Research Progress on Mechanism of Ovulation Disorder in Polycystic Ovary Syndrome

Li HUANG, Chong ZHOU*

Guangxi University of Chinese Medicine, Nanning 530200, Guangxi

Abstract Polycystic ovary syndrome (PCOS) is a reproductive endocrine disease characterized by ovulation disorder, hyperandrogenism and/or polycystic ovary. Follicular development disorder caused by PCOS accounts for up to 75% of anovulatory infertility, which is a common cause of infertility and affects up to 15% of reproductive aged women worldwide. Oxidative stress, chronic inflammation, endoplasmic reticulum stress and other pathological conditions coexist in the ovarian microenvironment of PCOS, which are further aggravated under the action of high levels of androgens, synergistically deteriorating the follicular microenvironment, leading to ovulation disorders in PCOS patients. This paper briefly reviewed the research on the mechanism of PCOS ovulation disorder in recent years.

Key words Polycystic ovary syndrome; Ovulation disorders; Research progress

DOI:10.19759/j.cnki.2164-4993.2023.05.019

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disease among women of childbearing age, which is essentially developed due to the interaction of reproductive dysfunction and metabolic disorder[1]. PCOS is a clinical syndrome group characterized by ovulatory dysfunction (OD), hyperandrogenism (HA) and/or polycystic ovarian morphology (PCOM), often accompanied by metabolic disorder, irregular menstruation, signs of hyperandrogenism and oxidative stress[2]. Ovarian follicle development disorder caused by PCOS is characterized by slow follicular growth, abnormal morphology, stagnant development, atresia and ovulation of young follicles[3], accounting for 75% of sterility due to anovulation, showing an increasing trend year by year[4]. PCOS is a common cause of infertility, which affects as many as 15% of women of childbearing age in the world, and may cause lifelong damage to patients' health[1].

PCOS is a gynecological disease regulated by multiple genes and factors, with complexity and heterogeneity, and its pathogenesis is still unclear. In recent years, with the in-depth study on the pathophysiology of PCOS, the follicular microenvironment has gradually become a research hotspot, attracting extensive attention from industry. The growth and development process of normal follicles includes initial growth stage, selection stage of dominant follicles, differentiation stage and mature stage of dominant follicles growing and developing independently. Abnormal follicular development is not only related to the imbalance of hypothalamus-pituitary-ovary axis, but also related to the dysregulation of local ovarian follicle microenvironment[5]. The follicular microenvironment is the site for the development and maturation of oocytes, mainly composed of follicular fluid and granulosa/cumulus cells, and plays a crucial role in ovarian diseases such as PCOS[6-7]. Studies have shown that multiple pathological states such as oxidative stress[8], chronic inflammation[9], and endoplasmic reticulum stress[10] coexist within the ovarian microenvironment of PCOS. Various pathological conditions promote each other, and are further aggravated by a high level of androgens. These pathological conditions synergistically worsen the follicular microenvironment, thus leading to ovulation disorder in PCOS patients[1]. This paper briefly reviewed the research on the mechanism of ovulation disorder in PCOS in recent years.

High Level of Androgens

The development of follicles depends on the balance of androgens and their receptors[11-12]. Androgens (mainly including androstenedione, dehydroepiandrosterone and testosterone) are the most common serological feature of PCOS patients, and the increased excessive secretion of testosterone (T) is an important cause of follicular development disorder[13]. Androgens play a dual role in the growth and development of follicles, and the deficiency or excess of androgens will directly or indirectly lead to follicular atresia. Androgens can directly promote the growth and proliferation of early follicles through their receptors. In the late stage of follicular development, estrogens replace androgens and become the dominant factor of follicular development[14]. Testosterone and androstenedione are converted into estrogens (estradiol and estrone) under the action of aromatase, and excessive androgens are converted into estrone in peripheral tissues and feed back to the hypothalamus and pituitary gland, so that the secretion of follicle-stimulating hormone (FSH) is reduced, and the sensitivity of follicles to luteinizing hormone (LH) is increased. As a result, the selection of dominant follicles cannot be carried out, which further causes follicular development disorder and promotes follicular

Received: July 10, 2023 Accepted: August 12, 2023

Supported by Guangxi Natural Science Foundation (2020GXNSFAA238022); National Natural Sciences Foundation of China (82060280); Doctoral Research Start-up Fund of Guangxi University of Chinese Medicine (2017BS011); Science and Technology Plan Project of Guangxi University of Chinese Medicine (2018ZD003).

