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REVIEW

Exosomes for Polycystic Ovary Syndrome Treatment: Mechanisms and Therapeutic Potential

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Abstract: Polycystic ovary syndrome (PCOS) is a major health concern for women of reproductive age and a leading cause of infertility and metabolic dysfunction. Current treatments mainly involve lifestyle modification and pharmacological therapies, such as oral contraceptives and metformin, and may also include laparoscopic ovarian drilling (LOD), acupuncture, and probiotic interventions. Although these approaches can be effective, they often produce adverse effects and show a high relapse rate after discontinuation. This review summarizes recent advances in exosome-based therapies as emerging strategies for PCOS. Exosomes derived from adipose-derived mesenchymal stem cells, menstrual blood–derived stem cells, bone marrow mesenchymal stem cells, brown adipocytes, and human umbilical cord–derived mesenchymal stem cells have demonstrated therapeutic potential. As nanosized extracellular vesicles carrying bioactive molecules, exosomes exhibit strong targeting capacity and low immunogenicity. We discuss the mechanisms by which exosomes may ameliorate PCOS, including suppression of chronic low-grade inflammation, enhancement of mitochondrial function, inhibition of apoptosis, modulation of angiogenesis, and improvement of metabolic disturbances. However, translating these promising findings into clinical practice faces significant challenges. The main obstacles include lack of standardization, high production costs, and limited clinical data to confirm safety and efficacy. Addressing these issues could pave the way for mechanism-based, personalized exosome treatments and offer new approaches for managing PCOS.

Keywords: polycystic ovary syndrome, exosome, personalized medicine

Introduction

PCOS is a common endocrine disorder that primarily affects women of reproductive age.[1] Clinically, it is characterized by hyperandrogenism, ovulatory dysfunction, and abnormal polycystic ovarian morphology.[2] The diagnostic criteria for PCOS are not singular; three different definitions have been established for the diagnosis of PCOS, and its prevalence varies depending on the diagnostic criteria used.[3] PCOS affects not only the reproductive system but also metabolic function. Metabolic dysfunction observed in patients with PCOS may be closely linked to androgen excess.[4] Approximately two-thirds of patients with PCOS exhibit metabolic disorders, including insulin resistance and type 2 diabetes, which are associated with dyslipidemia and an increased risk of cardiovascular disease (CVD).[5–7] Currently, PCOS treatment primarily aims to manage its main signs and symptoms.[2] As shown in Figure 1, This includes the use of a combination estrogen–progestin oral contraceptives and clomiphene citrate to address reproductive system symptoms, as well as metformin to improve insulin resistance and other metabolic disturbances.[8,9]

Exosomes are small membrane-bound vesicles secreted by various cell types under both physiological and pathological conditions and typically range in diameter from 30 to 150 nm. They have been identified as critical extracellular vesicles that carry various biomolecules including proteins, lipids, and nucleic acids, such as mRNA, miRNAs, and lncRNAs, enabling them to modulate the function of recipient cells. Exosome biogenesis can be divided into three main stages: formation of early endosomes, maturation into multivesicular bodies (MVBs), and subsequent fusion of MVBs

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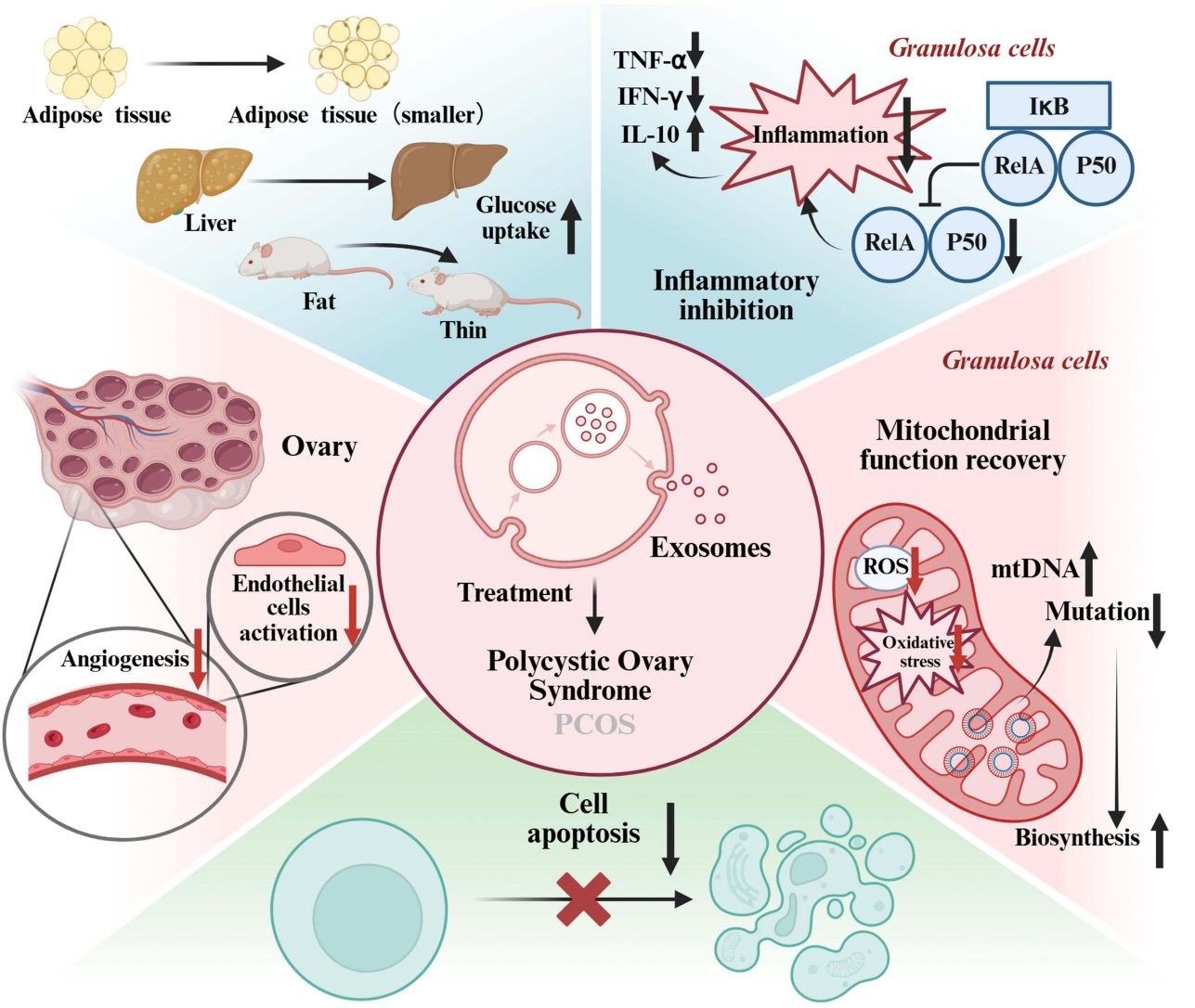
Graphical Abstract



with the plasma membrane, leading to the release of exosomes into the extracellular environment. Exosomes carry characteristic protein markers, such as tetraspanins CD9, CD63, and CD81, as well as ESCRT-associated proteins, including TSG101 and Alix, along with heat shock proteins.[10] These markers reflect the endosomal origin of exosomes. Exosomes are widely recognized as critical mediators of intercellular communication. Increasing attention has been directed toward elucidating their roles in disease progression and exploring their potential applications in disease diagnosis and therapy.

Endocrine and hormonal metabolic disorders during PCOS development are closely associated with abnormal expression of certain exosomes.[11,12] Additionally, exosomes in the plasma of patients with PCOS can induce reproductive phenotype alterations in healthy individuals.[13] The aberrant expression of bioactive molecules within exosomes is closely associated with PCOS pathogenesis, suggesting the potential of exosomes as biological markers for PCOS diagnosis.

