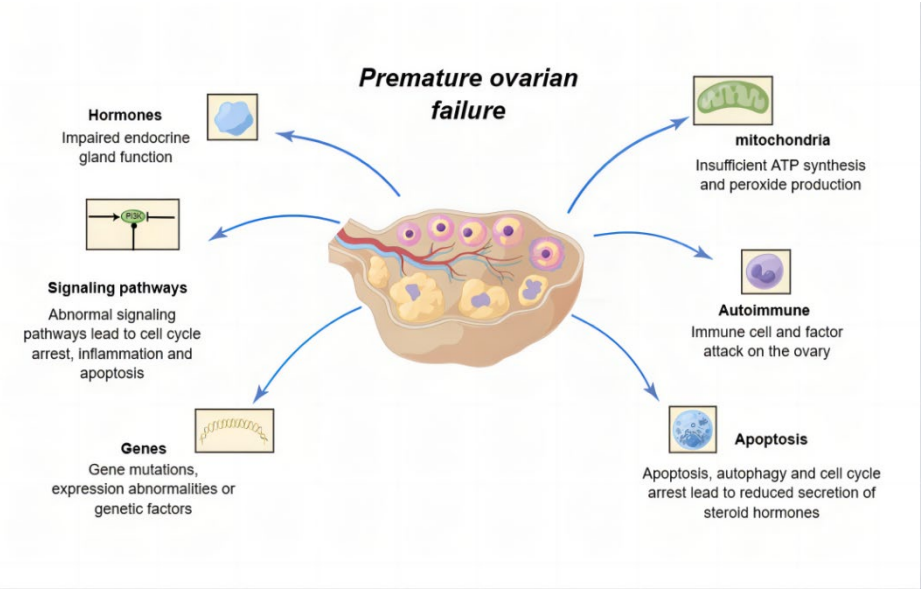

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Figure 1: Pathogenic mechanism of POF

2.1. Reproductive endocrine function and premature ovarian failure

2.1.1. FSH, LH, E2, and P

According to previous research, serum FSH and LH levels increase in POF patients, while E2 and progesterone (P) levels decrease [6]. The hypothalamic pituitary ovarian axis (HPO) can regulate female sex hormone levels, thereby maintaining normal reproductive function. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus, and its receptor can regulate the synthesis of FSH and LH by mediating the expression of GnRH, thereby inducing granulosa cells and the corpus luteum to secrete E2 and accelerating the growth, development, maturation, and ovulation of ovarian follicles [7][8]. E2 and progesterone act sequentially to maintain the transition of the menstrual cycle. Normal ovarian function requires comprehensive functional and interactive feedback from the HPO. Insufficient secretion of ovarian E2 leads to an increase in FSH and LH levels through negative feedback [9]. Modern medical treatment for POF relies mainly on hormone replacement therapy, which promotes the expression of E2 and has a negative feedback inhibitory effect on FSH and LH, reducing the premature luteinization effect of high-FSH levels on follicles, promoting ovulation, and improving premature ovarian function [10]. However, supplementing E2 cannot completely cure POF, and long-term hormone replacement therapy increases the risk of stroke, heart disease, and pulmonary embolism [3]. In addition, administering estrogen alone cannot meet the needs of pregnant individuals.

2.1.2. Anti-Mullerian hormone

Anti-Mullerian hormone (AMH) is secreted by granulosa cells of preantral and antral follicles and is expressed only in the gonads [11] (Figure 2). AMH can inhibit the development of follicles in two ways. First, AMH inhibits the recruitment of primordial follicles into the follicle growth pool, slows follicle development, prevents premature depletion of primordial follicles, and regulates the reproductive lifespan. Second, it reduces the sensitivity of antral follicles to FSH, inhibits ovulation, and can also slow follicle depletion [12]. As age increases, the functional ovarian reserve decreases due to depletion of the primordial follicle pool after FSH-dependent selection, resulting in a decrease in the number of sinusoidal follicles and a decrease in the serum AMH concentration. AMH expression disappears after menopause is reached [13]. After AMH levels decrease in the serum of POF patients, the recruitment of primordial follicles accelerates, and at the same time, the reserve of primordial follicles accelerates consumption, leading to a decrease in ovarian reserve and premature failure [7]. The number of growing follicles recruited from the primordial follicle pool reflects the number of primordial follicles, and the AMH concentration can reflect the number of growing follicles. Therefore, the AMH concentration can indirectly reflect the size of the primordial follicle pool and serve as a biomarker for functional ovarian reserve (FOR) [14]. Under normal conditions, AMH blood levels are not affected by menstrual cycle stage or by exogenous steroid hormones, and AMH levels are relatively stable at each stage [13].

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Therefore, AMH testing can be conducted on any day of the menstrual cycle, which is more convenient than traditional FSH testing. The measurement of AMH combined with the antral follicle count (AFC) can serve as an effective indicator of POF, with diagnostic validity and potential for more timely diagnosis [15].