Chong ZHOU (1976-), male, P. R. China, Associate Professor, devoted to research about Chinese herb medicine on prevention and treatment of reproductive disorder.

* Corresponding author.

atresia.

The high level of androgens in PCOS can induce the expression of aldose reductase in the ovary, which leads to the hyperactivity of the polyol pathway, and affects ovarian function by promoting oxidative stress, significantly reducing the total number of follicles in mice with PCOS, causing polycystic ovarian changes, increasing the proportion of atresia follicles and reducing the number of corpus luteum[15]. The high level of androgens in PCOS can enhance autophagic activity by increasing the content of homocysteine and inhibiting the mTOR signaling pathway[16]. The high level of Cyp1B1 in granulosa cells can transform estradiol into its inactive metabolite, and its mRNA expression is related to PCOS pathology[17]. A high level of androgens may impair the developmental ability of oocytes by affecting the signaling pathway of aryl hydrocarbon receptor (Ahr) and its downstream genes, such as *Arnt*, *Cyp1A1* and *Cyp1B1*[18]. The secretion of anti-Müllerianhormone (AMH) is related to the concentration and action time of testosterone, which promotes the secretion of AMH by granulosa cells, while AMH inhibits the activity of aromatase, thus inhibiting the transformation of testosterone and androstenedione into estrogens, forming a vicious circle and further increasing the level of androgens in the body[19].

Oxidative Stress

Oxidative stress is considered as one of the potential pathogenesis of PCOS ovulation failure. It is closely related to the molecular pathogenesis of PCOS[21] and plays a decisive role in the development of PCOS[22]. Oxidative stress affects follicular maturation, ovulation rate and oocyte quality in PCOS[23]. Oxidative stress is directly related to testosterone and androstenedione. Oxidative stress participates in steroid production in the ovary, thus promoting androgen production[40], and the high level of androgens promotes oxidative stress, forming a vicious circle and causing irreversible damage to oocytes[1,24]. Meanwhile, the disorder of sex hormone level will induce systemic and local oxidative stress in the ovary, which further exacerbates sexual hormone disorders and ultimately leads to ovulation disorders in PCOS patients[25].

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal pathway is a universally-expressed intracellular signal transduction pathway, which can be activated by reactive oxygen species (ROS) and other cytokines, hormones, growth factors and other ligands and their receptors, and participates in key physiological processes such as cell proliferation and differentiation, apoptosis and survival, metabolism and stress[26-28]. The JAK/STAT pathway is involved in the process of antioxidant stress. ROS can cause abnormal metabolism of components in extracellular matrix and abnormal expression of related factors through the JAK2/STAT3 signaling pathway[29]. Studies have shown that the phosphorylation levels of JAK2 and STAT3 in PCOS patients and rats are significantly increased[30]. Oxidative free radicals, malondialdehyde (MDA) and reactive oxygen species (ROS) in follicular fluid and serum of patients are higher than those in normal people, and they are oxidative markers that destroy the homeostasis of ovarian environment and aggravate ovulation disorder, hyperandrogenism and metabolic disorder. Nateglinide and octreotide reverse PCOS-induced atresia and degenerative follicular damage through TLR-4, antioxidant and anti-inflammatory pathways[31].