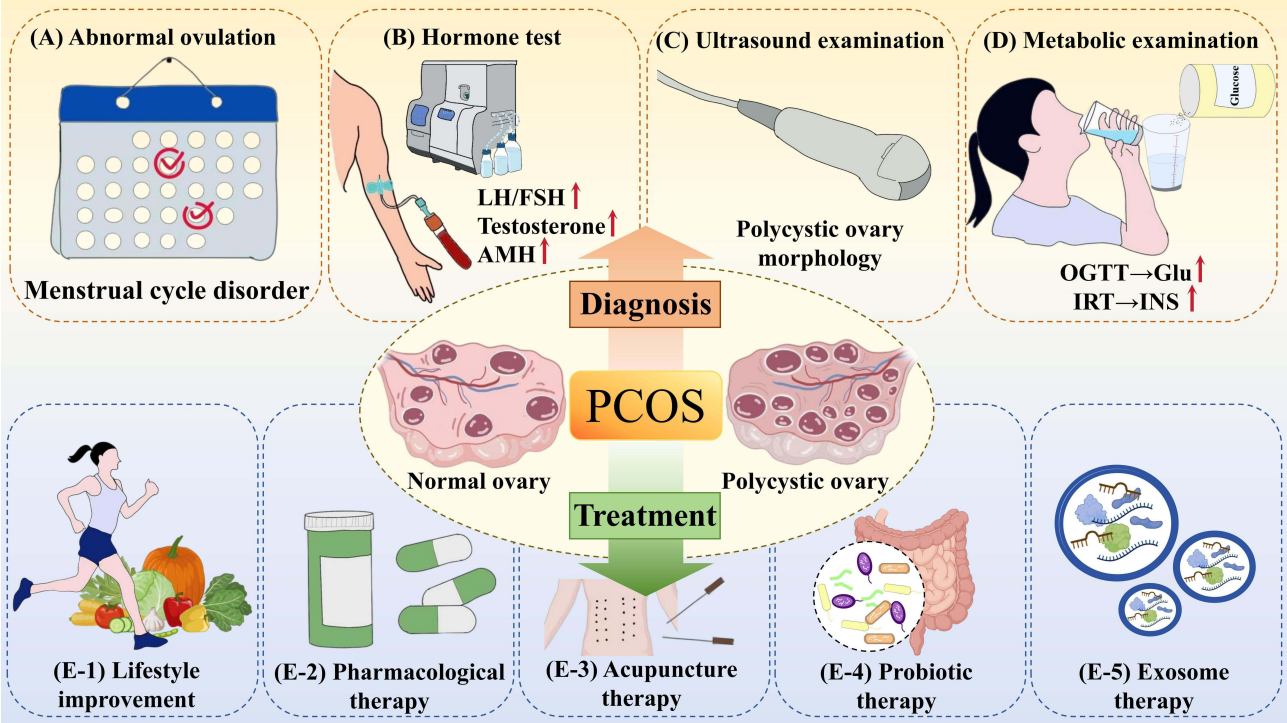


Figure 1 Diagnosis and Treatment of PCOS. Diagnostic methods and treatment strategies for polycystic ovary syndrome (PCOS). (**A–D**) in the upper row illustrate the diagnostic components: (**A**) abnormal ovulation manifested as menstrual cycle disorder; (**B**) hormone testing showing increased LH/FSH, testosterone, and AMH levels (upward arrows indicate elevation); (**C**) ultrasound examination demonstrating polycystic ovary morphology; and (**D**) metabolic examination with OGTT and IRT showing elevated glucose (Glu) and insulin (INS) levels (upward arrows indicate elevation). The central Orange upward arrow represents the direction from these assessments toward diagnosis. Panels (E1–E5) in the lower row display treatment options: (E-1) lifestyle improvement through exercise and dietary optimization; (E-2) pharmacological therapy; (E-3) acupuncture therapy; (E-4) probiotic therapy; and (E-5) exosome therapy. The central green downward arrow indicates the transition from diagnosis to treatment.

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone; OGTT, oral glucose tolerance test; IRT, insulin release test; Glu, glucose; INS, insulin.

Although prescription drugs are currently available for PCOS treatment, some have significant side effects. Moreover, most existing therapies are symptomatic rather than curative, and have limited efficacy.[14] These limitations highlight the urgent need for novel therapeutic strategies. Recent research in rodent models and in vitro systems has demonstrated promising preclinical effects of stem cell-derived exosomes on PCOS-related ovarian and metabolic abnormalities. Exosomes have lower immunogenicity than stem cells. This review highlights the role of stem cell-derived exosomes in PCOS treatment. The therapeutic mechanism of exosomes in treating PCOS primarily involves the regulation of intracellular signaling pathways by bioactive molecules contained within exosomes, such as microRNAs. These molecules modulate the expression of target genes, thereby suppressing inflammatory responses and apoptosis, reducing oxidative stress (OS), and ameliorating metabolic dysfunction. It is important to note that, at present, exosome-based interventions for PCOS are supported exclusively by preclinical data obtained from rodent models and in vitro systems. No PCOS-specific Phase I trials or randomized controlled clinical studies have yet been completed, and exosomes should therefore be regarded as an emerging experimental strategy rather than an established therapy.

Basics of PCOS and Current Treatment Strategies

Diagnosis

PCOS is one of the most common causes of infertility in women of reproductive age;[15] nevertheless, its diagnosis is challenging owing to the diverse and heterogeneous nature of patient phenotypes.[16] Currently, three main criteria are commonly used to diagnose PCOS. The 1990 National Institutes of Health criteria include clinical and/or biochemical hyperandrogenism and chronic anovulation.[17] The 2004 Rotterdam Criteria state that PCOS can be diagnosed if two of the following three conditions are met: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and

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polycystic ovaries (PCOs).[18] In 2006, the Androgen Excess and Polycystic Ovary Syndrome Society defined PCOS as the presence of clinical and/or biochemical hyperandrogenism, oligoovulation, and/or PCOs.[16] PCOS is currently considered a diagnosis of exclusion. Regardless of the diagnostic criteria used, ruling out other etiologies with similar symptoms such as congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome is essential.

As research on PCOS expands, the limitations of the diagnostic criteria have become increasingly apparent. The higher number of follicles in younger women indicates that a significant proportion of healthy young women may be misdiagnosed with PCOS.[19] Therefore, reliable diagnostic standards are urgently needed. Serum anti-Müllerian hormone (AMH) is produced by small antral follicles. Therefore, serum AMH levels can be used as a substitute for antral follicle count in the diagnosis of PCOS and exhibit good specificity.[20–22] Moreover, by collecting and analyzing clinical data, artificial intelligence can be used to diagnose PCOS with high accuracy.[23] Early diagnosis of PCOS can significantly reduce the risk of long-term complications, more effectively preserve fertility, and improve the overall quality of life and long-term health outcomes.