2.1.3. Inhibin B

Inhibin B (INHB) is a type of heterodimeric protein hormone and a member of the transforming growth factor family. It is expressed mainly in ovarian granulosa cells and inhibits the secretion of FSH induced by GnRH through paracrine and autocrine negative feedback [16] (Figure 2). Therefore, higher serum INHB levels in women of childbearing age are one of the important factors in maintaining lower serum FSH levels. In addition to the above effects, it can also stabilize T-cell function and inhibit excessive activation of immune factors, avoiding damage to ovarian epithelial tissue [17]. However, as age increases, the quality and quantity of ovarian follicles decrease, and the serum INHB concentration also gradually decreases, weakening the inhibitory effect on FSH. This is also one of the important reasons for the gradual increase in the serum FSH concentration in POF patients [18]. Studies have shown that with the progression of POF, INHB levels significantly continue to decrease and are positively correlated with AMH and the AFC but negatively correlated with age, FSH, LH, and the FSH/LH ratio [7]. The possible mechanism is that a decrease in INHB leads to high FSH expression, causing premature follicular atresia and luteinization and resulting in a decrease in ovarian reserve function. Because FSH and the AFC are traditional indicators of ovarian reserve, INHB has the potential to reflect ovarian reserve function to a certain extent. However, INHB is currently not a reliable indicator of ovarian reserve in clinical practice. The main reason may be that the INHB concentration varies with menstrual cycle fluctuations, and the absolute INHB concentration also varies significantly according to the population and test kit used in different studies. To date, there is no normal range of INHB values available [19]. When INHB participates in the process of follicular dominance, more mature eggs can be obtained when follicular dominance selection is inhibited. In clinical practice, oral contraceptives or estrogen are used for pretreatment to suppress the dominant selection of follicles, thereby obtaining more synchronously developing follicles and reducing the incidence of oocyte overmaturation or immaturity [20]. However, further exploration is needed on how to utilize INHB in the process of follicle dominance to monitor and control the process of ovulation induction and avoid excessive follicle occlusion leading to POF.

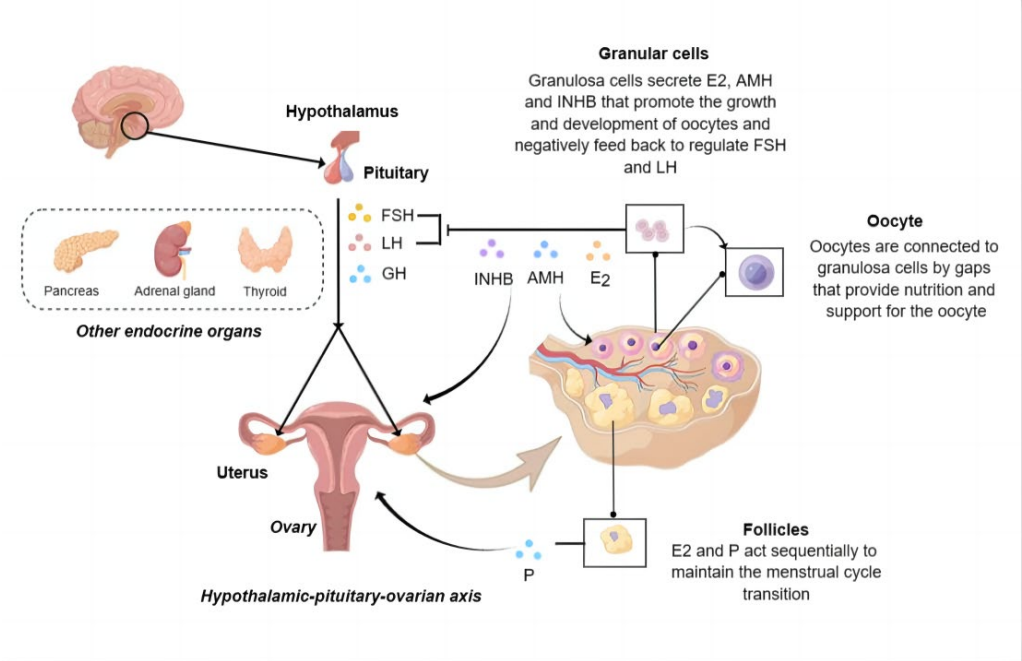

Figure 2: Relationships of the hypothalamic-pituitary-ovarian axis and other endocrine glands with POF

2.2. Granulosa cell apoptosis and premature ovarian failure

Granulosa cells located on the outside of the zona pellucida of oocytes can secrete estrogen in response to FSH and other cytokines and provide nutrients and support for oocytes through gap junctions.

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Granulosa cell apoptosis leads to a decrease in estrogen levels in the body, which affects oocyte development and is a key factor leading to follicular atresia; thus, the level of added granulosa cell value or apoptosis can respond to ovarian function [21]. Upon cellular stimulation, activated proteins hydrolysing cysteine aspartate-specific protease (caspase-9) degrade organelles and then mRNA. Caspase-9 leads to rupture of the proteocyte cytoskeleton, shrinkage of the cells into clumps, and condensation of the chromatin, which are major indicators of apoptosis [22]. Currently, the apoptotic pathways mainly include the mitochondrial pathway (endogenous pathway), death receptor-mediated pathway (exogenous pathway), and endoplasmic reticulum pathway, which involve cytokines, including the B-cell lymphoma-2 (bcl-2) family, Fas/Fas-L, p50, the tumor necrosis factor receptor (TNFR) family, reactive oxygen species (ROS), etc., which also include various noncoding RNAs [23]. (Figure 3) Factor receptor (TNFR) family, and reactive oxygen species (ROS), which also include various noncoding RNAs [24]. Radiation, chemotherapy, inflammation and oxidative stress may all lead to granulosa cell apoptosis [25][26]. MSC transplantation can be a better treatment for POF and can promote granulosa cell proliferation, inhibit apoptosis, and regulate the ovarian microenvironment [27]. Therefore, POF can be treated by improving granulosa cell apoptosis through MSC transplantation technology, but this method is still in the experimental stage and has not been applied in the clinic.

