FOXO3 is a potential biomarker and therapeutic target for premature ovarian insufficiency (Review)

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Abstract. Premature ovarian insufficiency (POI) is a common clinical disease of the reproductive system in which patients lose normal gonadal function prior to the age of 40. Common pathogenic factors include iatrogenic injury, genetics, inflammation, autoimmune, environmental and psychological factors. Patients with POI experience decreased estrogen secretion levels, ovulation disorder and infertility. POI appears frequently in clinical practice and the burden of the disease is heavy; however, the detailed pathological mechanism requires further experimental evaluation. Furthermore, there is a lack of effective treatment options. Certain causes of the pathogenesis of POI can be explained by epigenetic changes. Front fork transcription factor 3 (FOXO3) is a member of the forkhead box family of transcription factors. FOXO3 was initially considered to affect insulin/insulin growth factor signal transduction. However, the target gene range of FOXO3 includes numerous genes that affect metabolism and protein stability and are associated with aging. There is an association between decreased FOXO3 expression levels and POI. In the present review article, the role of FOXO3 in POI was evaluated, which emphasized the importance of this protein in the investigation of this disease. Moreover, the present review evaluated the evidence for the potential targets and biomarkers of FOXO3 that may be used in the treatment and diagnosis of POI.

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Abbreviations: FOXO3, front fork transcription factor 3; POI, premature ovarian insufficiency; WES, whole exome sequencing; Kip1, kinase interacting protein 1; SIRT, sirtuin; OTUD1, OTU domain containing protein 1; CXCL, CXC motif chemokine ligand; CD, cluster of differentiation; MHC, major histocompatibility complex; SLE, systemic lupus erythematosus; GC, glucocorticoid; CBX, Carbenoxolone; MHCI, Major histocompatibility complex class I; MHCII, Major histocompatibility complex class II; SIRT, sirtuin

Key words: premature ovarian insufficiency, FOXO3, autoimmunity, inflammation, heredity, environment, psychology, iatrogenic damage

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1. Introduction

Premature ovarian insufficiency (POI) is a key cause of menstrual disorder and infertility. It is defined as a non-physiological menstrual cessation and primary or secondary infertility that occurs prior to the age of 40, accompanied by systemic genital atrophy, increased gonadotropin levels and decreased estrogen levels (1). POI typically includes follicular failure or apoptosis caused by oocyte atresia and follicular dysfunction (2). Current research indicates that POI is caused by numerous factors, such as iatrogenic injury, genetic, immune, environmental and psychological factors that may trigger the onset of this condition (3). However, >50% of patients present with unknown etiology of POI, which is known as idiopathic POI. To the best of our knowledge, there is currently no effective treatment for POI, which seriously affects the physical and mental health of patients with this disease.

Although >50% of clinical POI cases are idiopathic, 20-25% of POI patients still have a family genetic history (4,5). These genetic changes may include chromosomal imbalance

(such as X chromosomes or autosome imbalance) and point mutations (6).

Recent study have reported that front fork transcription factor 3 (FOXO3) is the primary regulator and an effective inhibitor of primordial follicle activation; loss of FOXO3 function in mice is due to overall follicle activation (7). Screening genetic samples from patients with premature ovarian failure has demonstrated six mutations in the FOXO3 coding region (8). These missense mutations may result in abnormal oocyte apoptosis and primordial follicle activation, which leads to depletion of early follicles in the ovary (8). The mechanism by which FOXO3 affects the progression of POI requires further study. FOXO3 directly affects development of oocytes and POI via other factors. To the best of our knowledge, no literature review has fully elucidated the relationship between FOXO3 and the pathogenesis of POI, such as iatrogenic injury, genetics, inflammation and autoimmunity, as well as environmental and psychological factors. Therefore, it is imperative to summarize the latest research on the association between FOXO3 and POI to evaluate the role of this protein in the pathophysiology of POI. The present review article used POI, FOXO3, iatrogenic injury, heredity, inflammation, autoimmunity, psychology and environment as keywords to search relevant literature from electronic databases, such as PubMed (https://pubmed.ncbi.nlm.nih.gov/), Springer (https://link.springer.com/), Wiley (https://www.wiley.com/en-us/business) and ScienceDirect (https://www.sciencedirect.com). The mechanism by which FOXO3 is reported to affect POI was systematically summarized to provide evidence for the use of this protein as a potential treatment target and biomarker for POI.

2. Role of FOXO3 in iatrogenic injury-induced POI

Previous study have reported that pelvic surgery, such as ovariectomy, is an important cause of POI (9). Following removal of one ovary, levels of hormones secreted by the ovaries decrease and expression levels of the follicle-stimulating hormone secreted by the pituitary gland increase to compensate for this loss; therefore, the probability of developing POI in the remaining ovary increases (9-11). Concomitantly, when patients with cancer receive radiotherapy and chemotherapy, normal cells may also undergo damage. Radiation therapy to the abdomen or pelvis simultaneously damages normal ovarian tissue and germ cells (12,13).

A previous study have reported that iatrogenic injury is key in the pathogenesis of POI (14,15).In mammalian ovaries, the FOXO3 protein regulates atresia and follicular growth by promotion of the induction of apoptosis in ovarian granulosa cells. The PI3K/AKT and FOXO signaling pathways restore ovarian function and induce follicle formation, which suggests that FOXO3 phosphorylation may increase, which changes the balance of oocyte growth and apoptosis, and avoids numerous egg development disorders following ovariectomy (14). Furthermore, the establishment of postmenopausal osteoporosis animal models by removal of both ovaries in rats has been reported to demonstrate that inhibition of the expression of FOXO3a regulates the FOXO3a/Wnt2/β-catenin signaling pathway and effectively improves bone structure following ovariectomy (15-17). Increased porosity increases blood calcium content and decreases the bone density of the femur and vertebrae (15). FOXO3 also serves an important role in radiotherapy and chemotherapy treatment of patients with cancer. Previous study (18) have reported that melatonin decreases cisplatin-induced follicle loss by the prevention of phosphorylation of members of the PTEN/AKT/FOXO3a signaling pathway. Inhibition of FOXO3a phosphorylation increases the binding affinity of FOXO3a with the p27 [kinase interacting protein 1 (Kip1)] promoter, which affects the dormant state of primordial follicles, induces excessive activation of dormant primordial follicles and leads to loss of ovarian reserve in mice (19). Radiation therapy is a common cancer treatment. The inhibition of ovarian FOXO3 expression has been significantly reversed in a γ-ray irradiation mouse model, leading to an increase in the reserve of primordial follicles; this may provide a novel treatment method for radiation-associated POI (20).