Physiopathology

Endocrine Dysfunction

Endocrine dysfunction is a core feature of PCOS and involves imbalances in multiple hormonal systems. Among these, hyperandrogenism is the most significant and is characterized by elevated androgen levels. This leads to clinical manifestations, such as acne and hirsutism.[24] An imbalance in the hypothalamic–pituitary–ovarian axis plays a crucial role in endocrine dysfunction in PCOS. It causes a persistently rapid gonadotropin-releasing hormone (GnRH) pulse frequency, leading to increased luteinizing hormone (LH) synthesis and relatively decreased follicle-stimulating hormone (FSH) synthesis. Insufficient FSH impairs follicular development, resulting in the formation of PCOs. Meanwhile, elevated LH levels increase androgen production, which in turn reduces the hypothalamus's sensitivity to progesterone, creating a vicious cycle in PCOS. This dysregulation perpetuates the hormonal imbalance, further exacerbating PCOS.[25]

Insulin Resistance

Insulin resistance is a key feature of PCOS. Approximately 50–70% of women with PCOS exhibit insulin resistance, which leads to hyperinsulinemia.[2] High insulin levels overstimulate insulin-insensitive tissues, leading to an increased secretion of androgens by theca cells in the ovaries.[24] In addition, hyperinsulinemia can suppress the production of sex hormone-binding globulin (SHBG), further increasing the levels of free androgens in the blood.[26] This elevated androgen level is a core factor in the endocrine dysfunction of PCOS. This disrupts normal follicular development and prevents the transition of follicles from the primary stage to the mature stage, resulting in impaired ovulatory function. Women with PCOS often experience weight gain and abdominal fat accumulation. Abdominal adipose tissue secretes various cytokines during metabolism, which can impair insulin receptor function and exacerbate insulin resistance.[27]

Chronic Low-Grade Inflammation

Chronic low-grade inflammation is a key pathological feature of PCOS and has been identified recently as a crucial mechanism behind its onset and progression.[28] Patients with PCOS exhibit increased white blood cell count and elevated levels of inflammatory markers in the blood, such as serum C-reactive protein (CRP),[29] interleukin-6 (IL-6),[30] interleukin-18 (IL-18),[31] tumor necrosis factor-alpha (TNF-α),[32] monocyte chemoattractant protein-1, and macrophage inflammatory protein-1α.[33] Additionally, patients with PCOS often experience abdominal fat accumulation, and abdominal adipose tissue is a significant source of inflammatory responses.[34] Proinflammatory cytokines secreted by adipocytes (such as TNF-α, IL-6, etc.) play an important role in insulin resistance and metabolic abnormalities in PCOS. These inflammatory factors bind to insulin receptors, inhibit insulin action, and disrupt insulin signaling pathways, leading to insulin resistance.[35] This in turn promotes androgen secretion, further exacerbating the symptoms of PCOS.

Traditional Treatments for PCOS

Oral contraceptives produce exogenous hormones that suppress gonadotropin secretion from the pituitary glands. This regulates hormone levels and significantly alleviates the symptoms of hyperandrogenism.[36,37] Currently, commonly used

combined oral contraceptives (COCs) typically contain ethinylestradiol and anti-androgenic progestins (such as cyproterone acetate or drospirenone). These medications can both suppress excessive androgen production in the ovaries and increase plasma levels of SHBG, thereby reducing the concentration of free androgens in the blood and further alleviating symptoms associated with hyperandrogenism.[38] In addition, these oral contraceptives help regulate the menstrual cycle and reduce the risk of menstrual irregularities and endometrial hyperplasia.

For adolescents with obesity and PCOS, the first-line treatment includes lifestyle improvements, exercise, and dietary interventions. Therefore, weight loss and medical nutritional therapy are necessary.[39] Insulin resistance is a key factor in the treatment of PCOS. Metformin is the most commonly used drug and enhances insulin sensitivity in the liver, muscle, and fat cells.[40] Additionally, metformin alleviates hyperinsulinemia, which lowers androgen secretion and reduces hyperandrogenic symptoms in patients with PCOS.[41]

Ovulation-inducing drugs, particularly clomiphene citrate, act on the hypothalamus to inhibit the negative feedback of estrogen, thereby stimulating the release of follicle-stimulating hormone (FSH). This promotes follicular development and maturation and is commonly used to treat ovulatory dysfunction and infertility in patients with PCOS.[42] In addition, metformin may improve insulin resistance, indirectly modulate ovarian hormone secretion, and promote ovulation.[43] Compared with clomiphene citrate, aromatase inhibitors (such as letrozole) may improve live birth and pregnancy rates in anovulatory women with PCOS-related infertility.[44]

Overview of Exosomes

The various research advancements in PCOS indicate that exosome-based therapy is a promising therapeutic approach. As shown in Figure 2, exosomes are extracellular vesicles composed of lipid bilayer particles with diameters ranging from 30 nm to 150 nm. They share the same topological structure as the cells from which they originate.[45] They were first discovered in 1983.[46] Increasing research has shown that exosomes serve as carriers for intercellular communication, transporting various molecules such as RNA, proteins, and lipids, and playing crucial roles in both physiological and

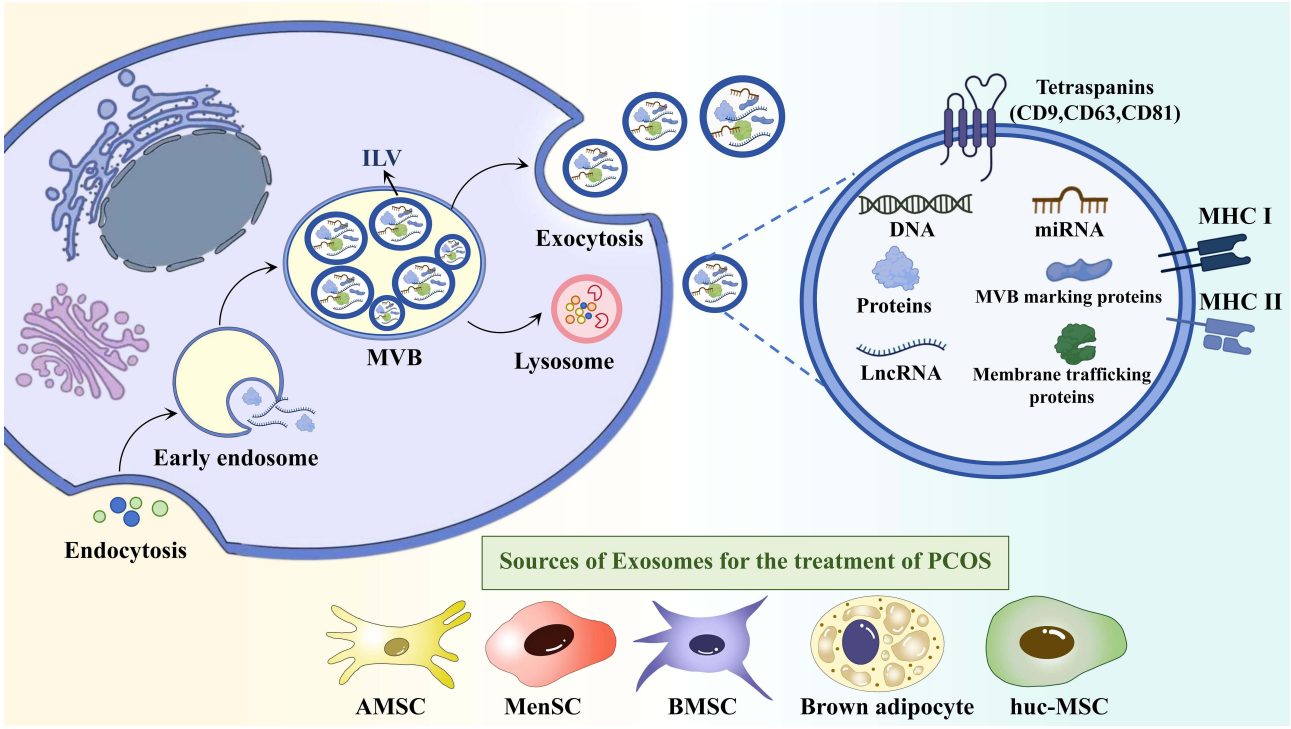

Figure 2 Biogenesis, payloads, and sources of exosomes. This diagram illustrates the process of exosome biogenesis and their therapeutic applications for PCOS treatment. It shows the formation of intraluminal vesicles (ILVs) within the early endosome, which mature into multivesicular bodies (MVBs). These MVBs fuse with the lysosome or undergo exocytosis, releasing exosomes containing therapeutic molecules such as DNA, miRNA, mRNA, proteins, and LncRNA. The diagram also highlights various sources of exosomes, including adipose-derived stem cells (AMSC), menstrual stem cells (MenSC), bone marrow stem cells (BMSC), brown adipocytes, and human umbilical cord mesenchymal stem cells (huc-MSC), for potential use in PCOS treatment.