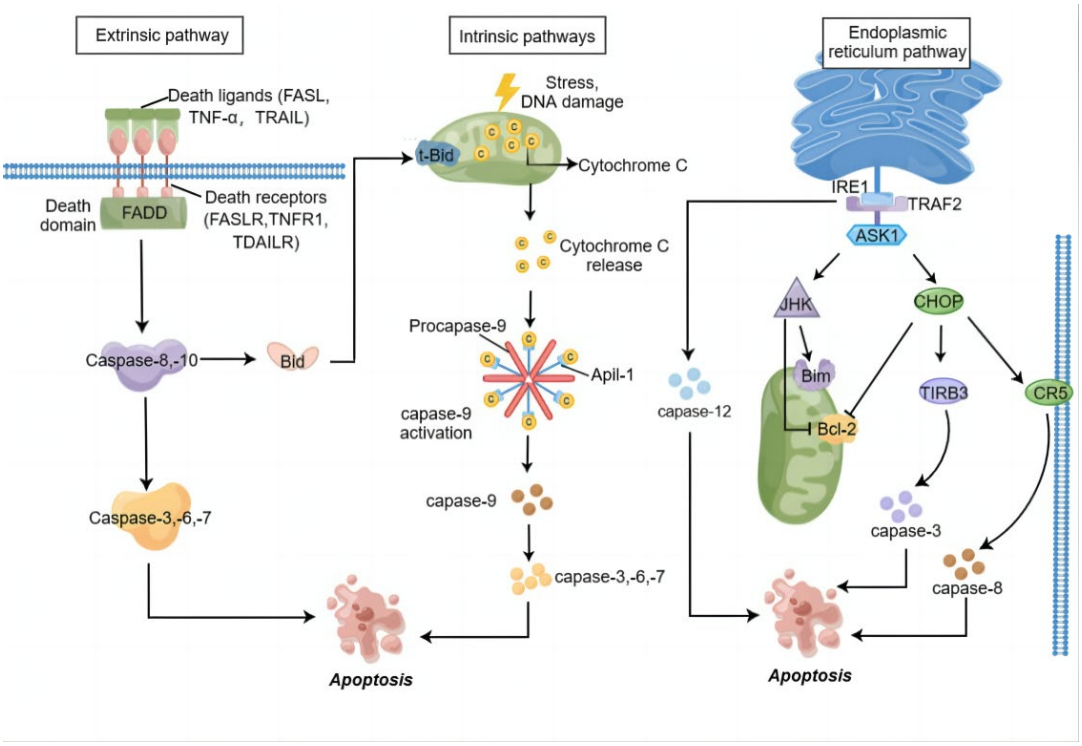

Figure 3: Mechanisms of granulosa cell apoptosis in POF

2.3. Mitochondrial dysfunction and premature ovarian failure

Recent studies have shown that oxidative stress levels are altered in POF models. Serum FSH levels, serum ROS, total oxidative stress, and oxidative stress indices were significantly greater in POF patients than in healthy individuals and were positively correlated with these alterations [28][29]. Therefore, inhibiting the oxidative stress state of ovarian cells via the mitochondrial pathway could be a direction for the treatment of POF. The mechanism of mitochondrial dysfunction is shown below (Figure 4).

2.3.1. Mitochondrial energy metabolism

Mitochondria are a source of biopower, and the energy released by mitochondria from the breakdown of organic matter, including sugars, lipids, and amino acids, through the process of oxidative phosphorylation drives the synthesis of ATP [30]. In eukaryotic cells, the systems involved in oxidative phosphorylation are distributed across the inner mitochondrial membrane in the form of five complexes that constitute the respiratory chain (RC), also known as the electron transport chain (ETC) [31]. Mitochondria provide energy to support transcription and translation during oocyte maturation, fertilization, and early embryo development in oocytes and during reproduction; thus, the quality of mitochondria in the oocyte determines the quality of the oocyte and the developing embryo.

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Mitochondrial biogenesis is critical for ovarian function. Regulatory coactivators of the PGC-1 (peroxisome proliferator-activated receptor γ coacti lalpha) family play a central role in the regulatory network controlling mitochondrial biogenesis, fatty acid β-oxidation and transcriptional control of respiratory function [32][33]. These coactivators target a variety of transcription factors, including peroxisome proliferator-activated receptor γ (PPARγ), estrogen-related receptor (ERR), and nuclear respiratory factor-1 and -2 (NRF-1,2). 2 (NRF-1,2), and so on. Ageing of the female germ line is accompanied by mitochondrial dysfunction associated with decreased oxidative phosphorylation and reduced ATP levels [34]. During the maturation process of oocytes, two meiotic divisions are needed, which require a significant amount of energy, with the formation of the spindle particularly consuming energy. A decrease in ATP levels leads to meiosis errors, altering the number of chromosomes in cells and resulting in abnormal oocyte development and even genetic diseases [35].