3. Role of FOXO3 in the development of POI induced by epigenetic changes

During the pathogenesis of POI, a series of extensive and complex biological processes occur, including DNA replication and repair, germ cell development, mRNA transport and translation and sex hormone regulation (21-24). These processes are often disrupted by both common and rare gene mutations, which constitute a complex genetic pathogenic mechanism for POI. As infertility is an important manifestation of POI, it is difficult to systematically collect family history. However, with the development of whole exome sequencing (WES), certain studies have reported the role of rare destructive coding variants in the ovary (25,26). By studying a single family and performing a comprehensive WES analysis of patients in multiple unrelated families, certain gene variants associated with POI have been identified, such as helicase for meiosis 1, eukaryotic translation initiation factor and basonuclin (27). Medical records of patients with POI indicate that 13% of cases involve changes in the number and structure of the X chromosomes (2). The more common chromosomal abnormalities include partial X chromosome deletion, inversion, balanced X chromosome ectopic, X monosomy and trisomy (28).

Numerous study have reported that genetic changes serve an indispensable role in the pathogenesis of POI (29,30). A previous study reported that aging of the reproductive system is closely related to DNA damage DNA damage in ovarian granulosa cells is closely related to the development of POI (31). The depletion of DNA-damaged oocytes occurs by different cell death mechanisms, such as apoptosis, autophagy and necrosis, which are primarily mediated via the PTEN/PI3K/AKT/FOXO3 signaling pathway. The activation of this pathway cascade increases cytoplasmic transport of FOXO3a in the follicles, which in turn increases the pool size of growing follicles and rapidly depletes the number of dormant follicles. The latter cannot be activated into the growth phase, which leads to final maturation and ovulation failure (32-34). Experiments have reported the location of the FOXO3 protein in the nucleus and cytoplasm and provided evidence for genetic study to examine this pathway (35). Furthermore, the increase in FOXO3a phosphorylation increases the binding affinity of FOXO3a to the p27 (Kip1) promoter in primordial follicles,

which results in activation of primordial follicles, an increase in the number of granulosa cells, a decrease in the number of atretic follicles and an increase in serum E2 and progestin levels. Therefore, repairing ovarian function may be a new strategy for the treatment of POI (36,37).

4. Role of FOXO3 in psychological and environmental factor-induced POI

A previous study reported that 10% of POI cases are caused by bisphenol A, phthalates and polycyclic aromatic hydrocarbons. These pollutants cause changes in the epigenetic modification that affect the growth of follicles, which results in decreased follicular activity (38).

Psychological factors are key in the pathogenesis of POI. Strong and long-term negative emotions, such as anxiety, depression, sadness and fear, affect ovarian function. These factors affect normal hormone (For example, testosterone, gonadotropin releasing hormone) secretion via the hypothalamic-pituitary-ovarian axis and lead to the occurrence of POI (39,40).

A study have reported that changes in psychological and environmental factors are key in the pathogenesis of POI (41). It has been reported that tetrachlorodibenzo-p-dioxin, polychlorinated biphenyls and polycyclic aromatic hydrocarbons, present in the environment, amplify the accumulation of nuclear p53 caused by benzo(a)pyrene or dibenzo(a,l)pyrene (42). This effect is associated with attenuation of polycyclic aromatic hydrocarbon)-induced apoptosis and decreased levels of FOXO3 phosphorylation at threonine 32 (43). This process may promote the translocation of the FOXO3a-p53 complex from the nucleus to the cytoplasm. Therefore, the dephosphorylation effect of FOXO3 has been previously studied (44). In addition, it is reported that FOXO3 is also related to environmental pollutants (such as cadmium and arsenic),which affect ovarian health, indicating that this protein may be an important factor leading to the development of POI caused by environmental factors (45). Increased phosphorylation of FOXO3a can alleviate adverse psychological states. A previous study reported that d-fenfluramine reduces nuclear FOXO1 and FOXO3a levels of these proteins, and enhances their phosphorylation, which thereby achieves a therapeutic effect (46). Previous results have indicated that the PI3K/AKT/FOXO3a signaling pathway has an antidepressant-like effect on depression caused by chronic stress (47-49). FOXO1 and FOXO3a can affect the processes related to anxiety and depression, which provides a molecular framework for potential therapeutic targets.

Oxidative stress is a common pathogenic factor in reproductive system disease. A previous study reported that oxidative stress may be a potential pathogenesis for POI induced by *Tripterygium wilfordii* polyglycosides (50). Subsequent studies have reported that SIRT (Sirtuins)-mediated signal transduction can reduce oxidative stress and apoptotic damage, which are required for development of POI (51,52). A study of clinical data reported that the levels of oxidative stress markers, such as nitric oxide synthase, myeloperoxidase and reactive oxygen species (ROS), are elevated in patients with POI. The upregulation of the expression levels of the nuclear factor erythroid 2-related factor 2/heme oxygenase pathway proteins improves ovarian function of patients with POI by the inhibition of oxidative stress, which suggests that the latter is associated with development of this disease (53).

A study have reported that oxidative stress is key in the pathogenesis of POI (54). FOXO3 may serve a key role in the development of oxidative stress and serves as a signaling molecule associated with autophagy, which inhibits oxidative stress by binding to cytoplasmic STAT3 (55). The internal regulatory mechanism of ROS-mediated autophagy is regulated by the ROS-FOXO3-light chain 3/Bcl-2 interacting protein 3 autophagic signaling pathway (56). Previous studies have reported that SIRT1 has a dual effect on the function of FOXO3; it increases the ability of FOXO3 to induce cell cycle arrest and resist oxidative stress and concomitantly inhibits the ability of FOXO3 to induce cell death (57). SIRT3 deacetylates FOXO3 to protect mitochondria from oxidative stress. It also regulates mitochondrial quality, ATP production and clearance of defective mitochondria, while ensuring the quantity and quality of the mitochondria and maintaining mitochondrial reserve capacity for oxidative damage (58). Taken together, this evidence indicates that FOXO3 may be a potential target for treatment or the delay of ovarian aging and POI-associated diseases.

5. Role of FOXO3 in inflammation-induced POI

Inflammatory aging refers to the chronic and low-grade pro-inflammatory state that occurs with age and is a new concept in the field of aging research (59). Increased levels of inflammatory cytokines and decreased levels of anti-inflammatory cytokines serve a key role in the development of POI (60). Recent studies have reported that TNF-α and IL-6 may serve a role in ovarian function; therefore, controlling the development of inflammation and aging may be a method to treat POI (61,62). The expression levels of TNF-α, IL family proteins and inflammatory proteins in plasma along with other inflammatory markers can be used to monitor ovarian function and treat POI (62).