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pathological processes.[47] Exosomes contain various types of RNA (such as messenger RNA, microRNA, non-coding RNA, ribosomal RNA, transfer RNA, small nuclear RNA, and long non-coding RNA) that play key roles in the progression of various diseases. Additionally, exosomes exhibit good stability under different storage conditions, leading to their recognition as novel biomarkers for early diagnosis and evaluation of disease outcomes.[48,49]

Exosomes also show promising potential for disease treatment. Exosomes are considered ideal drug delivery carriers because of their excellent biocompatibility, low immunogenicity, and unique ability to cross physiological barriers.[50] They can serve as gene delivery vehicles by transporting therapeutic RNA and DNA to target cells, thereby exerting therapeutic effects. Furthermore, exosomes can also bind to target cells through surface-specific molecular markers, enabling targeted drug delivery, reducing side effects, and enhancing drug efficacy.[51] With the recent rise in stem cell research, the paracrine function of stem cells has been discovered to be responsible for their regenerative potential.[52] Stem cell-derived exosomes possess therapeutic potential similar to that of stem cells but exhibit lower immunogenicity.[53] Stem cell-derived exosomes have demonstrated tremendous potential in the treatment of various diseases, especially CVDs,[54] neurodegenerative disorders,[47] liver diseases,[55] reproductive system diseases,[56] and cancer.[57]

The formation and release of exosomes are highly regulated multistep processes. The key stages include endocytosis, formation of MVBs, and the release of exosomes. Each stage is tightly regulated by molecular regulation.[58] Cells form early endosomes through endocytosis, after which the endosomal membrane buds inward to create intraluminal vesicles (ILVs), eventually forming MVBs. These vesicles are exosome precursors.[59] The ESCRT-dependent pathway is central to MVB formation. The ESCRT complex regulates inward budding of the endosomal membrane, facilitating the formation and maturation of ILVs.[60] The ESCRT system consists of several complexes, including ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III, and Vps4. ESCRT-0 recognizes ubiquitinated proteins on the outer membrane of the endosome, whereas ESCRT-I and ESCRT-II may initiate ILV budding. ESCRT-III plays a key role in separating intraluminal vesicles. The ESCRT-0 complex includes a hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) that recognizes and binds to phosphatidylinositol 3-phosphate on the endosomal membrane. HRS recruits the TSG101 protein from the ESCRT-I complex, and ESCRT-I, through ESCRT-II or ALIX, participates in the recruitment of ESCRT-III. Vps4, an ATPase, disassembles the ESCRT-III complex from the endosomal membrane by hydrolyzing ATP, completing the final separation of intraluminal vesicles.[61] Mature MVBs are regulated by the Rab GTPase family and transported to the cell membrane via the cytoskeletal system. Upon fusion with the plasma membrane, ILVs are released into the extracellular space to forming exosomes.[62]

Ultracentrifugation is the most commonly used method for exosome isolation. The samples were subjected to high-speed centrifugation, in which exosomes were precipitated owing to their unique density and size. Initially, low-speed centrifugation was performed to remove cells and cellular debris, followed by high-speed centrifugation of the exosome pellet. Finally, purified exosomes were resuspended in a buffer solution.[63]

After isolation, verification and identification are necessary to confirm the identity, quality, and purity of the isolated exosomes. The common methods for exosome characterization include transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA), and Western blotting.[64] TEM is the gold standard for the morphological identification of exosomes. Typically, exosomes appear as cup-shaped or bilobed disc structures with diameter of 30–150 nm, clear boundaries, and are free of contaminants. NTA utilizes the light-scattering and Brownian motion properties of particles to determine their size distribution in a suspension.[65] Western blot analysis is commonly used to detect surface marker proteins of exosomes, such as tetraspanins (eg, CD9, CD63, and CD81), ALIX, and TSG101. Additionally, the presence of endoplasmic reticulum protein Calnexin and Golgi protein GM130 must be absent to confirm the purity of the exosomes.[66]

Recently, stem cell-derived exosomes have shown remarkable potential in the treatment of various diseases, particularly in tissue repair, immune regulation, gene therapy, and targeted drug delivery.[67] Compared with mesenchymal stem cells (MSCs), exosome therapy does not require direct cell transplantation, reducing the risk of immune rejection and safety concerns. Compared with extracellular vesicle engineering (EV-engineering), natural exosomes are easier to prepare and can serve as an initial intervention, while engineered exosomes carrying specific therapeutic molecules allow precise treatment of particular pathological targets. CRISPR-loaded exosomes can deliver gene-editing tools to directly repair or knock out disease-causing genes, but they carry higher risks, including off-target effects and potential genomic instability. Although exosome therapy is still in the preclinical stage, stem cell-derived exosomes have shown broad

potential. Preclinical studies in cancer, neurodegenerative diseases, cardiovascular diseases, and reproductive system disorders have shown promising results. Moreover, exosomes' applications in drug delivery and gene therapy are expected to advance the development of precision medicine.[68]

Recent studies have demonstrated that exosomes derived from both stem cells and ovarian tissues play important roles in the pathological processes associated with PCOS. Wang et al reported that MSC-Exos combined with estrogen can synergistically alleviate inflammation and fibrosis by reducing the expression of TNF-α and TGF-β.[69] Jiao et al showed that exosomes released from human umbilical cord–derived mesenchymal stem cells (hUC-MSC-exos) not only indirectly reverse insulin resistance but also inhibit pancreatic β-cell apoptosis, highlighting their substantial potential in improving glucose metabolism and insulin sensitivity.[70] Additionally, the findings of Yamchi et al revealed that amniotic fluid–derived exosomes (AF-Exos) can restore baseline levels of several sex-related hormones in rats with premature ovarian insufficiency (POI), thereby ameliorating endocrine imbalance.[71] Moreover, ovarian-derived exosomes are also linked to PCOS-related pathological processes; however, unlike stem cell–derived exosomes, those originating from ovarian tissues tend to exacerbate disease progression. For instance, Li et al demonstrated that the follicular fluid–derived exosomal lncRNA LIPE-AS1 regulates steroid metabolism, leading to endocrine disruption and oocyte maturation arrest.[72] Similarly, Li et al reported that alterations in the expression of HSD17B1, CYP19A1, and CYP11A1 in follicular fluid exosomes can modify the steroid hormone profile, thereby impairing fertility.[11]

Mechanisms and Research Progress of Exosomes Therapy in PCOS

Exosomes Inhibit the Inflammatory Response by Blocking the Nuclear Factor Kappa B (NF-κB) Signaling Pathway

In patients with PCOS, elevated levels of inflammatory markers and mediators such as CRP, TNF-α, IL-6, IL-8, and IL-18 indicate chronic low-grade inflammation.[72] Local ovarian inflammation is closely linked to hyperandrogenism in PCOS, which results in impaired follicular development and reduced fertility.[73,74] Therefore, addressing inflammation in patients with PCOS plays a crucial role in restoring fertility. Current clinical trials have demonstrated that mesenchymal stem cell-derived exosomes can establish an anti-inflammatory microenvironment, alleviate chronic inflammation, and subsequently promote tissue repair and regeneration.[75] These findings support the clinical potential of exosomes in disease treatment through their anti-inflammatory effects.