2.3.2. Reactive oxygen species and oxidative stress

During the process of mitochondrial oxidative substances producing ATP, a series of hydrogen and electron donors can reduce O2 to ROS[36]. By the action of superoxide dismutase (SOD), superoxide anions are converted into hydrogen peroxide (H2O2), which is the second key participant in mitochondrial ROS[37]. H2O2 is further processed into water and oxygen through catalase (CAT) or into water and oxidized glutathione through glutathione peroxidase (GPX). The oxidative phosphorylation system is the main source of ROS in mitochondria, and the production of mitochondrial ATP and ROS is closely related to mitochondrial function [38]. Excessive ROS levels and imbalanced antioxidant defense systems can cause oxidative stress, leading to lipid peroxidation, DNA damage, protein oxidation, mitochondrial damage, and insufficient ATP production, ultimately leading to cell death [28]. Mitochondrial membrane components are particularly susceptible to oxidative damage from ROS, and their main phospholipid components are rich in unsaturated fatty acids. Due to the presence of double bonds, the double bonds undergo a series of oxidation reactions, increasing susceptibility to attacks from oxygen free radicals [39]. After oxidative damage, the permeability of the mitochondrial membrane increases, and a large amount of Ca2+ enters the mitochondria, leading to a decrease in transmembrane potential and inducing apoptosis in granulosa cells [28]. In addition, a decrease in the permeability of the outer mitochondrial membrane can lead to the release of cytochrome into the cytoplasm, thereby inducing cell apoptosis [40]. Malondialdehyde (MDA) is the main product of polyunsaturated fatty acid (PUFA) peroxidation. Exposure to ROS can lead to an increase in mitochondrial and plasma MDA levels, making MDA a useful biomarker for measuring and monitoring oxidative stress. Oxidative stress has also been shown to cause mitochondrial protein denaturation. ROS can cause various modifications of proteins, including tyrosine nitration, sulfonation, thiol oxidation, and 4-hydroxynonanal protein adducts. Damaged protein function further leads to abnormal activation or inactivation of signalling pathways required for normal ovarian physiology [41]. Some studies have shown that mtDNA mutations lead to dysfunction of ETC complexes, and ROS may disrupt the stability of mtDNA [42]. Genetic or random primary mtDNA mutations initially induce respiratory defects, leading to an increase in ROS leakage in the ETC. ROS may trigger the accumulation of secondary mtDNA mutations, exacerbating mitochondrial respiratory defects and increasing mitochondrial ROS production and lipid peroxidation [43]. Due to the lack of protein protection in telomeres, they are more susceptible to oxidative damage, increasing the rate of telomere shortening and causing cells to enter an aging state [44]. Studies have shown that telomeres in patients with POF are shortened and that telomerase activity is reduced [45]. The ROS produced by mitochondria can freely diffuse to the nucleus, and when mitochondrial dysfunction occurs, telomeres can also be damaged [46]. Silencing regulatory protein 6 (Sirtuin 6, Sirt 6) is believed to play an important role in the stability of telomeres in oocytes [47]. A study revealed that the mRNA and protein levels of Sirt6 are significantly reduced in aging oocytes, and this change is accompanied by a decrease in telomere length [48]. In addition, telomere injury activates p53 and inhibits PGC-1α. Pathways affect mitochondrial function, and p53 plays a role in telomere loss and DNA damage [48][49]. PGC-1α is a key regulatory factor in mitochondrial biosynthesis and metabolism [50]. Telomere loss can affect PGC-1α expression, ultimately leading to mitochondrial damage [51].

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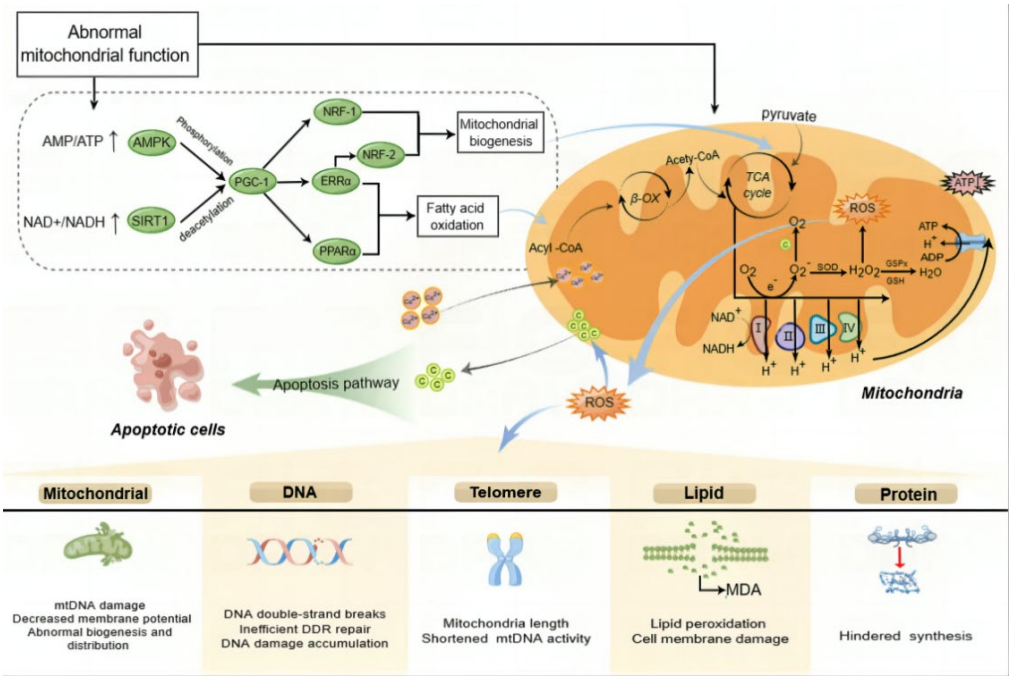