Previous study reported that inflammation is key in the pathogenesis of POI (63). FOXO3 may serve an important role in the development of inflammation. In the autophagic process of inflammation, the constitutively active form of FOXO3 induces autophagy, which indicates that this protein serves as a downstream target of the PI3K pathway to inhibit autophagy (64). Under inflammatory conditions, the inducible OTU domain containing protein 1 (OTUD1) serves as an immune checkpoint and the FOXO3 signal is necessary for the induction of OTUD1 following antigenic stimulation (65). A previous study reported that FOXO3 is significantly inactivated/phosphorylated in fibroblast-like synovial cells in rheumatoid synovitis (66). Furthermore, mRNA analysis has indicated that the inactivation of FOXO3 is important for the sustained pro-inflammatory interferon response to TNF-α, CXC motif chemokine ligand (CXCL) 9, CXCL10, CXCL11 and TNF superfamily member 18 (67). In terms of the mechanism of action, the inactivation of FOXO3 is caused by downregulation of phosphoinositide-3-kinase interacting protein 1, which is induced by TNF-α (68). Treatment of 16HBE cells with FOXO3 small interfering (si)RNA can increase IL-8 and decrease chemokine ligand 20 expression levels (69). FOXO3 can also promote translation

via N6-methyladenosine modifications of mRNA molecules. The increase in FOXO3 mRNA expression levels under steady-state conditions contributes to its role as a negative regulator of antiviral immunity and stabilizes the host's antiviral effect and immune function, which in turn prevents inflammation (70).

6. Role of FOXO3 in immunity-induced POI

According to a previous report, 5-30% of patients with POI suffer autoimmune diseases (71). It has been reported that during autoimmune ovarian inflammation, the immune antigens target the ovary; therefore, other autoimmune diseases are associated with POI (72). Furthermore, changes in cellular immunity involving macrophages and dendritic cells, changes in the ratio of cluster of differentiation (CD)4þ/CD8þ, as well as inappropriate expression of major histocompatibility complex (MHC) class II antigens by granular cells have been reported to be associated with development of POI (73). Moreover, weakened autoimmunity is the primary mechanism for the development of POI-associated autoimmune diseases (74). Thyroid disease, autoimmune polyglandular syndrome, systemic lupus erythematosus (SLE) and endometriosis have all been reported to negatively affect the physiology of the ovary (74).

Numerous studies have reported that immunological changes are key in the pathogenesis of POI (75-80). The expression of FOXO3 is important for the maintenance of the differentiation of regulatory T cells that are necessary for immune tolerance, which highlights the role of FOXO3 in controlling immune homeostasis (75). FOXO3 negatively regulates the cytotoxicity of $CD8^+$ T and natural killer cells to tumor cells, thereby serving as a driving force for cancer development (76). Furthermore, the gene expression levels of typical M1 markers, such as CD80 and CD86, in siFOXO3-transfected macrophages are decreased and the activation of FOXO3 results in increased expression of CD86, major histocompatibility complex class I (MHCI) and MHCII, which indicates that the FOXO3 transcription factor regulates the role of IL-10 (77). Moreover, in common autoimmune diseases, FOXO3 participates in complex regulatory processes. FOXO3 imbalance serves as a sign of thyroid cancer (78). The specific mechanism is as follows: The expression of FOXO3 target genes terminate induction of DNA damage inducing protein 45α and the Bcl-2 interacting cell death mediator, which leads to programmed cell death (78). FOXO3a has been reported as a molecule that is downregulated in SLE. FOXO3a serves a key role in glucocorticoid (GC) treatment of SLE by inhibiting the inflammatory response (79). Further studies have reported that upregulation of FOXO3a expression by GC depends on the inhibition of FOXO3a phosphorylation mediated by PI3K/AKT and the blockade of FOXO3a in the nucleus (80-82). FOXO3a is essential for the GC-mediated inhibition of the NF-κB activity, which may involve its interaction with NF-κB p65 protein (83). Overall, these data indicate that FOXO3 serves an important role in body immunity. Targeting FOXO3 may provide novel therapeutic strategies for numerous diseases.

7. Conclusion

The disease development of POI is related to molecular genetics. Several genetic changes have an effect on the pathogenesis of POI, including oocyte-specific transcription factors (folliculogenesis specific basic helix-loop-helix transcription factor and newborn ovary homeobox-encoding) and other transcription factors that affect follicle formation (Wilms tumor 1, forkhead box L2 and nuclear receptor subfamily 5 group A member 1) (83-85). However, the regulatory role of other genes in the development of POI is still unclear. Therefore, additional attention should be paid in the future to their functional mechanisms, which may provide ideas for the design of novel treatment methods for patients with POI.

FOXO3 is expressed in numerous tissues in the human body; however, its expression levels, functions and targets are specific. The function of FOXO3 includes regulation of key biological processes, such as cell death and survival, substrate metabolism and protein conversion (7,8). FOXO3 has also been reported to be a type of longevity gene, which regulates the aging process and is related to the aging of the ovary in POI (86,87). Numerous studies have reported that expression levels of FOXO3 in patients with polycystic ovary syndrome significantly increase and that FOXO3 may serve a key role in the development of POI (88-90). Furthermore, autoimmune factors are key causes of POI. FOXO3 serves an indispensable regulatory role in the progression of various autoimmune diseases. FOXO3 also serves an important role in the development of follicular cells and iatrogenic damage (35). In summary, these results indicated that FOXO3 is a potential therapeutic target and biomarker for POI and may be a key mediator that affects the occurrence and development of this condition (Fig. 1).

FOXO3 exerts various effects through numerous molecular signaling pathways in the progression of POI from iatrogenic injury. Through regulation of phosphorylation of the PI3K/AKT signaling pathway and reverse regulation of the downstream Wnt2/β-catenin signaling pathway, these pathways are involved in induction of apoptosis of follicle cells in different medical injury models. These results suggested that FOXO3 is linked with complex apoptotic mechanisms. Therefore, the progression of POI may be inhibited by prevention of FOXO3-induced decrease of the follicular reserve. FOXO3 interferes with primordial follicle dormancy by its effects on certain epigenetic processes, such as phosphorylation and acetylation (14). This is a double-edged sword. In infertile patients who require cryopreservation of follicles for future artificial insemination, strengthening the activation of FOXO3 increases the success rate of fertilization (19,34). In patients with POI with excessive loss of ovarian follicular reserve, enhanced FOXO3 activation further accelerates disease progression (33). A number of environmental pollutants inhibit the cell cycle by the induction of cell cycle arrest (42). FOXO3a participates in regulation of the cell cycle by changing the phosphorylation levels of p53 in cells, activation of oxidative stress and induction of the DNA damage response (43); FOXO3a also affects regulation of follicle dormancy. Furthermore, under stress conditions caused by psychological factors, FOXO3 can slow down the development of depression and play a role in alleviating POI (46) (Fig. 2).