The NF-κB signaling pathway is a crucial intracellular signaling cascade, extensively involved in regulating immune responses, inflammatory reactions, cell survival, proliferation, differentiation, and stress responses.[76] The NF-κB signaling pathway consists of multiple protein complexes, typically existing in dimeric forms, with the p65/p50 dimer being the most common. In the canonical activation pathway, inflammatory cytokines or infectious stimuli promote the degradation of IκB, thereby releasing NF-κB, which subsequently translocate into the nucleus to regulate the expression of genes associated with inflammation, immunity, and cell survival. The NF-κB signaling pathway plays a pivotal role in PCOS-related inflammation[77] and has also become an important target for improving inflammation in PCOS.[78]

Exosomes derived from human umbilical mesenchymal stem cells exert anti-inflammatory effects through the NF-κB signaling pathway.[79] In a study by Zhao et al, hUC-MSC-exos significantly suppressed the inflammatory response in ovarian granulosa cells from patients with PCOS. The underlying mechanism primarily involves blocking the NF-κB signaling pathway, reducing the nuclear translocation of p65, thereby decreasing the expression of pro-inflammatory cytokines TNF-α and IFN-γ, while upregulating the anti-inflammatory cytokine IL-10. This effect has also been confirmed in lipopolysaccharide-induced chronic inflammation models,[80] suggesting that exosomes may serve as a potential anti-inflammatory therapeutic strategy for alleviating PCOS-related inflammation.

Exosomes Alleviate Mitochondrial Dysfunction and Reduce OS

Mitochondria are closely related to cellular energy production and serve as the primary sites for aerobic respiration. Abnormal mitochondrial function can lead to systemic metabolic disorders. Mitochondrial dysfunction is a critical factor in type 2 diabetes, CVDs, and cancer, and is also closely associated with symptoms caused by PCOS, such as excessive androgen production, insulin resistance, chronic inflammation, and abnormal follicular development.[81] Mitochondrial

dysfunction in patients with PCOS is caused by mutations in mitochondrial genes, OS, and abnormalities in mitochondrial biogenesis.

Mitochondrial DNA (mtDNA) is a small segment of DNA located within mitochondria that encodes several key proteins required for mitochondrial function.[82] Since mtDNA lacks repair mechanisms similar to those of nuclear DNA, it is more prone to mutations. Mutations or defects in mitochondrial genes can lead to mitochondrial dysfunction, thereby affecting cellular energy production and metabolism and generating excessive reactive oxygen species (ROS), which can cause devastating damage to various cellular membranes and DNA, eventually triggering cell death.[83] Recent studies have summarized the mtDNA mutations identified in patients with PCOS, with 33 mtDNA mutations identified to be associated with PCOS.[84]

Under normal conditions, mitochondria generate ATP through OXPHOS; however, this process produces a significant amount of reactive oxygen species (ROS). Superoxide anion (O2–), hydroxyl radicals (OH–), peroxyl radicals (ROO), alkoxyl radicals (RO), and hydroperoxyls (HO2) are the most biologically important ROS.[85] ROS play a crucial role in cellular signal transduction; however, excessive ROS levels can lead to lipid peroxidation, protein modification, and DNA damage.[86] In PCOS, ROS accumulation affects the function of granulosa cells and oocytes, leading to arrest of follicular development, deterioration of oocyte quality, and anovulation.[87]

Mitochondrial biogenesis is significantly impaired in patients with PCOS.[81] Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a key transcriptional coactivator that regulates mitochondrial biogenesis and energy metabolism. PGC-1α promotes mitochondrial proliferation and functional maintenance by activating the transcription and replication of mitochondrial genes. In patients with PCOS, PGC-1α expression is often reduced, leading to restricted mitochondrial biogenesis.[88] Owing to the reduction in PGC-1α, mtDNA replication is suppressed, resulting in a decline in mitochondrial numbers. Thus, the cell's energy production capacity is limited, and in energy-demanding tissues such as the ovaries, a decrease in mtDNA content directly affects follicular development and oocyte quality.

Exosomes have shown great potential for alleviating OS in the mitochondria. They can mitigate granulosa cell damage by correcting mitochondrial OS, thereby preserving ovarian function.[89] These findings suggest a novel therapeutic approach for treating PCOS by improving mitochondrial function through exosome-based interventions. In the study by Mansoori et al, menstrual blood-derived stem cells and their exosomes reduce OS levels (as indicated by decreased MDA), upregulate PGC-1α expression, and increase mtDNA content, thereby promoting mitochondrial biogenesis and enhancing cellular energy metabolism.[90] However, it should be emphasized that current evidence directly showing that exosomes improve follicle development and oocyte quality by regulating mitochondrial function is still very limited. Most studies have been done in animals, and the lack of clinical trials means these effects cannot yet be confirmed in humans. More research is needed to clarify these mechanisms.

Exosomes Inhibit Cell Apoptosis

In the normal ovarian cycle, apoptosis helps eliminate immature, damaged, or outdated follicular cells, ensuring the health of the ovarian tissue, balance of hormone secretion, and proper follicular development.[91] In PCOS, apoptosis is dysregulated, particularly in the Granule cells (GCs), cumulus cells (CCs), and oocytes. Granulosa cells play a crucial role in maintaining ovarian function. On one hand, they supply oocytes with small-molecule nutrients such as amino acids and nucleotides; on the other hand, they receive signals from pituitary gonadotropins, indirectly regulating oocyte maturation and follicular development. When apoptosis is excessive, the number of granulosa cells decreases, leading to impaired follicular development and insufficient nutrients and signals for the oocyte, which may ultimately result in follicular atresia or arrest.[92] BAX (Bcl-2-associated X protein) is a pro-apoptotic protein that is activated when cells are exposed to stress signals. BAX can integrate into the mitochondrial outer membrane, increase its permeability, trigger the release of cytochrome C, activate downstream caspase family members, and ultimately initiate apoptosis. BCL-2 (B-cell lymphoma 2) is an anti-apoptotic protein that can inhibit BAX activation and prevent changes in mitochondrial membrane permeability, thereby protecting cell survival. In granulosa cells, an elevated BAX/BCL-2 ratio indicates that pro-apoptotic signals predominate, making the cells more prone to enter the apoptotic process. Bas et al have reported that the BAX/BCL-2 ratio in granulosa cells during the antral follicle phase was significantly elevated in the PCOS group, indicating increased apoptosis.[93] Research has summarized the abnormalities in apoptosis and related signaling pathways

in the ovaries of patients with PCOS, such as PI3K-Akt, TNF, NF-κB, and p53.[92] Therefore, regulating the process of apoptosis and reversing apoptotic abnormalities in PCOS provide new insights for the treatment of PCOS.

