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Fundamental mechanisms of cell death for polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of childbearing age with complex symptoms and multiple hormone imbalances. Patients usually present with irregular menstruation, ovarian cysts, and metabolic abnormalities. Current research has been found that multiple cell death programs may be involved in the occurrence of the disease. This article focuses on the mechanism between PCOS and six cell death processes including apoptosis, autophagy, ferroptosis, pyroptosis, NETosis and necroptosis. Ovarian granulosa cell apoptosis, autophagy, and ferroptosis play key roles in PCOS. In addition, pyroptosis and NETosis may also be involved, but the specific mechanism needs further study. In general, a deeper understanding of these cell death mechanisms will help develop innovative treatments for PCOS.

1. Introduction

The history of cell death research can be traced back to the embryonic period of modern biology [1,2]. Scientists have gradually discovered that cell death is a highly regulated biological process. Among them, apoptosis, as the most classic form of programmed death, has completely changed our understanding of cell fate [3]. When a cell initiates the apoptotic program, it undergoes characteristic morphological changes: cell shrinkage, chromatin condensation, and eventually decomposition into apoptotic bodies that are cleared by neighboring cells or professional phagocytes. In the early 21st century, scientists discovered a unique iron-dependent death mode - ferroptosis. Unlike apoptosis, ferroptosis is more like an“oxidative disaster”of cells. When iron ion accumulation in cells triggers lipid peroxidation, the cell membrane system will suffer fatal damage. This mode of death is tightly connected to a range of metabolic irregularities, especially dysfunction of the glutathione system [4,5]. Autophagy, the breakdown of cellular components by lysosomes [6]. Pyroptosis, a form of inflammatory cell death triggered by infection or cellular stress [7]. Furthermore, several additional cell death programs have surfaced, such as NETotic cell death [8] and necroptosis [9]. These cell death processes are regulated by a complex regulatory network consisting of key molecules represented by the caspase protease family and the Bcl-2 protein family [10–13]. When this system loses balance, it may cause major diseases such as tumors and autoimmune diseases [14,15]. Therefore, analyzing the mechanism of cell death is not only of theoretical significance, but also can provide new targets for disease treatment (see Table 1).

Polycystic ovary syndrome (PCOS) is a common endocrinopathy occurring in reproductive-age women [16]. Hyperandrogenism, polycystic ovaries, chronic anovulation, and metabolic aberrations are the common features in PCOS [17,18]. The development of PCOS is complex, influenced by a mix of genetic and environmental factors [19–24]. Recent research suggests that dysregulated cell death processes may serve as a critical link among these contributing factors. For instance, increased follicular atresia appears to be associated with imbalanced apoptosis; impaired autophagy may hinder normal follicular development; and insulin resistance may further disrupt these cellular pathways. Together, these disturbances contribute to ovarian dysfunction and are closely associated with metabolic abnormalities. A deeper understanding of the molecular mechanisms behind PCOS could offer valuable insights into its pathogenesis and open new avenues for clinical intervention.

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Table 1
Definition of cell death and its pathogenesis in PCOS.