FOXO3 inhibitors may serve an important auxiliary role in the treatment of POI. In certain studies, medium flux fluorescence polarization analysis was used to screen drugs. These studies reported that carbenoxolone (CBX), a derivative of glycyrrhetinic acid, is a potential FOXO3 inhibitor (91). Pharmacological correlation with FOXO3 inhibition was

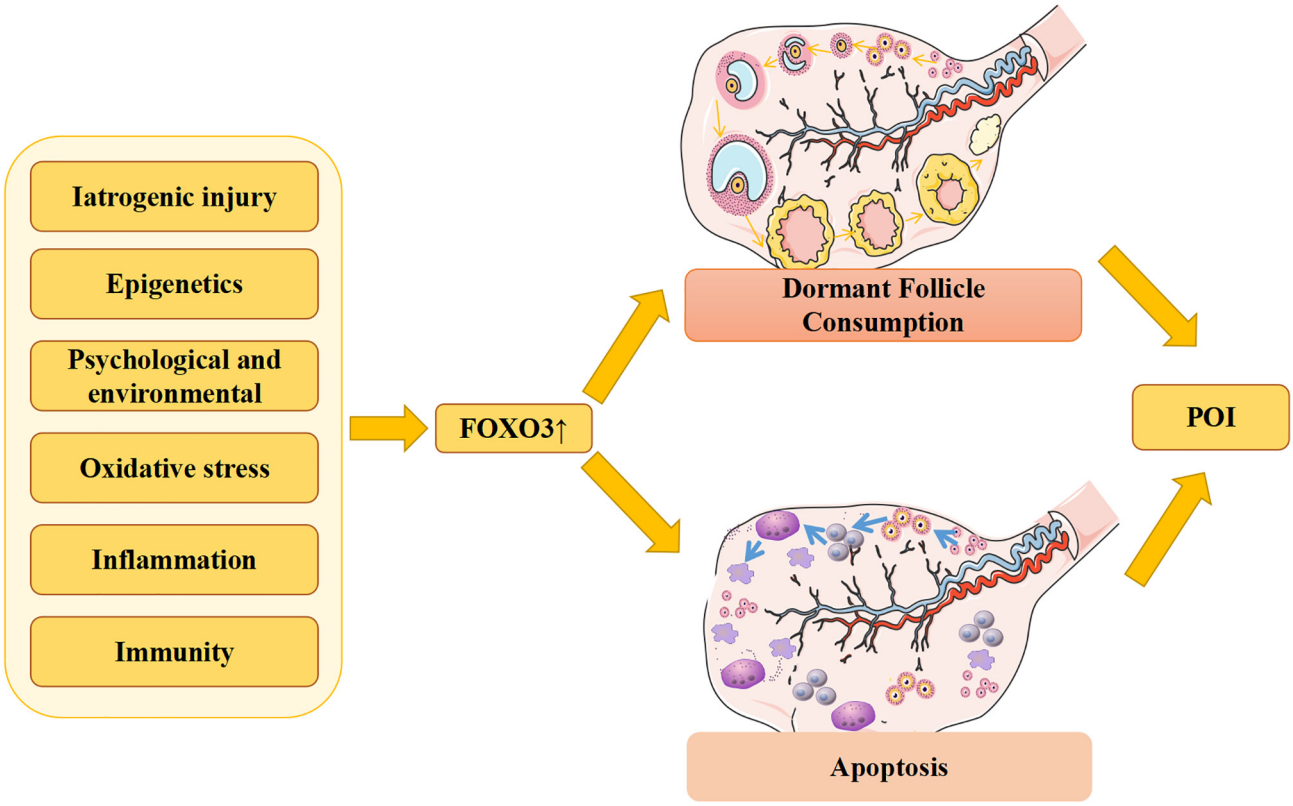

Figure 1. Development of POI is associated with numerous factors. Common causative factors include iatrogenic injury and epigenetic factors. The role of FOXO3 is associated with iatrogenic injury, epigenetics, inflammation, autoimmunity, environmental and psychological factors. The figure was constructed using Procreate 5.2 (Savage Software Group Pty. Ltd.) and Microsoft PowerPoint 2010 (Microsoft Corporation). POI, premature ovarian insufficiency.