Chronic Inflammation

Inflammatory factors in blood circulation, ovarian tissue matrix and follicular fluid of PCOS patients, including c-reactive protein (CRP), tumor necrosis factors (TNF-α) and interleukin (IL), increase to varying degrees, and the body is in a state of low-grade chronic inflammation[32]. A high level of TNF-α in serum can promote the reduction of granulosa cells and interstitial cells of theca, and function declines, even apoptosis, which leads to the decrease of estrogen content and the increase of androgen content *in vivo*, which reduces the quality of oocytes, which develop into immature follicles having no normal fertilization function, and the eggs shrink by themselves, leading to ovulation difficulties or infertility[33]. IL-6 and IL-8 can interfere with cell signal transmission through the induction of inflammatory reaction, which leads to insulin resistance and hinders the growth and development of follicles and the selection of dominant follicles[34].

Total flavonoids regulate the serum sex hormone level of PCOS and improve ovulation through the JAK2/STAT3 pathway mediated by IL-6[35]. Bushen Huatan Formula combined with acupoint catgut embedding can effectively improve the levels of sex hormones and glucolipid metabolism in PCOS patients with kidney deficiency and phlegm-dampness syndrome, which may play a role by inhibiting the activation of TLR4/NF-κB signaling pathway and alleviating inflammatory reaction[36]. TGF-β is highly expressed in the serum of PCOS patients, and activated GF-βR1 and SMAD2/SMAD3 participate in the regulation of PCOS diseases[37-39]. Liuwei Dihuang Pill can effectively inhibit PCOS by inhibiting the TGF-β1/SMAD signaling pathway, relieving polycystic ovary and uterine cavity dilatation, and regulating endocrine metabolism[40].

Autophagy

Autophagy is involved in maintaining the reserve of ovarian primordial follicles and regulating the development, atresia and formation and degeneration of corpus luteum[41-42]. Under normal circumstances, autophagy is necessary for follicular granulosa cells to maintain oocyte growth, follicular development and follicular atresia. Autophagy abnormalities exist in ovarian granulosa cells of PCOS patients[43-44].

Chemerin is an endogenous ligand of G protein-coupled receptor, chemokine receptor-like 1 (CMKLR1), and it is a new type of fat factor related to obesity and metabolic syndrome, which mainly plays a role by activating the biological activity of CMKLR1. Chemokines can promote autophagy of PCOS granulosa cells by inhibiting the PI3K/AKT/mTOR signaling pathway[45]. Metformin decreases the autophagy level in granulosa cells of

PCOS rats through the PI3K/AKT/mTOR pathway, as well as the oxidative stress and autophagy level in the cell model with high autophagy level induced by hydrogen peroxide[46]. Guizhi Fuling Pill can inhibit autophagy of granulosa cells and promote follicular development by activating the PI3K/AKT/mTOR signaling pathway, so as to alleviate ovulation disorder in PCOS-IR rats[47]. Acupuncture can down-regulate the expression of LncMEG3, thus inhibiting the PI3K/AKT/mTOR pathway, reducing autophagy of granulosa cells, normalizing their proliferation and correcting abnormal follicular development[48].

Apoptosis

Follicular atresia is induced by the degeneration of theca cells after ovarian granulosa cells start apoptosis[49-50]. Under normal conditions, apoptosis and normal division coexist in granulosa cells in follicles, but when the apoptosis rate of granulosa cells exceeds 10%, it indicates that follicles suffer from atresia. In the process of follicular development, the gap junction between granulosa cells and oocytes is very important[51], and granulosa cells transmit apoptosis information to oocytes, which leads to the decline of oocyte quality. Therefore, ovarian granulosa cell apoptosis is considered as the direct cause of follicular atresia[52].

MiR-18b-5p produced by exosomes derived from follicular fluid can reduce PTEN expression, promote the activation of the PI3K/Akt/mTOR signaling pathway and inhibit apoptosis, so as to improve PCOS[54-55]. Curcumin can protect GCs from apoptosis induced by androgen in PCOS model rats by inhibiting the IRE1 α/XBP1 pathway related to oxidative stress and activating the PI3K/AKT signaling pathway[55]. The MAPK signaling pathway is related to the growth, differentiation and apoptosis of ovarian granulosa cells[56-57]. Jiawei Shaoyao Gancao Decoction may inhibit apoptosis and autophagy of ovarian granulosa cells in PCOS and promote cell proliferation by inhibiting p38 AMPK signaling pathway[58]. miR-184 inhibits the proliferation of ovarian granulosa cells by activating the expression of p38 MAPK and ERK1/2 proteins[59]. Bushen Huatan Formula can promote and inhibit the proliferation and differentiation of ovarian granulosa cells by reducing APN/p38MAPK signal transduction[60]. Bushen Zhuyun Decoction can restore ovarian lesions and improve apoptosis through the PI3K/AKT/mTOR pathway mediated by estrogen receptor α, which may be partly helpful for the treatment of PCOS[61].