Zhao et al encoding miR-323-3p were used to transfect adipose-derived mesenchymal stem cells (AMSCs) to obtain exosomes enriched with miR-323-3p, which were then co-cultured with CCs from patients with PCOS. Thus, exosomes with upregulated miR-323-3p expression targeted the 3′UTR region of PDCD4, reducing its expression and thereby delaying the apoptosis process of CCs.[94] Exosomes can serve as carriers to inhibit PCOS-related cell apoptosis in rodent models and granulosa or cumulus cell cultures, which is associated with improved ovarian structural and functional parameters in these preclinical settings. These findings indicate a mechanistic potential to modulate ovarian function. Certain stem cell-derived exosomes also possess the ability to inhibit cell apoptosis. For example, in mouse ovarian cells treated with bone marrow mesenchymal stem cell-derived exosomes, the number of TUNEL-positive cells was significantly reduced,[95] and the apoptosis rate of granulosa cells from patients with PCOS markedly decreased after treatment with hUC-MSC-exos.[80] Additionally, exosomes derived from BMSCs, which are rich in miRNA-21, downregulated PTEN and PDCD4 expression, thereby inhibiting phosphamide mustard-induced GC apoptosis. This results in a beneficial therapeutic effect on chemotherapy-induced premature ovarian failure while also providing insights into the treatment of PCOS, which involves an imbalance in cell apoptosis.[81] These experiments still have limitations, as the molecular mechanisms by which exosomes inhibit cell apoptosis are not well understood. Most studies are limited to observing reduced granulosa cell apoptosis and improved ovulatory function. Therefore, further studies are needed to investigate how exosomes inhibit cell apoptosis at the molecular level in PCOS treatment.

Exosomes Regulate Angiogenesis in PCOS

Abnormal angiogenesis is commonly associated with many diseases, and clinical trials have demonstrated that stem cell-derived exosomes have the potential to regulate angiogenesis and improve endothelial cell function, thereby treating diabetes and its complications.[96] This provides a novel approach for correcting angiogenic abnormalities in PCOS.

Ovarian angiogenesis is a highly regulated process requiring the coordinated action of multiple angiogenic factors. Ovarian angiogenesis is essential for follicle maturation, ovulation, and corpus luteum formation: newly formed blood vessels supply follicles and oocytes with the nutrients, oxygen, and hormonal signals needed for growth and maturation; during ovulation, adequate blood flow supports follicle rupture and luteinization; and corpus luteum formation depends on sufficient vascular supply for progesterone secretion. Therefore, dysregulation of angiogenic factors may be closely associated with ovulatory dysfunction and reduced fertility in patients with PCOS.[97] Patients with PCOS exhibit an increased total ovarian 3D power Doppler flow index,[98] along with enhanced ovarian stromal angiogenesis.[99] Thus, the incidence of ovarian neovascularization in patients with PCOS may be higher.[100] The increased ovarian angiogenesis observed in patients with PCOS may seem beneficial at first, but in reality, the abnormally increased blood vessels are often associated with immature microvascular networks, follicular stromal inflammation caused by excessive secretion of angiogenic factors, and uneven blood distribution within the ovary, all of which negatively affect ovarian function. Therefore, improving angiogenesis in this population is a promising therapeutic approach. Several studies have focused on correcting ovarian angiogenesis disorders to alleviate PCOS symptoms.[101–103]

Exosomes carry therapeutic cargo, regulate the local tissue microenvironment, and normalise the angiogenesis.[104] Therefore, modulating angiogenic activity using exosomes to treat diseases has gained significant attention.[105] CD31, also known as platelet endothelial cell adhesion molecule-1, is an important cell surface glycoprotein belonging to the immunoglobulin superfamily. It is widely expressed in endothelial cells, platelets, megakaryocytes, and immune cells. CD31 is commonly used as a biological marker for endothelial cells.[106] Teng et al demonstrated that CD31 expression was significantly increased in the corpus luteum of ovaries in a PCOS mouse model, indicating abnormal angiogenesis. However, after treatment with bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos), CD31 expression was markedly reduced, showing the potential of exosomes to suppress excessive ovarian angiogenesis in PCOS and restore normal vascular growth.[95] It is worth noting that this study used a DHEA-induced rodent model of PCOS. This model is widely used to study hyperandrogenism and ovarian inflammatory changes, but it is essentially a simplified model of inflammation and hyperandrogenism. It does not reproduce the metabolic abnormalities observed in many patients with PCOS, especially insulin resistance. Therefore, when interpreting the effects of exosomes on angiogenesis, this model mainly reflects changes in the local ovarian microenvironment and may not fully represent the responses seen

in metabolic-type PCOS. This limitation highlights the need to test exosome therapy in PCOS models that better capture metabolic features, so that its therapeutic value can be assessed more comprehensively.

Exosomes Improve Metabolic Dysfunction in PCOS

PCOS is not only a reproductive system disorder but is increasingly being recognized as a metabolic disease.[107] Patients with PCOS often experience various types of metabolic dysfunction, with insulin resistance and subsequent hyperinsulinemia being the most significant. In addition, patients with PCOS may exhibit liver metabolic abnormalities,[108] adipose tissue dysfunction,[109] impaired glucose metabolism,[110] lipid metabolism disturbances,[111] and metabolic syndrome.[112]

In PCOS, metabolic abnormalities do not occur independently but form a complex network of mutual interactions and causal relationships. First, insulin resistance leads to hyperinsulinemia, which further stimulates the ovaries to produce excess androgens. Hyperandrogenism not only affects follicle development but also disrupts insulin signaling pathways by acting on adipose tissue and muscles, further exacerbating metabolic abnormalities, increasing visceral fat accumulation, and contributing to weight gain.[113] Insulin resistance also reduces the ability of tissues to efficiently utilize glucose, leading to elevated fasting blood glucose levels and impaired glucose tolerance.[114] Additionally, the decreased response of adipocytes to insulin promotes the release of free fatty acids, which stimulate triglyceride synthesis upon entering the liver, leading to dyslipidemia and further accumulation of visceral fat.[115] Moreover, visceral adipose tissue is a major source of inflammatory factors, with increased secretion of adipokines (such as leptin and adiponectin) and proinflammatory cytokines (such as TNF-α and IL-6), which contribute to chronic low-grade inflammation, worsening PCOS.[116]

Exosomes can regulate metabolic state, as shown in Figure 3. Exosomes exert anti-inflammatory, antioxidant, and lipid-regulating effects through the active molecules they carry, such as microRNAs and proteins, and improve insulin sensitivity to