Figure 4: Mechanisms of mitochondrial dysfunction in POF

2.4. Immune function and premature ovarian failure

2.4.1. Autoimmune diseases

A survey showed that more than 30% of POF patients have immune dysfunction [52]. The most closely related diseases are thyroid-related diseases, such as hypothyroidism, Hashimoto's thyroiditis, and Grave's disease.[53] After thyroid disease, the second most common autoimmune disease is related to the adrenal gland. According to the literature, up to 10-20% of patients with Addison's disease will experience POF [54]. Women with diabetes also have a higher risk of POF, with an estimated incidence of 2.5% [55]. POF is also associated with many other diseases, including rheumatoid arthritis, Crohn's disease, myasthenia gravis, systemic lupus erythematosus, and multiple sclerosis [56].

2.4.2 Inflammation

The process of ovulation is a normal physiological process and is similar to an inflammatory response, as it is characterized by leukocyte infiltration and the involvement of proinflammatory cytokines such as interleukin (interleukin, IL) and tumor necrosis factor-α (tumor necrosis factor-α, TNF-α). Current research suggests that the pathogenesis of POF may be related to the inflammatory response induced by radiotherapy, oxidative stress and autoimmune diseases. Senescent cell cycle arrest produces a series of secretory groups called the senescence-associated secretory phenotype (SASP) that involve proinflammatory environmental factors, including IL-1, TNFα and IL-6 [57]. The production of SASP inflammatory factors is primarily driven by nuclear factor kappa-B (NF-κB), a fast-acting transcription factor that orchestrates responses to a range of cellular stressors [58]. The SASP diffuses proinflammatory factors secreted by senescent cells to other normal cells through paracrine senescence [59]. Proinflammatory factors also cause an increase in the ratio of Th1 to Th2 cells and their cytokines, activating monocytes to regulate the immune response and leading to follicular atresia and ovarian failure [60]. (Figure 5) It has been shown that the proinflammatory cytokines IL-1α, IL-1β and TNF-α are significantly elevated in follicular fluid and serum samples from patients with POF, whereas the anti-inflammatory factors IL-4 and IL-10 are reduced [61]. Elevated levels of proinflammatory cytokines in the follicular fluid of patients with POF may regulate follicular atresia by promoting the apoptosis of oocytes, stromal cells and granulosa cells [62]. Increased absolute counts and percentages of peripheral blood T-lymphocytes, especially CD4+ T cells, have been found in patients with POF, whereas the number and activity of natural killer (NK) cells appear to be reduced, with lower levels of CD8+/CD57+ T cells and an overall elevated CD4+/CD8+ ratio [63]. Regulatory cells (Tregs) are also CD4+ T cells and are directly derived from the thymus. TGF-β1 and IFN-γ are cytokines secreted by Treg cells. Treg cells are also reduced in patients with POF, accompanied by alterations in the expression of these two factors. Patients with ovarian insufficiency have a decreased number of effector Treg cells and an

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increased number of CD4+ CD69+ activated T cells in the peripheral blood [64]. These findings suggest that POF is an immunologic disorder. Organismal immunity consists of both cellular and humoral immunity. In addition to the humoral immune system mentioned above, cellular immune systems may be involved in the immunological mechanisms of POF. Cytokines secreted by T cells can act directly on B cells to mediate the production of corresponding antibodies, which are polyclonal immunoglobulins of the IgG class that attack ovarian cells, leading to follicular destruction and atresia and even premature failure [64]. In addition, antibodies can act on the hormone-producing corpus luteum, zona pellucida, granulosa cells, oocytes, maternal antigen that embryos require (MATER), and steroidogenic enzymes [55][64]. According to the current research, autoantibodies related to POF are known to be anti-ovarian antibodies, anti-thyroid antibodies, anti-nuclear antibodies and anti-cardiolipin antibodies, and several of these antibodies lead to decreased ovarian function, follicular dysplasia and ovulation disorders via different mechanisms [63]. There is no better treatment for autoimmune POF, and immunomodulatory therapies can maintain the normalization of ovarian function in patients, especially the use of high-dose corticosteroids and intravenous immunoglobulin therapy; however, the long-term use of glucocorticoids at high doses can result in serious complications [65].