In addition, microcirculation disturbance and intestinal flora imbalance are also important pathological factors for the occurrence and development of POCS. To sum up, pathological conditions such as endoplasmic reticulum stress, oxidative stress, chronic inflammatory autophagy and apoptosis exist in the follicular microenvironment of PCOS, and interact with the level of androgens and glucose and lipid metabolism disorder to jointly damage and worsen the follicular microenvironment, thus leading to abnormal follicular development and maturation in PCOS patients and ultimately to infertility in PCOS patients. Therefore, how to treat PCOS and protect women's fertility has become an urgent focus scientific issue. This paper reviewed the molecular mechanism of PCOS, hoping to provide molecular targets and therapeutic strategies for the diagnosis and treatment of anovulatory infertility and ovarian diseases.

References

[1] HARADA M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research[J]. Reprod Med Biol., 2022, 21(1): e12487.

[2] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)[J]. Hum Reprod., 2004 (19): 41-47.

[3] LI LJ, DING YF, LI L. Study on the theory of regulating menstruation and promoting pregnancy in the treatment of PCOS ovulation disorder by zelan (Lycopi Herba) and its modern pharmacological research[J]. Guiding Journal of Traditional Chinese Medicine and Pharmacology, 2022, 28(11): 199-202. (in Chinese).

[4] TANNUS S, TAN J, SON WY, *et al.* Prevalence, clinical characteristics, and reproductive outcomes of polycystic ovary syndrome in older women referred for tertiary fertility care[J]. Arch Gynecol Obstet., 2018, 297(4): 1037-1042.

[5] XU P. Study on the action mechanism of factors related to androgen metabolism and signal pathways in follicular development[D]. Nanjing: Nanjing University, 2013. (in Chinese).

[6] DUMESIC DA, MELDRUM DR, KATZ-JAFFE MG, *et al.* Oocyte environment: follicular fluid and cumulus cells are critical for oocyte health[J]. Fertil Steril., 2015(103): 303-316.

[7] DA BROI MG, GIORGI VSI, WANG F, *et al.* Influence of follicular fluid and cumulus cells on oocyte quality: Clinical implications[J]. J Assist Reprod Genet., 2018(35): 735-751.

[8] GONZÁLEZ F, ROTE NS, MINIUM J, *et al.* Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome[J]. J Clin Endocrinol Metab., 2006(91): 336-340.

[9] ADAMS J, LIU Z, REN YA, *et al.* Enhanced inflammatory transcriptome in the granulosa cells of women with polycystic ovarian syndrome[J]. J Clin Endocrinol Metab., 2016(101): 3459-3468.

[10] TAKAHASHI N, HARADA M, HIROTA Y, *et al.* Activation of endoplasmic reticulum stress in granulosa cells from patients with polycystic ovary syndrome contributes to ovarian fibrosis[J]. Sci Rep., 2017(7): 10824.

[11] EMAMI N, MOINI A, YAGHMAEI P, *et al.* Differences in expression of genes related to steroidgenesis in abdominal subcutaneous adipose tissue of pregnant women with and without PCOS: A case control study[J]. BMC Pregnancy Childbirth., 2021, 21(1): 490.

[12] KUMARI S, CHAURASIYA V, ONTERU SK, *et al.* Regulation of granulosa cell functions through NRP-1 mediated internalization of follicular fluid non-exosomal miR-210[J]. Cell Tissue Res., 2021, 386 (3): 649-660.