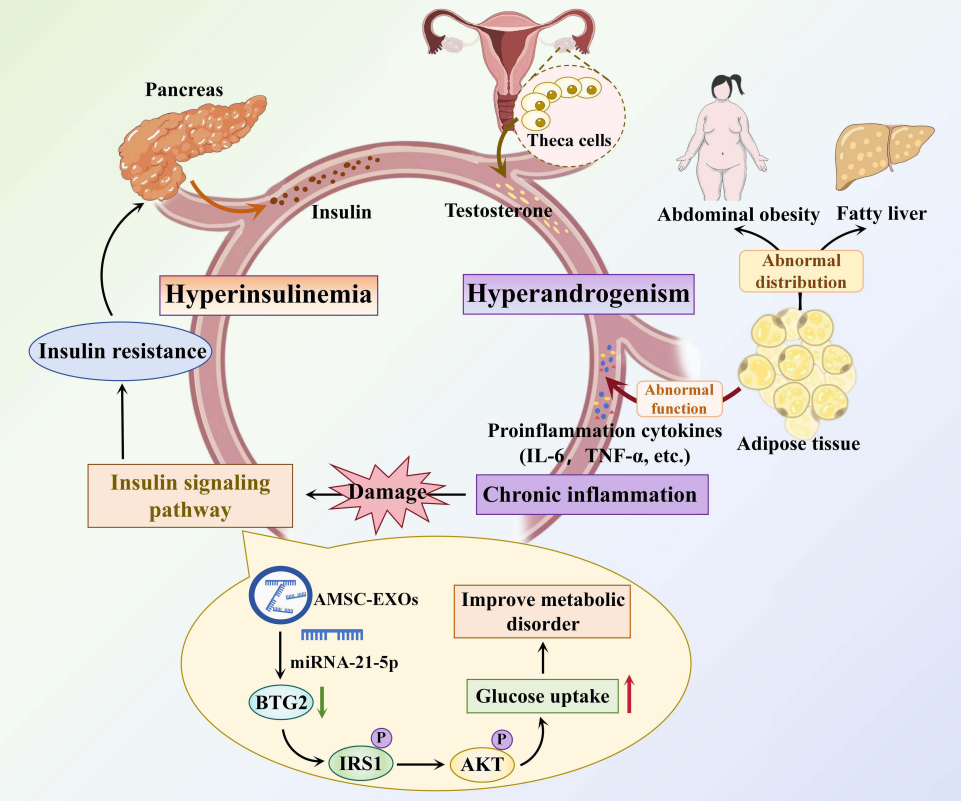

Figure 3 Exosomes improve the body's metabolic state by regulating signaling pathways. In patients with PCOS, insulin resistance promotes compensatory insulin secretion from the pancreas (black arrows indicate physiological or pathological directional relationships), leading to hyperinsulinemia. Elevated insulin (Orange arrows) stimulates ovarian theca cells, increasing androgen production and resulting in hyperandrogenism. Circulating excess androgens impair adipose tissue function, causing abnormal fat distribution—manifested as abdominal obesity and fatty liver—and inducing release of proinflammatory cytokines (IL-6, TNF-α, etc.), which further aggravate chronic inflammation. These inflammatory signals damage insulin signaling (red arrows highlight pathological aggravation), thereby worsening insulin resistance and forming a vicious cycle. The figure illustrates that exosomes alleviate insulin resistance by suppressing the expression of B-cell translocation gene 2 (Btg2) and activating the IRS1/AKT signaling pathway.

multiple targets.[117] Fang et al have demonstrated that brown adipose tissue-derived exosomes (BAT-Exos) effectively correct metabolic abnormalities and restore ovarian function by targeting the STAT3/GPX4 antioxidant pathway.[118] Similarly, Cao et al confirmed that adipose-derived mesenchymal stem cell exosomes (AMSC-Exos), enriched with miR-21-5p accumulated in the livers of PCOS rats, suppressed the expression of B-cell translocation gene 2, activated the IRS1/AKT pathway, enhanced hepatic metabolism, and improved metabolic dysfunction associated with PCOS.[119]

Recent studies on exosome-based therapies for PCOS have shown significant therapeutic effects in improving metabolic disorders. These effects mainly manifest as enhanced systemic metabolism, reduced body weight, lowered blood glucose levels, improved glucose tolerance and insulin sensitivity, alleviation of hepatic steatosis, and normalization of adipocyte size. However, these studies have some notable discrepancies. For example, treatment with AMSC-Exos did not significantly improve insulin resistance in rats with PCOS, whereas treatment with BAT-Exos markedly alleviated insulin resistance. Additionally, AMSC-Exo treatment did not significantly influence body weight, whereas other studies have reported considerable weight reduction following exosome therapy. These inconsistencies may be attributed to the different sources of exosomes, which directly determine the composition of the carried microRNAs, proteins, and signaling molecules, thereby affecting the type or strength of the regulated signaling pathways. Furthermore, variations in the methods used to establish PCOS models may contribute to these differences.[120] Therefore, an in-depth investigation of the molecular mechanisms underlying exosome therapy in PCOS is crucial to advance their clinical applications. The differences in therapeutic effects of exosomes from different sources suggest that, in the future, clinical trials could be conducted to evaluate efficacy by selecting appropriate exosome sources and designing specific targets based on the metabolic characteristics of PCOS patients.

Discussion

Women with PCOS had higher survival and reproductive abilities in ancient times, when their reproductive and nutritional conditions were poor.[121] With improved living conditions, PCOS has become a significant threat to women's health. The typical features of PCOS include elevated androgen levels, impaired ovulation, and ultrasound-detected polycystic ovarian morphology. In addition to hyperandrogenism and ovulatory dysfunction, patients with PCOS frequently exhibit insulin resistance, obesity, and metabolic syndromes. These individuals are at increased risk of developing type 2 diabetes mellitus and CVDs. Given the considerable heterogeneity in clinical manifestations among patients with PCOS, individualized therapeutic strategies tailored to specific metabolic and reproductive profiles are essential for effective management.

Current therapeutic strategies for PCOS primarily focus on lifestyle modifications and pharmacological interventions. The overall goals are to restore ovulatory function, alleviate the symptoms of hyperandrogenism, correct metabolic disturbances, and prevent long-term complications. For patients with PCOS with overweight and obesity, lifestyle interventions, such as dietary control, aerobic exercise, and weight reduction, are considered the first-line treatment because of their non-invasive nature, lack of side effects, and suitability for long-term management. Pharmacotherapy remains the cornerstone of PCOS treatment. Combined oral contraceptives are commonly used to regulate the menstrual cycle, and spironolactone is administered to mitigate hyperandrogenic symptoms.[122] Metformin is widely used to improve insulin resistance. For ovulation induction, clomiphene citrate or letrozole is often prescribed, and in cases of ovulatory failure, LOD may be considered.[123] In patients who do not respond to pharmacological ovulation induction or present with male factor infertility, in vitro fertilization combined with embryo transfer is recommended.[124] Novel therapeutic approaches for PCOS have recently emerged, including acupuncture,[125] probiotic-mediated gut microbiota modulation,[126] and exosome-based therapies.

As an emerging therapeutic strategy, exosomes have shown great potential in the treatment of various diseases in recent years, particularly in areas such as cancer and neurodegenerative disorders. Compared with conventional therapies, exosome-based treatments offer stronger targeting capabilities and can deliver multiple bioactive molecules simultaneously, thereby enhancing therapeutic efficacy while reducing systemic toxicity and side effects. Unlike traditional cell therapies or xenogeneic cell transplantation, exosomes have low immunogenicity and a reduced risk of immune rejection. Moreover, by selecting exosomes from specific cellular sources and engineering their cargo (such as miRNAs or proteins), personalized treatment strategies can be developed to target abnormal signaling pathways in specific patients. For example, weakened or disrupted PI3K-AKT signaling and reduced AMPK activity are core molecular mechanisms underlying insulin resistance. Exosomes can be used to target these pathways, enhancing insulin signaling, promoting

cellular energy metabolism, and improving fatty acid oxidation and glucose metabolism, making them suitable for treating PCOS patients whose symptoms are predominantly metabolic.

The therapeutic effects of exosomes vary across studies, which may be related to differences in their cellular sources and the molecules they carry. Exosomes contain bioactive molecules, such as miRNAs, proteins, and lipids, which are largely determined by the parent cell. Stem cells possess self-renewal and reparative capacities, and their exosomes—for example, those derived from mesenchymal stem cells—are rich in anti-inflammatory, anti-apoptotic, pro-angiogenic, and metabolic regulatory molecules. This may explain their superior efficacy in improving ovarian function and alleviating PCOS-related abnormalities. In contrast, exosomes from mature tissues or body fluids are more heterogeneous and may lack the necessary reparative or regulatory signals, generally serving as carriers for therapeutic molecules.

Exosomes can improve the ovarian microenvironment in PCOS models by reducing inflammation, inhibiting apoptosis, enhancing mitochondrial function, regulating angiogenesis, and limiting fibrosis. They can also improve systemic metabolic parameters in rodents by activating the PI3K–AKT pathway, increasing insulin sensitivity, and supporting liver and adipose tissue function. In these preclinical settings, such changes are associated with improved ovulatory function and partial normalization of endocrine and metabolic indices. However, whether similar short-, medium-, or long-term benefits (eg, restored ovulation, improved menstrual cycles and hyperandrogenic symptoms, or reduced metabolic and cardiovascular risk) can be achieved in women with PCOS remains unknown. Based on current evidence, exosome-based approaches are unlikely to replace conventional PCOS treatments; instead, they should be regarded as investigational, mechanism-enhancing adjuncts that may complement ovulation induction, assisted reproductive techniques, and metabolic therapies such as metformin, provided that future clinical trials confirm their safety and efficacy.