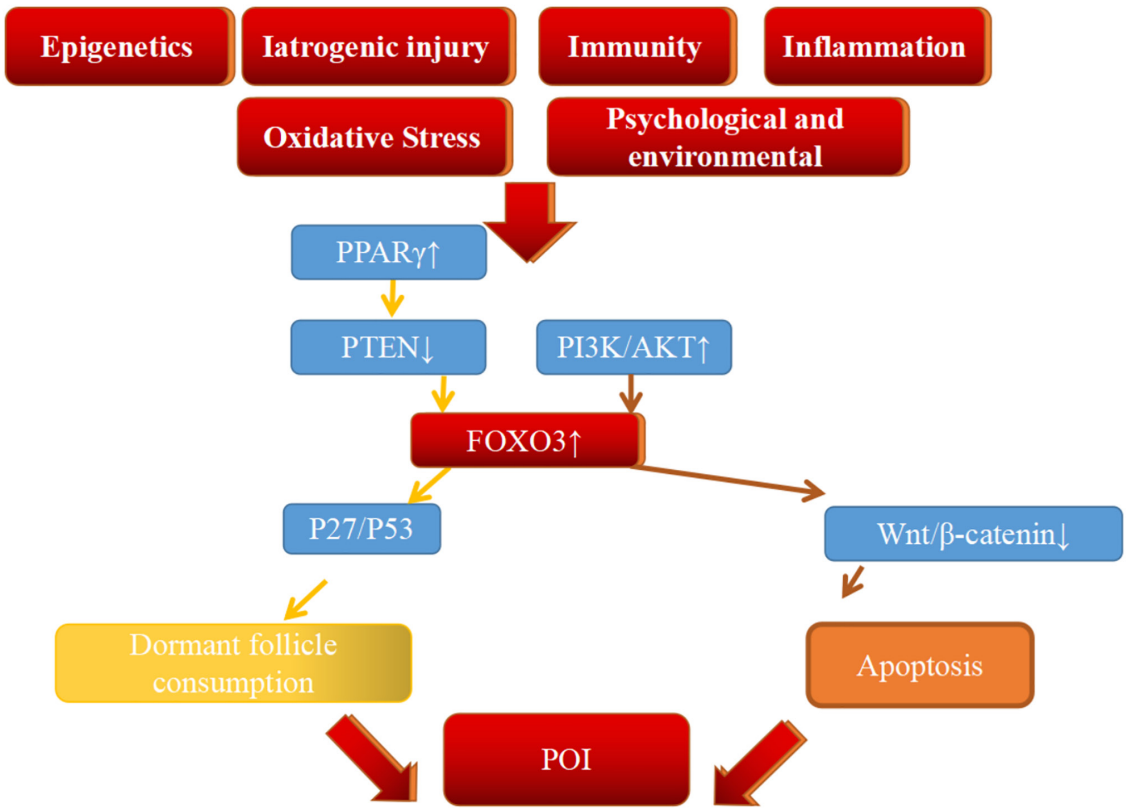

Figure 2. FOXO3 serves a role in the progression of POI through numerous molecular signaling pathways. FOXO3 affects POI by participation in the induction of apoptosis or the depletion of dormant follicles via the regulation of PPARγ, PTEN, PI3K/AKT and other signaling pathways. The figure was constructed using Procreate 5.2 (Savage Software Group Pty. Ltd.) and Microsoft PowerPoint 2010 (Microsoft Corporation). PPAR, peroxisome proliferator activated receptor; POI, premature ovarian insufficiency.

reported in CBX treatment study (92). However, similar drugs are still in the laboratory research stage and are some distance from entering the clinical stage, which suggests more attention to the progress of drug research is required.

Nevertheless, several questions are worthy of further study and attention. Firstly, FOXO3 serves a complex regulatory role in the pathogenesis of POI; therefore, other FOX family member proteins with the same promoter target sequence may have similar effects. Secondly, the role of FOXO3 is primarily mediated by certain signaling pathways; however, the role of mRNA in the regulation of FOXO3 needs to be further evaluated. Thirdly, given the complex role of FOXO3, crosstalk with other transcription factors should be considered. The role of FOXO3 in the development of POI requires further assessment. Finally, certain differences exist with regard to FOXO3 gene polymorphisms. Therefore, the effect of different ethnicities/races should be considered in a clinical data analysis.

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Author's contributions

SL and XW contributed to the design of the study. XM and LP wrote the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Laven JS: Primary ovarian insufficiency. Semin Reprod Med 34: 230-234, 2016.
2. Barros F, Carvalho F, Barros A and Dória S: Premature ovarian insufficiency: Clinical orientations for genetic testing and genetic counseling. Porto Biomed J 5: e62, 2020.
3. Qin Y, Jiao X, Simpson JL and Chen ZJ: Genetics of primary ovarian insufficiency: New developments and opportunities. Hum Reprod Update 21: 787-808, 2015.
4. Sullivan SD, Sarrel PM and Nelson LM: Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril 106: 1588-1599, 2016.
5. Cai X, Fu H, Wang Y, Liu Q and Wang X: Depletion of GPSM1 enhances ovarian granulosa cell apoptosis via cAMP-PKA-CREB pathway in vitro. J Ovarian Res 13: 136, 2020.
6. Katari S, Aarabi M, Kintigh A, Mann S, Yatsenko SA, Sanfilippo JS, Zeleznik AJ and Rajkovic A: Chromosomal instability in women with primary ovarian insufficiency. Hum Reprod 33: 531-538, 2018.
7. Lee HN and Chang EM: Primordial follicle activation as new treatment for primary ovarian insufficiency. Clin Exp Reprod Med 46: 43-49, 2019.
8. Wang B, Mu Y, Ni F, Zhou S, Wang J, Cao Y and Ma X: Analysis of FOXO3 mutation in 114 Chinese women with premature ovarian failure. Reprod Biomed Online 20: 499-503, 2010.
9. Donnez J, García-Solares J and Dolmans MM: Ovarian endometriosis and fertility preservation: A challenge in 2018. Minerva Ginecol 70: 408-414, 2018.
10. Jin M, Yu Y and Huang H: An update on primary ovarian insufficiency. Sci China Life Sci 55: 677-686, 2012.
11. Day JR, David A, Barbosa MGM, Brunette MA, Cascalho M and Shikanov A: Encapsulation of ovarian allograft precludes immune rejection and promotes restoration of endocrine function in immune-competent ovariectomized mice. Sci Rep 9: 16614, 2019.
12. Cattoni A, Parissone F, Porcari I, Molinari S, Masera N, Franchi M, Cesaro S, Gaudino R, Passoni P and Balduzzi A: Hormonal replacement therapy in adolescents and young women with chemo- or radio-induced premature ovarian insufficiency: Practical recommendations. Blood Rev 45:100730, 2021.
13. DeWire M, Green DM, Sklar CA, Merchant TE, Wallace D, Lin T, Vern-Gross T, Kun LE, Krasin MJ, Boyett JM, *et al*: Pubertal development and primary ovarian insufficiency in female survivors of embryonal brain tumors following risk-adapted craniospinal irradiation and adjuvant chemotherapy. Pediatr Blood Cancer 62: 329-334, 2015.
14. Cui C, Han S, Yin H, Luo B, Shen X, Yang F, Liu Z, Zhu Q, Li D and Wang Y: FOXO3 Is expressed in ovarian tissues and acts as an apoptosis initiator in granulosa cells of chickens. Biomed Res Int 2019: 6902906, 2019.
15. Ou L, Wei P, Li M and Gao F: Inhibitory effect of Astragalus polysaccharide on osteoporosis in ovariectomized rats by regulating FoxO3a/Wnt signaling pathway. Acta Cir Bras 34: e201900502, 2019.
16. Elseweidy MM, El-Swefy SE, Shaheen MA, Baraka NM and Hammad SK: Effect of resveratrol and mesenchymal stem cell monotherapy and combined treatment in management of osteoporosis in ovariectomized rats: Role of SIRT1/FOXO3a and Wnt/β-catenin pathways. Arch Biochem Biophys 703: 108856, 2021.
17. Choi JH, Seok J, Lim SM, Kim TH and Kim GJ: Microenvironmental changes induced by placenta-derived mesenchymal stem cells restore ovarian function in ovariectomized rats via activation of the PI3K-FOXO3 pathway. Stem Cell Res Ther 11: 486, 2020.
18. Li L, Shi X, Shi Y and Wang Z: The signaling pathways involved in ovarian follicle development. Front Physiol 12: 730196, 2021.
19. Jang H, Na Y, Hong K, Lee S, Moon S, Cho M, Park M, Lee OH, Chang EM, Lee DR, *et al*: Synergistic effect of melatonin and ghrelin in preventing cisplatin-induced ovarian damage via regulation of FOXO3a phosphorylation and binding to the $p27^{Kip1}$ promoter in primordial follicles. J Pineal Res 63, 2017.
20. Tang YL, Zhou Y, Wang YP, He YH, Ding JC, Li Y and Wang CL: Ginsenoside Rg1 protects against Sca-1^{+} HSC/HPC cell aging by regulating the SIRT1-FOXO3 and SIRT3-SOD2 signaling pathways in a γ-ray irradiation-induced aging mice model. Exp Ther Med 20: 1245-1252, 2020.
21. Lew R: Natural history of ovarian function including assessment of ovarian reserve and premature ovarian failure. Best Pract Res Clin Obstet Gynaecol 55: 2-13, 2019.
22. Kirshenbaum M and Orvieto R: Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal. J Assist Reprod Genet 36: 2207-2215, 2019.
23. Laven JSE: Genetics of menopause and primary ovarian insufficiency: Time for a paradigm shift? Semin Reprod Med 38: 256-262, 2020.