[13] ALEMZADEH R, KICHLER J, CALHOUN M. Spectrum of metabolic dysfunction in relationship with hyperandrogenemia in obese adolescent girls with polycystic ovary syndrome[J]. Eur J Endocrinol, 2010, 162 (6): 1093-1099.

[14] PARKER CR JR, AZZIZ R, POTTER HD, *et al.* Adrenal androgen production in response to adrenocorticotropin infusions in men[J]. Endocr Res., 1996, 22(4): 717-722.

[15] WANG YC, MA YD, LIU H, *et al.* Hyperandrogen-induced polyol pathway flux increase affects ovarian function in polycystic ovary syndrome via excessive oxidative stress[J]. Life Sci., 2022 (313):

121224.
[16] LI T, DONG G, KANG Y, *et al.* Increased homocysteine regulated by androgen activates autophagy by suppressing the mammalian targetof rapamycin pathway in the granulosa cells of polycystic ovarysyndrome mice [J]. Bioengineered, 2022, 13(4): 10875 – 10888.
[17] HAOUZI D, ASSOU S, MONZO C, *et al.* Altered gene expression profile in cumulus cells of mature MII oocytes from patients with polycystic ovary syndrome[J]. Hum Reprod., 2012, 27(12): 3523 – 3530.
[18] EINI F, KUTENAEI MA, FOROUTAN T, *et al.* High levels of follicular fluid testosterone could impair oocyte developmental competency via affecting aryl hydrocarbon receptor pathway in PCOS patients[J]. BMC Mol Cell Biol., 2022, 23(1): 47.
[19] ZHANG Y. Study on the mechanism of testosterone-induced follicular dysplasia[D]. Jinzhou: Jinzhou Medical University, 2014. (in Chinese).
[20] QIU YL, LI QZ, ZHENG YQ, *et al.* Interaction between endoplasmic reticulum stress and oxidative stress? [J]. Practical Pharmacy and Clinical Remedies, 2016, 19(8): 1037 – 1041. (in Chinese).
[21] EINI F, NOVIN MG, JOHARCHI K, *et al.* Intracytoplasmic oxidative stress reverses epigenetic modifications in polycystic ovary syndrome[J]. Reprod Fertil Dev, 2017, 29(12): 2313 – 2323.
[22] PAPALOU O, VICTOR VM, DIAMANTI-KANDARAKIS E. Oxidative stress in polycystic ovary syndrome[J]. Curr Pharm Des, 2016, 22(18): 2709 – 2722.
[23] ROSTAMTABAR M, ESMAEILZADEH S, TOURANI M, *et al.* Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome[J]. J Cell Physiol, 2021, 236(2): 824 – 838.
[24] SURESH S, VIJAYAKUMAR T. Correlations of insulin resistance and serum testosterone levels with LH: FSH ratio and oxidative stress in women with functional ovarian hyperandrogenism[J]. Indian J Clin Biochem, 2015, 30(3): 345 – 350.
[25] SAVIĆ-RADOJEVIĆ A, MAŽIBRADA I, DJUKIĆ T, *et al.* Glutathione S-transferase (GST) polymorphism could be an early marker in the development of polycystic ovary syndrome (PCOS): An insight from non-obese and non-insulin resistant adolescents [J]. Endokrynol Pol., 2018, 69(4): 366 – 374.
[26] MURRI M, LUQUE-RAMÍREZ M, INSENSER M, *et al.* Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): A systematic review and meta-analysis[J]. Hum Reprod Update, 2013, 19(3): 268 – 288.
[27] XIN P, XU X, DENG C, *et al.* The role of JAK/STAT signaling pathway and its inhibitors in diseases[J]. Int Immunopharmacol., 2020(80):106210.
[28] MURRAY PJ. The JAK-STAT signaling pathway: Input and output integration[J]. J Immunol, 2007, 178(5): 2623 – 2629.
[29] ZHANG R, JIAO J, ZHANG W, *et al.* Effects of cereal fiber on leptin resistance and sensitivity in C57BL/6J mice fed a high-fat/cholesterol diet[J]. Food Nutr Res, 2016(60) 31690.
[30] WU Y, WANG LN, LI YN, *et al.* Effects of high glucose on the JAK2/STAT3 signal transduction pathway and reactive oxygen species in mesangial cells[J]. Chinese Journal of Integrated Traditional and Western Nephrology, 2009, 10(5): 386 – 391. (in Chinese).
[31] YU Y, CHEN T, LIU XM. Mechanism of melatonin in treatment of polycystic ovary syndrome based on network pharmacology and molecular docking[J]. Drugs & Clinic, 2022, 37(10): 2197 – 2205. (in Chinese).
[32] KIRICI P, KAPLAN S, ANNAC E, *et al.* The effect of nateglinide and octreotide on follicular morphology and free radical scavenging system in letrazole-induced rat model of PCOS[J]. Eur Rev Med Pharmacol Sci., 2022, 26(23): 8893 – 8902.