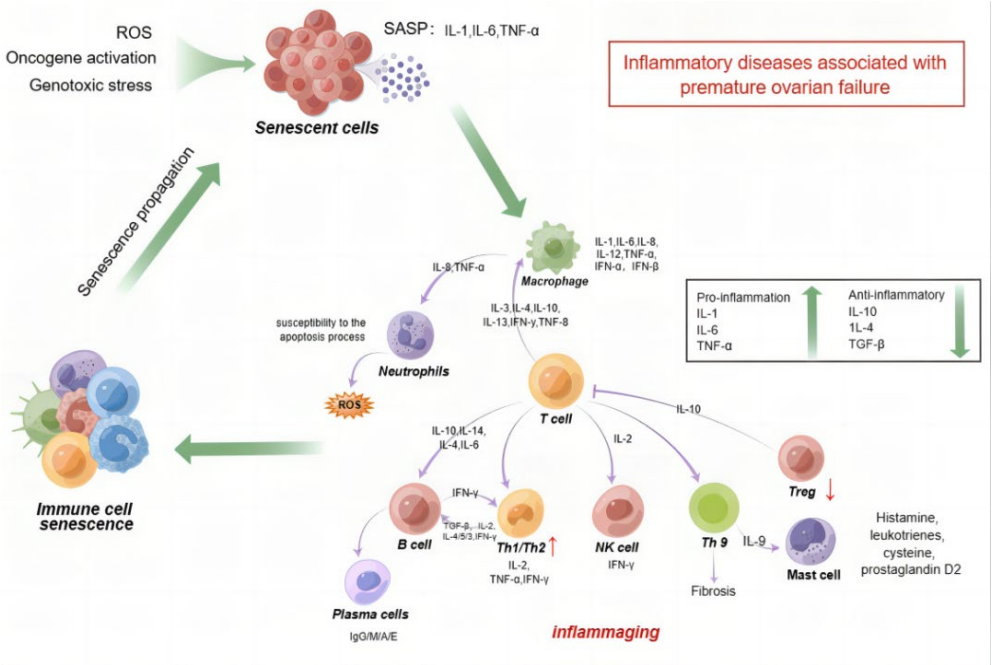

Figure 5: Inflammatory response in premature ovarian failure

2.5 Associated signalling pathways and POF

2.5.1 TGF-β/Smad signalling pathway

The transforming growth factor-β (TGF-β) pathway consists of a number of genes involved in cell growth, differentiation, migration, and apoptosis. TGF-β ligands bind to TGF-β receptor kinases to form a complex of phosphorylated receptor-activated Smads, allowing the recruitment of Smad4 to the nucleus to regulate transcriptional activities [66]. TGF-β1/Smad signalling pathway-related molecules are secreted by ovarian tissues and contribute to ovarian senescence by downregulating the expression of the TGF-β1/Smad3 signalling pathway factors while promoting Smad2 expression in the follicular cytoplasm [67] (Figure 6). During ovarian aging, the Smad7 compensatory inhibitory pathway may regulate the biological effects of this signalling pathway [67]. Smad7 is expressed in granulosa cells, oocytes and oocytes and is also highly expressed in the ovarian vasculature [68]. Previous studies have shown that Smad2 and Smad3 regulate follicular development, ovulation, and oocyte expansion to promote ovarian function and that Smad3 knockout mice exhibit ovulation defects and lack a corpus luteum in the ovary [69]. Knockdown of Smad5 expression increased the rate of apoptosis as well as the protein levels of Fas/FasL, cysteinyl asparagin-8 (caspase 8, CASP8) and cysteinyl asparagin-3 (caspase 3, CASP3) in germ cells [69]. According to the results of other experiments, the expression of the TGF-β1, TGFR-β1, Smad3 and Smad4 proteins in the ovarian tissues of POF rats was significantly reduced, and the expression of the Smad7 protein was significantly elevated; the opposite results were observed after the administration of different dosages of kidney tonics and menstruation-regulating formula and

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ethinyl estradiol-cyclopropylpropanedione interventions [70]. These results are consistent with those of the above studies, indicating that the TGF-β/Smad signalling pathway is involved in the process of POF.

2.5.2 PI3K/AKT signalling pathway

The phosphatidylinositol-3-kinase/serine-threonine protein kinase (PI3K/Akt) signalling pathway regulates the cell cycle, participates in angiogenesis, promotes follicular development, and regulates biological processes such as granulosa cell growth and apoptosis [71][72] (Figure 6). Forkhead box O (FOXO) transcription factors are downstream targets of PI3K/Akt. p-Akt phosphorylates PI3K, which in turn phosphorylates downstream effector molecules and activates Akt. p-Akt phosphorylation of FOXOs represses the transcriptional function of FOXOs and contributes to cell survival, growth and proliferation [73]. As a member of the FOXO family, FOXO1 plays an important role in upregulating the expression of downstream proapoptotic genes, which subsequently induces apoptosis in granulosa cells through the mitochondrial pathway induced by the cysteine asparaginase family [74]. In a previous study, cytotoxic drugs were found to cause granulocyte apoptosis and increase the risk of POF by significantly inhibiting the PI3K/AKT signalling pathway [75]. However, PI3K and AKT overactivation can accelerate the depletion of primordial follicles, which can also lead to POF [62]. Therefore, improving follicular development and granulosa cell survival and proliferation by upregulating the expression of the PI3K/Akt signalling pathway through FSH supplementation, thereby restoring ovarian function, may be a therapeutic direction for POF.