PCOS is a highly heterogeneous disorder, with patients showing different phenotypes such as lean PCOS, obese PCOS, insulin-resistant PCOS, and hyperandrogenic PCOS.[127] Because the underlying causes differ, exosome therapy may work differently in each type. In lean PCOS, ovulatory dysfunction is the main problem, and exosomes may help restore ovulation by improving the ovarian microenvironment. In obese and insulin-resistant PCOS, patients often have metabolic problems, inflammation in fat tissue, and insulin signaling issues.[128] Exosomes may improve insulin sensitivity through PI3K-AKT or AMPK pathways and help regulate liver and fat metabolism, indirectly supporting ovarian function. In hyperandrogenic PCOS, high androgen levels are the main issue, and exosomes may reduce local ovarian inflammation and adjust androgen-related signals, potentially easing symptoms.

Another important research direction in exosome therapy for PCOS is the choice of the administration route, as shown in Figure 4. Currently, the most common routes of administration are intravenous and ovarian injections. Intravenous injection delivers exosomes through the bloodstream, allowing their distribution to multiple organs such as the liver, fat, muscles, and ovaries. This route is more effective for treating metabolic abnormalities associated with PCOS, including insulin resistance and metabolic syndrome. However, this method suffers from an inadequate targeting. By contrast, ovarian injection directly delivers exosomes into the ovarian tissue or surrounding ovarian region, resulting in a significantly higher concentration of exosomes in the ovaries. This method offers greater targeting specificity and is effective in restoring normal ovarian function. However, studies on its effects on systemic metabolic disorders are limited.[129] Therefore, selecting an appropriate route of administration is a key aspect of personalized treatment.

Despite the promising potential of exosome-based therapies for PCOS, some challenges and limitations remain in translating this approach into clinical practice.[130] Exosomes have lower immunogenicity than cell transplants, but they are not completely risk-free. Exosomes from different sources may carry proteins or membrane antigens that could trigger immune reactions. Intravenously injected exosomes are often taken up by the liver and kidneys, which can lower their concentration at the target site, reducing effectiveness and possibly causing side effects in other organs. Local injections, such as into the ovary, improve targeting, but their effects on the whole body need more clinical study. Off-target effects are another concern. The miRNAs, proteins, or other molecules in exosomes can affect non-target cells. For example, when exosomes regulate the PI3K-AKT signaling pathway, they are intended to improve insulin sensitivity and metabolism in the ovaries or adipose tissue, but they may also affect the liver, heart, or muscle cells. This can abnormally activate or inhibit cell proliferation, apoptosis, and glucose or lipid metabolism, potentially leading to liver steatosis, cardiac myocyte hypertrophy, or skeletal muscle metabolic disorders. In addition, exosome preparation lacks standardized protocols. Exosomes from different sources or prepared using different methods vary in the types and concentrations of active molecules, which may

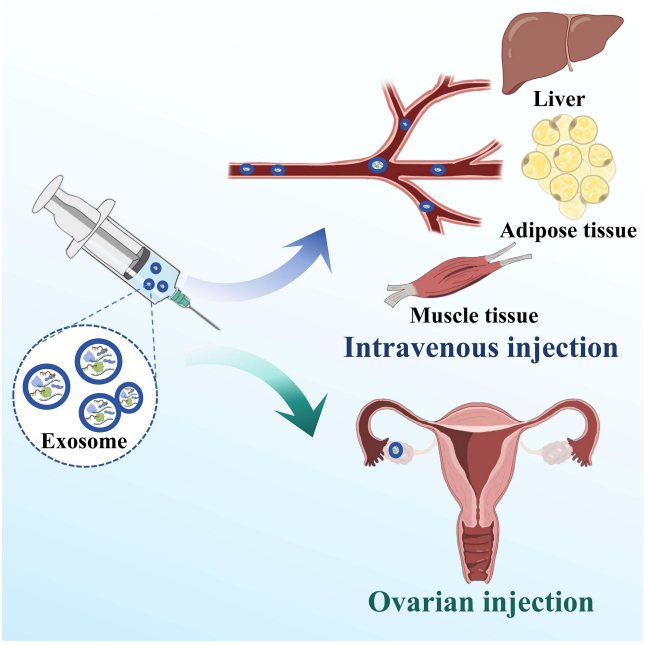

Figure 4 Comparison of Exosome Delivery Routes for PCOS Treatment. This diagram compares intravenous and ovarian injection routes for exosome delivery. Intravenous injection distributes exosomes systemically through blood circulation, targeting tissues such as the liver, adipose tissue, and muscle, which improves insulin resistance and metabolic syndrome but provides limited ovarian targeting. In contrast, ovarian injection delivers a higher local concentration to the ovary, improves the ovarian microenvironment, and restores ovulation, though it offers limited systemic metabolic improvement.

further increase the risk of affecting non-target tissues. Therefore, in the study and clinical application of exosome therapy for PCOS, careful evaluation of in vivo distribution and off-target effects is essential to ensure safety and control.

The clinical application of exosomes is not only limited by uncertainties regarding their safety, in vivo distribution, and off-target effects, but also faces significant challenges in production and regulation. Current isolation techniques include ultracentrifugation, ultrafiltration, precipitation, immunoaffinity capture, and size-exclusion chromatography, each of which yields exosomes with varying purity and quantity. The lack of standardized good manufacturing practices for exosome processing and characterization remains a major obstacle to their clinical translation. For example, ultracentrifugation may break some exosomes or cause proteins to clump together, while immunoaffinity capture, though very specific, may collect exosomes from only certain subgroups, making the results less representative. Encouragingly, an increasing number of studies are focusing on improving and standardizing exosome production, isolation, and downstream purification.[10] In addition, as a novel biological product, the clinical application of exosomes is also limited by regulatory barriers, including complex approval procedures, lengthy review processes, and a lack of clear guidelines. Addressing these production and regulatory issues is crucial for the safe and effective clinical application of exosome therapies.

Future research should systematically investigate how exosomal heterogeneity influences therapeutic outcomes in PCOS. Specifically, studies are needed to compare exosomes derived from different cellular sources, isolated through distinct purification methods, or produced under varying culture conditions, as these factors markedly affect their molecular cargo and biological activity. Additionally, the disease status of the donor tissue may alter exosome composition and function, potentially leading to differential therapeutic efficacy. Addressing these dimensions of heterogeneity will be essential for identifying the most effective exosome populations, optimizing manufacturing protocols, and ultimately advancing exosome-based therapies toward clinical translation in PCOS.

Conclusion

Exosomes show promising potential as an emerging, mechanism-based adjunctive strategy for the management of PCOS. Preclinical studies indicate that exosomes can improve ovarian function by reducing chronic low-grade inflammation, enhancing mitochondrial function, inhibiting apoptosis, and regulating ovarian angiogenesis, and can modulate key

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signaling pathways to increase insulin sensitivity and correct metabolic abnormalities. However, these findings are derived exclusively from rodent models and in vitro experiments, and PCOS-specific Phase I trials or randomized controlled clinical studies are currently lacking. In addition, major challenges remain, including uncertainties regarding long-term safety, immunogenicity, biodistribution, and off-target effects, as well as insufficient standardization of GMP-grade production and quality control. Future efforts should prioritize rigorous pharmacokinetic and toxicological evaluation, followed by well-designed early-phase clinical trials and randomized controlled studies, to determine whether exosome-based therapies can be safely and effectively translated into clinical practice for women with PCOS.

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Disclosure

The author(s) report no conflicts of interest in this work.

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