[33] MEI YY, XIE QZ. Inflammatory mechanism of polycystic ovary syndrome with metabolic disorders[J]. Chinese Journal of Family Planning & Gynecotokology, 2021, 13(4): 20 – 23. (in Chinese).
[34] ZHANG RJ, LIU HW, BAI H, *et al.* Recent advance on relationship between oxidative stress and hyperandrogenism in polycystic ovary syndrome[J]. Chinese Journal of Obstetrics & Gynecology and Pediatrics (Electronic Edition), 2017, 13(6): 633 – 639. (in Chinese).
[35] HE SW, WANG X, ZHOU F, *et al.* Correlation analysis of the expression of IRS-2 protein and changes in serum inflammatory factor levels with the onset of polycystic ovary syndrome[J]. Experimental and Laboratory Medicine, 2019, 37(1): 68 – 70. (in Chinese).
[36] ZHOU Y, LV L, LIU Q, *et al.* Total flavonoids extracted from Nervilia Fordii function in polycystic ovary syndrome through IL-6 mediated JAK2/STAT3 signaling pathway [J]. Biosci Rep., 2019, 39(1): BSR20181380.
[37] ZHOU HH, LIU HS, MENG RR, *et al.* Effects of Liuwei Dihuang Pills on endocrine metabolism in rats with polycystic ovary syndrome by inhibiting TGF-β1/SMAD signal pathway[J]. Progress in Modern Biomedicine, 2022, 22(21): 4130 – 4134. (in Chinese).
[38] TAKAHASHI N, HARADA M, HIROTA Y, *et al.* Activation of endoplasmic reticulum stress in granulosa cells from patients with polycystic ovary syndrome contributes to ovarian fibrosis[J]. Sci Rep, 2017, 7(1): 10824
[39] MASSAGUÉ J. TGFβ signalling in context[J]. Nat Rev Mol Cell Biol, 2012, 13(10): 616 – 630.
[40] ZHOU YY, LAN H, DONG ZW, *et al.* Rhamnocitrin attenuates ovarian fibrosis in rats with letrozole-induced experimental polycystic ovary syndrome[J]. Oxid Med Cell Longev, 2022(2022) 5558599.
[41] YAN X, MA SG, LEI Q, *et al.* Effects of Liuwei Dihuang Pills on endocrine metabolism in rats with polycystic ovary syndrome by inhibiting TGF-β1/SMAD signal pathway[J]. Drug Evaluation Research, 2022, 45(12): 2494 – 2500.
[42] BHARDWAJ JK, PALIWAL A, SARAF P, *et al.* Role of autophagy in follicular development and maintenance of primordial follicular pool in the ovary[J]. J Cell Physiol, 2022, 237(2): 1157 – 1170.
[43] KUMARIYA S, UBBA V, JHA RK, *et al.* Autophagy in ovary and polycystic ovary syndrome: role, dispute and future perspective[J]. Autophagy, 2021, 17(10): 2706 – 2733.
[44] YE W, XIE T, SONG Y, *et al.* The role of androgen and its related signals in PCOS[J]. J Cell Mol Med, 2021, 25(4): 1825 – 1837.
[45] QIN Y, LI T, ZHAO H, *et al.* Integrated transcriptomic and epigenetic study of PCOS: impact of Map3k1 and Map1lc3a promoter methylation on autophagy[J]. Front Genet, 2021(12): 620241.
[46] LUO X, GONG Y, CAI L, *et al.* Chemerin regulates autophagy to participate in polycystic ovary syndrome [J]. J Int Med Res, 2021, 49(11): 3000605211058376.
[47] XU B, DAI W, LIU L, *et al.* Metformin ameliorates polycystic ovary syndrome in a rat model by decreasing excessive autophagy in ovarian granulosa cells via the PI3K/AKT/mTOR pathway [J]. Endocr J, 2022, 69(7): 863 – 875.
[48] LIU M, ZHU H, ZHU Y, *et al.* Guizhi Fuling Wan reduces autophagy of granulosa cell in rats with polycystic ovary syndrome via restoring the PI3K/AKT/mTOR signaling pathway [J]. J Ethnopharmacol., 2021(270): 113821.
[49] CHEN X, TANG H, LIANG Y, *et al.* Acupuncture regulates the autophagy of ovarian granulosa cells in polycystic ovarian syndrome ovulation disorder by inhibiting the PI3K/AKT/mTOR pathway through LncMEG3 [J]. Biomed Pharmacother., 2021(144): 112288.
[50] MIKAEILI S, RASHIDI BH, SAFA M, *et al.* Altered FoxO3 expression and apoptosis in granulosa cells of women with polycystic ovary syndrome [J]. Archives of Gynecology and Obstetrics, 2016, 294(1): 185 – 192.
[51] FU X, HE Y, WANG X, *et al.* MicroRNA-16 Promotes ovarian granulosa cell proliferation and suppresses apoptosis through targeting PDCD4