Cell death	Year	Definition	Pathogenesis in PCOS	Reference NOS
Apoptosis	1972	Apoptosis is currently best identified by a series of morphological changes in dying cells.	The regulation of GCs' growth and apoptosis during follicular development in the ovarian follicles relies heavily on the crucial involvement of the PI3K/Akt pathway, as well as downstream pro-apoptotic genes such as FOXO1, Bax, caspase-9, and caspase-3.	[3,50,51]
Autophagy	1963	Autophagy is a highly conserved eukarytotic cellular recycling process. Through the degradation of cytoplasmic organelles, proteins, and macromolecules, and the recycling of the breakdown products, autophagy plays important roles in cell survival and maintenance.	The abundance of autophagy-related genes ATG5, ATG7, BECN1 mRNA and the ratio of autophagy marker protein light chain 3B II/I (LC3 II/I) were significantly increased whereas the abundance of the autophagy substrate SQSTM1/p62 was decreased in ovarian granulosa cells from PCOS patients.	[6,61–64]
Ferroptosis	2012	Ferroptosis is dependent upon intracellular iron, but not other metals, and is morphologically, biochemically, and genetically distinct from apoptosis, necrosis, and autophagy.	The quantity and location of polyunsaturated fatty acids (PUFAs) in PCOS determine the extent of lipid peroxidation within cells, and to some extent, determine ferroptosis. The role of iron metabolism in regulating ferroptosis has gained significant attention in recent studies investigating ferroptosis-mediated therapy for PCOS.	[4,5, 80–82]
Pyroptosis	2001	Cell pyroptosis is a programmed cell death characterized by a highly inflammatory response.	TLR4, IL-6 and IL-1β levels in hyperandrogenism-induced PCOS-like mice were highly increased, moreover, pyroptosis factors such as NLRP3, ASC, caspase-1, GSDMD, IL-1β and IL-18 in the ovary were activated by LPS.	[88, 104–106]
NETosis	2004	NETosis is a form of regulated cell death that involves the release of neutrophil extracellular traps by neutro	Research has shown that women with PCOS have increased levels of neutrophils and inflammatory cytokines, which are involved in the process of NETosis. Some studies have proposed that NETosis may contribute to the inflammatory environment observed in PCOS.	[109,120, 121]
Necroptosis	2005	Necroptosis is a regulated form of necrotic cell death that serves as an alternative to apoptosis, particularly when apoptotic pathways are inhibited.	As a result, the simultaneous necroptosis of GCs and oocytes contributes to follicular atresia, a hallmark of PCOS-related ovarian dysfunction. Moreover, elevated levels of ROS and pro-inflammatory cytokines have been shown to upregulate RIPK1 and RIPK3 expression in GCs, further amplifying necroptotic signaling pathways	[9,127]

2. Cell death and PCOS

2.1. Apoptosis and PCOS

Under steady-state conditions, caspase-dependent apoptosis accounts for approximately 90 % of cell turnover. Its homeostatic role is closely related to its non-inflammatory properties [25,26]. These pathways are activated by different types of death signals and exhibit distinct molecular mechanisms. The extrinsic pathway, also known as the death receptor pathway, is initiated by external signals binding to specific cell surface receptors [27–29]. In contrast, the mitochondrial pathway is more like the cell's "internal monitoring system ". When internal crises such as DNA damage occur, members of the pro-apoptotic protein Bcl-2 family break the balance with anti-apoptotic proteins [30,31]. This change causes mitochondria to release cytochrome *c*, which in turn activates the caspase cascade and completes programmed cell death. Sheena L.P. et al. identified three major regulatory mechanisms that orchestrate granulosa cell (GC) apoptosis: growth factors that increase cyclic AMP (cAMP) levels, which can promote apoptosis via granzyme B; mitochondrial pathways modulated by Bcl-2 family proteins, such as Bax and Bcl-2, that determine mitochondrial membrane integrity; and death receptor–mediated signaling triggered by TNFα and FasL-Fas interactions [32]. These pathways can be activated at multiple stages of follicular development, highlighting the central role of apoptosis in maintaining ovarian follicle homeostasis and regulating follicular atresia.

Given the importance of apoptosis in follicular dynamics, its dysregulation can have profound implications in reproductive disorders such as PCOS. Granulosa cells are essential somatic cells that support oocyte maturation within the ovarian follicles. Among women diagnosed with PCOS, an increased number of follicular cysts is often observed [33,34]. These cysts are thought to arise from impaired follicular maturation, potentially resulting from altered granulosa cell function [35,36]. Indeed, several studies suggest a reduction in GC apoptosis in PCOS, which may contribute to the persistence of immature follicles and the development of polycystic ovarian morphology [37–40]. Furthermore, oxidative stress (OS) has been identified as a key pathological factor exacerbating GC dysfunction in PCOS. OS results from an imbalance between reactive oxygen species (ROS) and antioxidant defenses. Elevated ROS levels in PCOS patients may be attributed to hormonal imbalances such as reduced estrogen and progesterone levels. ROS overproduction can lead to mitochondrial damage and trigger intrinsic