24. Abidin Z and Treacy EP: Insights into the pathophysiology of infertility in females with classical galactosaemia. Int J Mol Sci 20: 5236, 2019.
25. Yang X, Zhang X, Jiao J, Zhang F, Pan Y, Wang Q, Chen Q, Cai B, Tang S, Zhou Z, *et al*: Rare variants in FANCA induce premature ovarian insufficiency. Hum Genet 138: 1227-1236, 2019.
26. Jiao X, Ke H, Qin Y and Chen ZJ: Molecular genetics of premature ovarian insufficiency. Trends Endocrinol Metab 29: 795-807, 2018.
27. Liu H, Wei X, Sha Y, Liu W, Gao H, Lin J, Li Y, Tang Y, Wang Y, Wang Y and Su Z: Whole-exome sequencing in patients with premature ovarian insufficiency: Early detection and early intervention. J Ovarian Res 13: 114, 2020.
28. Leng L, Tan Y, Gong F, Hu L, Ouyang Q, Zhao Y, Lu G and Lin G: Differentiation of primordial germ cells from induced pluripotent stem cells of primary ovarian insufficiency. Hum Reprod 30: 737-748, 2015.
29. Poteet B, Ali N, Bellcross C, Sherman SL, Espinel W, Hipp H and Allen EG: The diagnostic experience of women with fragile X-associated primary ovarian insufficiency (FXPOI). J Assist Reprod Genet: Nov 30, 2022 (Epub ahead of print).
30. Kline BL, Jaillard S, Bell KM, Bakhshalizadeh S, Robevska G, van den Bergen J, Dulon J, Ayers KL, Christodoulou J, Tchan MC, *et al*: Integral role of the mitochondrial ribosome in supporting ovarian function: MRPS7 variants in syndromic premature ovarian insufficiency. Genes (Basel) 13: 2113, 2022.
31. Wang X, Zhang X, Dang Y, Li D, Lu G, Chan WY, Leung PCK, Zhao S, Qin Y and Chen ZJ: Long noncoding RNA HCP5 participates in premature ovarian insufficiency by transcriptionally regulating MSH5 and DNA damage repair via YB1. Nucleic Acids Res 48: 4480-4491, 2020.
32. Miyamoto K, Araki KY, Naka K, Arai F, Takubo K, Yamazaki S, Matsuoka S, Miyamoto T, Ito K, Ohmura M, *et al*: Foxo3a is essential for maintenance of the hematopoietic stem cell pool. Cell Stem Cell 1: 101-112, 2007.
33. Yoon SY, Kim R, Jang H, Shin DH, Lee JI, Seol D, Lee DR, Chang EM and Lee WS: Peroxisome proliferator-activated receptor gamma modulator promotes neonatal mouse primordial follicle activation in vitro. Int J Mol Sci 21: 3120, 2020.
34. Li J, Kawamura K, Cheng Y, Liu S, Klein C, Liu S, Duan EK and Hsueh AJ: Activation of dormant ovarian follicles to generate mature eggs. Proc Natl Acad Sci USA 107: 10280-10284, 2010.
35. Chang EM, Lim E, Yoon S, Jeong K, Bae S, Lee DR, Yoon TK, Choi Y and Lee WS: Cisplatin induces overactivation of the dormant primordial follicle through PTEN/AKT/FOXO3a pathway which leads to loss of ovarian reserve in mice. PLoS One 10: e0144245, 2015.
36. Thanatsis N, Kaponis A, Koika V, Georgopoulos NA and Decavalas GO: Reduced Foxo3a, FoxL2, and p27 mRNA expression in human ovarian tissue in premature ovarian insufficiency. Hormones (Athens) 18: 409-415, 2019.
37. Jang H, Lee OH, Lee Y, Yoon H, Chang EM, Park M, Lee JW, Hong K, Kim JO, Kim NK, *et al*: Melatonin prevents cisplatin-induced primordial follicle loss via suppression of PTEN/AKT/FOXO3a pathway activation in the mouse ovary. J Pineal Res 60: 336-347, 2016.
38. Hu Y, Yuan DZ, Wu Y, Yu LL, Xu LZ, Yue LM, Liu L, Xu WM, Qiao XY, Zeng RJ, *et al*: Bisphenol A initiates excessive premature activation of primordial follicles in mouse ovaries via the PTEN signaling pathway. Reprod Sci 25: 609-620, 2018.
39. Huang Y, Qi T, Ma L, Li D, Li C, Lan Y, Chu K, Chen P, Xu W, Cao Y, *et al*: Menopausal symptoms in women with premature ovarian insufficiency: Prevalence, severity, and associated factors. Menopause 28: 529-537, 2021.
40. Menezes C, Pravata GR, Yela DA and Benetti-Pinto CL: Women with premature ovarian failure using hormone therapy do not experience increased levels of depression, anxiety and stress compared to controls. J Affect Disord 273: 562-566, 2020.
41. McDonald IR, Welt CK and Dwyer AA: Health-related quality of life in women with primary ovarian insufficiency: A scoping review of the literature and implications for targeted interventions. Hum Reprod 37: 2817-2830, 2022.
42. Al-Anati L, Kadekar S, Högberg J and Stenius U: PCB153, TCDD and estradiol compromise the benzo[a]pyrene-induced p53-response via FoxO3a. Chem Biol Interact 219: 159-167, 2014.
43. Al-Anati L, Högberg J and Stenius U: Non-dioxin-like PCBs interact with benzo[a]pyrene-induced p53-responses and inhibit apoptosis. Toxicol Appl Pharmacol 249: 166-177, 2010.