in polycystic ovarian syndrome[J]. Cell Physiol Biochem, 2018, 48(2): 670-682.
[52] ZHANG H, LI C, WEN D, *et al.* Melatonin improves the quality of maternally aged oocytes by maintaining intercellular communication and antioxidant metabolite supply[J]. Redox Biol., 2022(49): 102215.
[53] WANG CL, FAN YC, TSENG CH, *et al.* Salmonella Enteritidis infection slows steroidogenesis and impedes cell growth in hen granulosa cells [J]. Avian Dis, 2014, 58(4): 511-517.
[54] ZHOU Z, TU Z, ZHANG J, *et al.* Follicular fluid-derived exosomal MicroRNA-18b-5p regulates PTEN-mediated PI3K/Akt/mTOR signaling pathway to inhibit polycystic ovary syndrome development[J]. Mol Neurobiol., 2022, 59(4): 2520-2531.
[55] ZHANG Y, WANG L, WENG Y, *et al.* Curcumin inhibits hyperandrogen-induced IRE1α-XBP1 pathway activation by activating the PI3K/AKT signaling in ovarian granulosa cells of PCOS model rats[J]. Oxid Med Cell Longev., 2022(2022): 2113293.
[56] DONG XM, LI R, YANG J, *et al.* Effect and mechanism of miR-204-5p on apoptosis of ovarian granulosa cells in rats with premature ovarian failure[J]. Medical Journal of West China, 2021, 33(5): 636-643. (in Chinese).
[57] JIN J, MA Y, TONG X, *et al.* Metformin inhibits testosterone-induced endoplasmic reticulum stress in ovarian granulosa cells via inactivation of p38 MAPK[J]. Hum Reprod, 2020, 35(5): 1145-1158.
[58] ZHU J, CAI WX, MA J, *et al.* Effects of modified Shaoyao Gancao Decoction on the apoptosis, autophagy and p38 AMPK signaling pathway of ovarian granulosa cells[J]. Maternal and Child Health Care of China, 2022, 37(24): 4722-4726. (in Chinese).
[59] CHEN L, WANG M, LIU LP. MiR-184 promotes the proliferation of ovarian granulosa cells in polycystic ovary syndrome by MAPK signaling pathway[J]. Journal of Clinical and Pathological Research, 2019, 39(1): 1-8. (in Chinese).
[60] LI XW, LANG L, JI YB, *et al.* Study on process of the signaling pathway of follicle stimulating hormone to promote the ovarian granulosa cell proliferation and differentiation[J]. Journal of Beijing Union University: Natural Sciences, 2012, 26(4): 46-50. (in Chinese).
[61] JIANG X, YUAN Y, SHI M, *et al.* Bu-shen-zhu-yun decoction inhibits granulosa cell apoptosis in rat polycystic ovary syndrome through estrogen receptor α-mediated PI3K/AKT/mTOR pathway[J]. J Ethnopharmacol., 2022(288): 114862.