2.5.3 Wnt/β-catenin signalling pathway

According to modern medicine, the ovarian Wnt (wingless) signalling pathway may be an important signalling pathway involved in the regulation of steroidogenesis via gonadotropin signalling [76]. The Wnt ligand family activates the β-catenin signalling pathway, which is highly correlated with POF (Figure 6). Binding of Wnt to its receptor Frizzled activates the Dsh protein, which inhibits the activity of the glycogen synthase kinase GSK-3β, thereby inhibiting the phosphorylation of β-catenin by GSK-3β, allowing β-catenin to accumulate in the cytoplasm, interacting with the T-cell factor (TCF/LEF) family of transcription factors in the nucleus, and ultimately regulating target gene expression [77]. In addition, β-catenin is involved in the synthesis of ovarian steroid hormones and luteinogenesis, and Wnt2 can affect the cellular localization of β-catenin to regulate granulosa cell proliferation [67]. Normal expression of β-catenin in the ovary enhances FSH secretion and reduces GC apoptosis, thereby promoting follicular development. In one study, chemotherapeutic agents were used to induce in order to create a POF model, and it was found that Wnt/β-catenin signalling activity was reduced in the POF group, and the ovarian function was restored after treatment with ghrelin; moreover, the expression levels of proteins related to the Wnt/β-catenin signalling pathway all showed significant restoration when compared with those in the POF group [78].

2.5.4 SIRT signalling pathway

The family of silencing regulatory proteins (sirturins, SIRTs) is a class of nicotinamide adenine dinucleotide-dependent deacetylases, and there are seven known members of this family, SIRT1-7 [67]. SIRTs are known to regulate a variety of cellular processes, including DNA repair, adipose differentiation, glucose export, insulin sensitivity, fatty acid oxidation, inflammation and aging. One study revealed that SIRT is associated with redox signalling. SIRT1, SIRT3 and SIRT5 protect cells from ROS, SIRT2, SIRT6 and SIRT7 regulate key oxidative stress genes and mechanisms [79], and SIRT4 also has an antioxidant effect; however, recent studies have confirmed that SIRT4 also induces ROS production [80]. SIRTs, especially SIRT1 and SIRT6, which play significant roles in protecting against cellular senescence, are important factors in delaying cellular senescence and extending the lifespan of organisms [81]. SIRT1 regulates the redox state by reducing oocyte destruction due to oxidative stress damage [82]. It has been shown that Zigui Yi Chongfang can activate the SIRT1/FOXO1 signalling pathway to improve the function of naturally aging ovaries [83]. SIRT6 ensures the correct segregation of genetic material during meiosis, and the inhibition of SIRT6 expression in oocytes significantly reduces the activity of phosphorylated cyclin-dependent kinase (CDK1), which in turn inhibits the expression of genes connecting signals related to oocytes in oocytes [84]. Therefore, POF activates the SIRT signalling pathway in aging-related diseases to regulate oxidative stress, the inflammatory response, mitochondrial dysfunction, autophagy and apoptosis.

2.5.5 Other signalling pathways related to POF

In addition to the classical signalling pathways mentioned above, there are other signalling pathways related to POF. For example, the two-sided Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway mediates the transition from primordial to primary follicles[85]. The

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mitogen-activated protein kinase (MAPK) pathway has important roles in inflammation, the stress response and apoptosis[86]. The NF-kB family plays important roles in physiological and pathological processes such as inflammation, the immune response, the oxidative stress response, cell proliferation and apoptosis [86]. The specific mechanism of action of the above pathways is shown below (Figure 6).

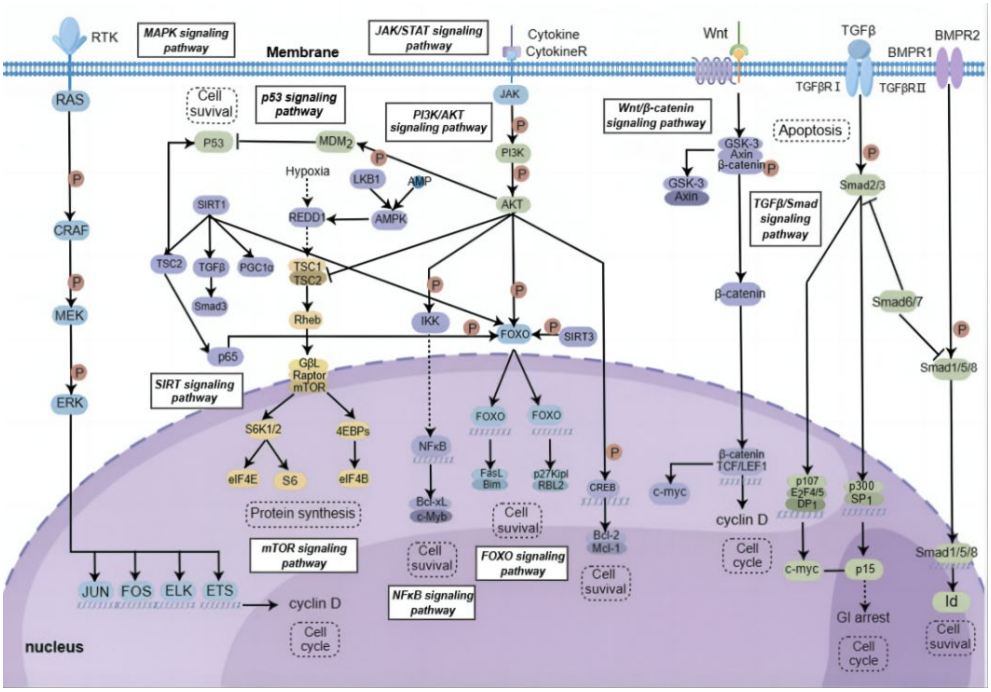

Figure 6: Signalling pathways involved in POF.