44. Drukteinis JS, Medrano T, Ablordeppey EA, Kitzman JM and Shiverick KT: Benzo[a]pyrene, but not 2,3,7,8-TCDD, induces G2/M cell cycle arrest, p21CIP1 and p53 phosphorylation in human choriocarcinoma JEG-3 cells: A distinct signaling pathway. Placenta 26 (Suppl A): S87-S95, 2005.
45. Fujiki K, Inamura H and Matsuoka M: Phosphorylation of FOXO3a by PI3K/Akt pathway in HK-2 renal proximal tubular epithelial cells exposed to cadmium. Arch Toxicol 87: 2119-2127, 2013.
46. Polter A, Yang S, Zmijewska AA, van Groen T, Paik JH, Depinho RA, Peng SL, Jope RS and Li X: Forkhead box, class O transcription factors in brain: Regulation and behavioral manifestation. Biol Psychiatry 65: 150-159, 2009.
47. Wang H, Quirion R, Little PJ, Cheng Y, Feng ZP, Sun HS, Xu J and Zheng W: Forkhead box O transcription factors as possible mediators in the development of major depression. Neuropharmacology 99: 527-537, 2015.
48. Xia M, Wang X, Xu J, Qian Q, Gao M and Wang H: Tris (1-chloro-2-propyl) phosphate exposure to zebrafish causes neurodevelopmental toxicity and abnormal locomotor behavior. Sci Total Environ 758: 143694, 2021.
49. Fan J, Li D, Chen HS, Huang JG, Xu JF, Zhu WW, Chen JG and Wang F: Metformin produces anxiolytic-like effects in rats by facilitating $GABA_A$ receptor trafficking to membrane. Br J Pharmacol 176: 297-316, 2019.
50. Chen Y, Zhao R, Li X, Luan YP, Xing LW, Zhang XJ, Wang J, Xia XY and Zhao R: Preventive electroacupuncture alleviates oxidative stress and inflammation via Keap1/Nrf2/HO-1 pathway in rats with cyclophosphamide-induced premature ovarian insufficiency. Biomed Res Int 2022: 6718592, 2022.
51. Ma WR and Tan Y: The effect and mechanism of hyperin on ovarian reserve of tripterygium glycosides-induced POI mice. Sichuan Da Xue Xue Bao Yi Xue Ban 52: 458-466, 2021 (In Chinese).
52. Ding C, Qian C, Hou S, Lu J, Zou Q, Li H and Huang B: Exosomal miRNA-320a is released from hAMSCs and regulates SIRT4 to prevent reactive oxygen species generation in POI. Mol Ther Nucleic Acids 21: 37-50, 2020.
53. Chen S, Lu Y, Chen Y, Xu J, Chen L, Zhao W, Wang T, Wang H and Wang P: The effect of Bu Shen Huo Xue Tang on autoimmune premature ovarian insufficiency via modulation of the Nrf2/Keap1 signaling pathway in mice. J Ethnopharmacol 273: 113996, 2021.
54. Chen Y, Fan X, Ma K, Wang K, Tian C, Li M and Gong L: Bushen culuan decoction ameliorates premature ovarian insufficiency by acting on the Nrf2/ARE signaling pathway to alleviate oxidative stress. Front Pharmacol 13: 857932, 2022.
55. You L, Wang Z, Li H, Shou J, Jing Z, Xie J, Sui X, Pan H and Han W: The role of STAT3 in autophagy. Autophagy 11: 729-739, 2015.
56. Zhang J and Ney PA: Role of BNIP3 and NIX in cell death, autophagy, and mitophagy. Cell Death Differ 16: 939-946, 2009.
57. Das S, Mitrovsky G, Vasanthi HR and Das DK: Antiaging properties of a grape-derived antioxidant are regulated by mitochondrial balance of fusion and fission leading to mitophagy triggered by a signaling network of Sirt1-Sirt3-Foxo3-PINK1-PARKIN. Oxid Med Cell Longev 2014: 345105, 2014.
58. Tseng AHH, Shieh SS and Wang DL: SIRT3 deacetylates FOXO3 to protect mitochondria against oxidative damage. Free Radic Biol Med 63: 222-234, 2013.
59. Müller L, Di Benedetto S and Pawelec G: The immune system and its dysregulation with aging. Subcell Biochem 91: 21-43, 2019.
60. Huang Y, Hu C, Ye H, Luo R, Fu X, Li X, Huang J, Chen W and Zheng Y: Inflamm-aging: A new mechanism affecting premature ovarian insufficiency. J Immunol Res 2019: 8069898, 2019.
61. He L, Wang X, Cheng D, Xiong Z and Liu X: Ginsenoside Rg1 improves pathological damages by activating the p21-p53-STK pathway in ovary and Bax-Bcl2 in the uterus in premature ovarian insufficiency mouse models. Mol Med Rep 23: 37, 2021.
62. Domniz N and Meirow D: Premature ovarian insufficiency and autoimmune diseases. Best Pract Res Clin Obstet Gynaecol 60: 42-55, 2019.
63. Lv SJ, Hou SH, Gan L and Sun J: Establishment and mechanism study of a primary ovarian insufficiency mouse model using lipopolysaccharide. Anal Cell Pathol (Amst) 2021: 1781532, 2021.
64. Cao Y, Chen J, Ren G, Zhang Y, Tan X and Yang L: Punicalagin prevents inflammation in LPS-induced RAW264.7 macrophages by inhibiting FoxO3a/autophagy signaling pathway. Nutrients 11: 2794, 2019.