Editor: Yingzhi GUANG Proofreader: Xinxiu ZHU

(Continued from page 77)

regulatory role of institutional mechanisms. Through institutional construction, we aim to address the shortcomings of practical teaching bases for agricultural masters in local colleges and universities under the background of new agricultural sciences, thereby enabling students to focus their papers on practical problems discovered during practice processes, effectively solve agricultural practical problems, and write papers on the land of China to assist in the revitalization and construction of rural areas in the country.

Conclusions

Under the background of "New Agricultural Sciences", building stable research and teaching practice bases is an important carrier for agricultural professional degree postgraduates to exercise their practical ability. Constructing practice bases of professional degree postgraduates with the characteristics of "integrating production and education" allows the organic integration of industry-teaching and scientific research, which effectively solves the problem of the absence of off-campus practice teaching and provides a new idea for exploring the long-term operation mechanism of practice bases.

References

[1] HAO ZP, ZAI XM, FAN JJ, *et al.* The construction and practice of the "three Hua and three combinations" practical education system for undergraduate education under the background of new agricultural science construction[J]. Higher Agricultural Education, 2023(2): 54-62. (in Chinese).
[2] WANG HJ, XIA T. The path selection and thinking of local agricultural and forestry universities in serving rural revitalization under the background of the emerging agricultural education: Taking Anhui agricultural university as an example[J]. China Agricultural Education, 2022, 23(4): 9-15. (in Chinese).
[3] ZHANG W. Construction of practical teaching system for new majors in agricultural colleges under the background of the emerging agricultural education: Taking Northeast Agricultural University as an example[J]. China Agricultural Education, 2022, 23(3): 39-41. (in Chinese).
[4] LI JC. An Exploration on characteristic school-running and cultivation mode of practical talents of high level[J]. Journal of Zhejiang Gongshang University, 2010, (4): 84-91. (in Chinese).
[5] HE XY, CHENG N, LI W, *et al.* Exploration of the practice base construction and long-term mechanism of "industry-science-education trinity"[J]. Ke Ji Feng, 2023(13): 65-67. (in Chinese).
[6] ZHANG L, NING ZX, GU C. Research on the cooperative training mechanism of professional master degree students' integration of production and education based on industrial colleges[J]. China Modern Educational Equipment, 2023(11): 166-168. (in Chinese).
[7] ZHANG XT, MENG ZB, ZHAO QS. Research and practice on the practical teaching system of master of engineering in local universities: Taking Liaocheng University as an example[J]. Jiaoyu Guancha, 2022, 11(16): 18-21. (in Chinese).
[8] SI HB, ZHANG WY, SHEN SB, *et al.* Thinking of training mode of cultivating "five haves" leading agricultural professional talents under the background of new agricultural discipline combined with the integration of industry and education[J]. Genomics and Applied Biology, 2022, 41(6): 1377-1381. (in Chinese).
[9] LIU SH, WEI H, GU TT, *et al.* Innovation in teaching of the "four integrations and three combinations" course under the background of new agricultural sciences: Taking the course of facility environment and regulation as an example[J]. Journal of Smart Agriculture, 2023, 3(7): 130-133. (in Chinese).

Editor: Yingzhi GUANG Proofreader: Xinxiu ZHU