2.6 Genes and premature ovarian failure

2.6.1 Chromosomal abnormalities and gene mutations

The genetics of POF involve a complex network of molecular pathways. Chromosomal abnormalities, single-gene mutations and genetic polymorphisms are now recognized as causes of POF. It is estimated that 50%-90% of cases are idiopathic, with 10%-30% of these idiopathic cases also affecting first-degree relatives with a potential genetic etiologic basis [5]. One of the most common conditions is Turner syndrome (TS) [87][88]. TS is a disorder caused by partial or complete deletion of the X chromosome with typical features such as short stature, POF, and cardiovascular abnormalities. A wide range of karyotypes and phenotypes are present in TS, with approximately 50% of cases due to complete deletion of one of the sex chromosomes (45,X) [89]. Compared to normal fetuses, 45X fetuses develop an increased rate of oocyte turnover and fewer primordial follicles, which may contribute to the development of POF [90]. The Fragile X mental retardation 1 (FMR1) gene is a single gene that causes Fragile X-related primary ovarian insufficiency (FXPOI). This difference is caused by amplification of CGG trinucleotide repeats in the 5′ untranslated region of the Fragile X Mental Retardation 1 (FMR1) gene, which results in silencing of its transcript and loss of the encoded Fragile X Mental Retardation protein 1 (FMR1). Most affected individuals have more than 200 rCGG repeats; these repeats are called full mutant alleles [91]. Individuals with multiple repeats are usually at risk for FXPOI [92]. FXPOI occurs in approximately 16-20% of women carrying mutations in the FMR1 gene, and it is hypothesized that these mutations may lead to mRNA accumulation that has a toxic effect on the egg and a decrease in follicle number, resulting in impaired ovarian function [93]. Heterozygous mutations in bone morphogenetic protein-15 (BMP-15) are the second major pathogenetic cause of POF pathogenesis after pre-FMR1 mutations. BMP-15, a member of the TGF-β superfamily, has been shown to stimulate granulosa cell growth and promote the progression of folliculogenesis from the primary stage to the FSH-dependent stage [94]. Recent studies have identified new BMP15 mutations in patients with POF that result in reduced maturation protein activity [95].

2.6.2 Noncoding RNA

Exosomes are vesicles released by MSCs that can mediate intercellular communication by transporting a variety of biomolecules, including mRNAs, microRNAs (microRNAs, miRNAs), long noncoding RNAs (lncRNAs), and proteins. Studies have shown that MSC exosomes from human umbilical cord MSCs inhibit apoptosis in mouse ovarian granulosa cells [96]. miRNAs are the main

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functional factors carried by exosomes. Several studies have shown that miRNAs play important roles in ovarian granulosa cells, angiogenesis, and regulation of the antioxidant microenvironment, mainly through their own regulatory functions and after pharmacological intervention [97]. lncRNAs are a class of noncoding RNAs with lengths greater than 200 nt [98]. The lncRNA HCP5 has a well-defined function in the granulosa cells of POF patients, and it is involved in POF by regulating DNA damage repair [99]. Circular RNAs (circRNAs) are a class of noncoding RNA molecules that do not have a circular structure with a 5'-terminal cap or a 3'-terminal poly(A) tail and are important players in normal cell differentiation and tissue homeostasis, as well as in disease progression. It has been found that circRNAs in the cytoplasm inhibit miRNA function and that circRNAs may be involved in the pathogenesis of biochemical POF through the FOXO signalling pathway and cellular senescence pathway in biochemical POF [100].

2.7 Enzyme deficiencies

There are 2 main groups of enzyme deficiency disorders associated with POF: galactosemia and 17a-hydroxylase/17,20-cleaving enzyme (17-hydroxylase/17,20-lyase deficiency, 17-OHD) deficiency. Galactose-1-phos-phate Uri-dyltransferase (GALT) is a key enzyme in lactose metabolism, and GALT deficiency leads to the accumulation of D-galactose in the body, which reacts with free amines from amino acids in proteins and peptides to form glycosylation end products (advanced glycation end products, AGEs), which ultimately produce acetaldehyde and hydrogen peroxide in the presence of galactose oxidase, thereby increasing ROS levels and leading to cellular aging [101]. Higher levels of galactose cause patients to exhibit high gonadotropin levels, and abnormal metabolites can also directly damage the ovarian parenchyma [102]. In the absence of 17-OHD, pregnenolone cannot be converted to 17α-hydroxypregnenolone, which leads to a decrease in the secretion of sex hormones, such as cortisol, androstenedione, testosterone, and estrogen [103], which in turn affects the normal function of the ovaries.

3. Conclusions

In summary, POF has a complex etiology, and its incidence has been increasing gradually this year, which greatly jeopardizes women's health. The efficacy of traditional hormone therapy for POF has certain limitations, and new technologies such as gene therapy and stem cell therapy are still being tested. Therefore, there is an urgent need to explore pathways and targets with potential advantages for the prevention and pretreatment of POF. In addition, there is a lack of long-term efficacy tracking and follow-up observation for people with pregnancy needs in the above literature. In the future, there is a need to develop uniform implementation standards and efficacy evaluation criteria to seek optimal treatment options.

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