65. Lu D, Song J, Sun Y, Qi F, Liu L, Jin Y, McNutt MA and Yin Y: Mutations of deubiquitinase OTUD1 are associated with autoimmune disorders. J Autoimmun 94: 156-165, 2018.
66. Liu N, Feng X, Wang W, Zhao X and Li X: Paeonol protects against TNF-α-induced proliferation and cytokine release of rheumatoid arthritis fibroblast-like synoviocytes by upregulating FOXO3 through inhibition of miR-155 expression. Inflamm Res 66: 603-610, 2017.
67. Brandstetter B, Dalwigk K, Platzer A, Niederreiter B, Kartnig F, Fischer A, Vladimer GI, Byrne RA, Sevelda F, Holinka J, *et al*: FOXO3 is involved in the tumor necrosis factor-driven inflammatory response in fibroblast-like synoviocytes. Lab Invest 99: 648-658, 2019.
68. Lee A, Qiao Y, Grigoriev G, Chen J, Park-Min KH, Park SH, Ivashkiv LB and Kalliolias GD: Tumor necrosis factor α induces sustained signaling and a prolonged and unremitting inflammatory response in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 65: 928-938, 2013.
69. Di Vincenzo S, Heijink IH, Noordhoek JA, Cipollina C, Siena L, Bruno A, Ferraro M, Postma DS, Gjomarkaj M and Pace E: SIRT1/FoxO3 axis alteration leads to aberrant immune responses in bronchial epithelial cells. J Cell Mol Med 22: 2272-2282, 2018.
70. Lin Z, Niu Y, Wan A, Chen D, Liang H, Chen X, Sun L, Zhan S, Chen L, Cheng C, *et al*: RNA m^6A methylation regulates sorafenib resistance in liver cancer through FOXO3-mediated autophagy. EMBO J 39: e103181, 2020.
71. Li X, Xie J, Wang Q, Cai H, Xie C and Fu X: miR-21 and pellino-1 expression profiling in autoimmune premature ovarian insufficiency. J Immunol Res 2020: 3582648, 2020.
72. Sharif K, Watad A, Bridgewood C, Kanduc D, Amital H and Shoenfeld Y: Insights into the autoimmune aspect of premature ovarian insufficiency. Best Pract Res Clin Endocrinol Metab 33: 101323, 2019.
73. Otsuka N, Tong ZB, Vanevski K, Tu W, Cheng MH and Nelson LM: Autoimmune oophoritis with multiple molecular targets mitigated by transgenic expression of mater. Endocrinology 152: 2465-2473, 2011.
74. Hsieh YT and Ho JYP: Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency-a nationwide health insurance research database study. Hum Reprod 36: 1621-1629, 2021.
75. Becher J, Simula L, Volpe E, Procaccini C, La Rocca C, D'Acunzo P, Cianfanelli V, Strappazzon F, Caruana I, Nazio F, *et al*: AMBRA1 controls regulatory T-cell differentiation and homeostasis upstream of the FOXO3-FOXP3 axis. Dev Cell 47: 592-607.e6, 2018.
76. Deng Y, Wang F, Hughes T and Yu J: FOXOs in cancer immunity: Knowns and unknowns. Semin Cancer Biol 50: 53-64, 2018.
77. Bouzeyen R, Haoues M, Barbouche MR, Singh R and Essafi M: FOXO3 transcription factor regulates IL-10 expression in mycobacteria-infected macrophages, tuning their polarization and the subsequent adaptive immune response. Front Immunol 10: 2922, 2019.
78. Klagge A, Weidinger C, Krause K, Jessnitzer B, Gutknecht M and Fuhrer D: The role of FOXO3 in DNA damage response in thyrocytes. Endocr Relat Cancer 18: 555-564, 2011.
79. Lu M, Xu W, Gao B and Xiong S: Blunting autoantigen-induced FOXO3a protein phosphorylation and degradation is a novel pathway of glucocorticoids for the treatment of systemic lupus erythematosus. J Biol Chem 291: 19900-19912, 2016.
80. Zhao X, Petursson F, Viollet B, Lotz M, Terkeltaub R and Liu-Bryan R: Peroxisome proliferator-activated receptor γ coactivator 1α and FoxO3A mediate chondroprotection by AMP-activated protein kinase. Arthritis Rheumatol 66: 3073-3082, 2014.
81. Kato M, Yuan H, Xu ZG, Lanting L, Li SL, Wang M, Hu MC, Reddy MA and Natarajan R: Role of the Akt/FoxO3a pathway in TGF-beta1-mediated mesangial cell dysfunction: A novel mechanism related to diabetic kidney disease. J Am Soc Nephrol 17: 3325-3335, 2006.
82. Ock CW and Kim GD: Harmine hydrochloride mediates the induction of G2/M cell cycle arrest in breast cancer cells by regulating the MAPKs and AKT/FOXO3a signaling pathways. Molecules 26: 6714, 2021.
83. Wang H, Li G, Zhang J, Gao F, Li W, Qin Y and Chen ZJ: Novel WT1 missense mutations in Han Chinese women with premature ovarian failure. Sci Rep 5: 13983, 2015.
84. Bouali N, Francou B, Bouligand J, Lakhal B, Malek I, Kammoun M, Warszawski J, Mougou S, Saad A and Guiochon-Mantel A: NOBOX is a strong autosomal candidate gene in Tunisian patients with primary ovarian insufficiency. Clin Genet 89: 608-613, 2016.
85. Turkyilmaz A, Alavanda C, Ates EA, Geckinli BB, Polat H, Gokcu M, Karakaya T, Cebi AH, Soylemez MA, Guney Aİ, *et al*: Whole-exome sequencing reveals new potential genes and variants in patients with premature ovarian insufficiency. J Assist Reprod Genet 39: 695-710, 2022.
86. Morris BJ, Willcox DC, Donlon TA and Willcox BJ: FOXO3: A major gene for human longevity-a mini-review. Gerontology 61: 515-525, 2015.
87. Morris BJ, Willcox BJ and Donlon TA: Genetic and epigenetic regulation of human aging and longevity. Biochim Biophys Acta Mol Basis Dis 1865: 1718-1744, 2019.
88. Zhang W, Zuo M, Lu J and Wang Y: Adiponectin reduces embryonic loss rate and ameliorates trophoblast apoptosis in early pregnancy of mice with polycystic ovary syndrome by affecting the AMPK/PI3K/Akt/FoxO3a signaling pathway. Reprod Sci 27: 2232-2241, 2020.
89. Mikaeili S, Rashidi BH, Safa M, Najafi A, Sobhani A, Asadi E and Abbasi M: Altered FoxO3 expression and apoptosis in granulosa cells of women with polycystic ovary syndrome. Arch Gynecol Obstet 294: 185-192, 2016.
90. Zhang S, Deng W, Liu Q, Wang P, Yang W and Ni W: Altered m^6A modification is involved in up-regulated expression of FOXO3 in luteinized granulosa cells of non-obese polycystic ovary syndrome patients. J Cell Mol Med 24: 11874-11882, 2020.
91. Salcher S, Spoden G, Hagenbuchner J, Führer S, Kaserer T, Tollinger M, Huber-Cantonati P, Gruber T, Schuster D, Gust R, *et al*: A drug library screen identifies carbenoxolone as novel FOXO inhibitor that overcomes FOXO3-mediated chemoprotection in high-stage neuroblastoma. Oncogene 39: 1080-1097, 2020.
92. Dong S, Zhang K and Shi Y: Carbenoxolone has the potential to ameliorate acute incision pain in rats. Mol Med Rep 24: 520, 2021.