apoptotic pathways [41–44]. The PI3K/Akt signaling pathway plays a crucial role in regulating granulosa cell growth and apoptosis during folliculogenesis. Downstream apoptotic regulators, including FOXO1, Bax, caspase-9, and caspase-3, are critically involved in this process [45–47]. Among them, Bcl-2 serves as a key anti-apoptotic molecule. It forms homodimers that stabilize the mitochondrial membrane potential (MMP); however, under apoptotic stress, heterodimerization with Bax reduces MMP, increases mitochondrial permeability, and promotes cytochrome *c* release, thereby activating caspases [48,49]. Studies have demonstrated altered expression of these key factors in PCOS patients, including elevated levels of pro-apoptotic FOXO1, Bax, caspase-9, and caspase-3, as well as decreased expression of PI3K, Akt, and Bcl-2 [50,51]. Taken together, these findings underscore that both insufficient apoptosis and excessive apoptosis can disrupt follicular development. Apoptotic mechanisms, operating at all stages of folliculogenesis, are crucial for maintaining a balance between follicle survival and atresia. Disruption of these finely tuned processes may lead to follicular arrest, anovulation, and the characteristic polycystic morphology observed in PCOS.

2.2. Autophagy and PCOS

Autophagy is an important process for cells to maintain homeostasis, and its initiation is like a carefully choreographed molecular ballet. When cells sense nutrient deprivation, the inhibitory effect of the mTOR pathway is released, and the ULK complex including ULK1/2, ATG13 and other proteins is activated [52,53]. This key "start switch" recruits the PI3K complex composed of Beclin 1 and VPS34 to generate PI3P phospholipid molecules on specific membrane structures, laying the foundation for subsequent steps [54]. As the process progresses, the cell will form a unique cup-shaped structure - the phagophore. The maturation of this structure depends on two major protein modification systems: ATG12-ATG5-ATG16L1 complex system and LC3 protein lipidation system. It is particularly worth mentioning that LC3-II is like a "molecular tag" of the autophagosome, which not only promotes the extension of the membrane structure, but also selectively identifies the substances to be degraded through receptor proteins such as P62 [55–57]. These receptors can specifically mark damaged organelles or misfolded proteins to ensure that they are accurately transported to the autophagosome. Finally, the mature autophagosome fuses with the lysosome to form an autophagolysosome. This critical step requires the precise coordination of multiple proteins such as syntaxins and Rab GTPases [58]. Under the action of lysosomal enzymes, the encapsulated "cellular garbage"is completely degraded, and the released nutrients re-participate in cell metabolism, helping cells cope with various stress environments.

Building upon this fundamental role, recent research has increasingly linked dysregulated autophagy to reproductive disorders, particularly PCOS. Studies have found that there is an abnormal increase in autophagic activity in the granulosa cells of PCOS patients. This may lead to excessive degradation of essential cellular components, thereby impairing cell viability and function [59,60]. By comparing and analyzing the ovarian granulosa cells of PCOS and non-PCOS patients, the researchers found that the expression profile of autophagy-related genes changed: ATG5, ATG7 and BECN1 mRNA levels were significantly increased, the autophagy marker protein LC3 II/I ratio increased, and the autophagy substrate SQSTM1/p62 protein level decreased [61]. Moreover, HMGB1 levels in serum and follicular fluid of PCOS patients with combined insulin resistance are significantly increased [62,63], suggesting that it may be involved in the development of insulin resistance and related inflammatory responses. In-depth studies have found that HMGB1 plays an important regulatory role in the autophagic activity of ovarian granulosa cells. Specifically, it increases the ratio of LC3B-II to LC3B–I, increases the expression level of ATG7, and reduces the content of SQSTM1 protein [64]. Animal model studies provide more in-depth insights into the pathogenesis of PCOS. Xing Y et al. found that the PCOS rat model induced by testosterone propionate (TP) showed that the expression levels of Beclin-1 and LC3 were significantly increased. After intervention with Guizhi Yikun Formula (GZYKF), the increase of Beclin-1 induced by TP was significantly inhibited [65], which indicate that GZYKF may inhibit the autophagy process by activating the TP53-AMPK signaling pathway and upregulating mTOR expression. Thus, autophagy dysregulation may interfere with follicular development by disrupting the signaling of key hormones such as insulin and androgens. These changes lead to increased follicular atresia and ovulatory dysfunction. It is worth noting that OS, as an important feature of PCOS, forms a complex interaction network with autophagy regulation: the increased ROS level in PCOS patients is accompanied by a decrease in antioxidant capacity, and autophagy dysfunction leads to the obstruction of the clearance of ROS-producing organelles, thus forming a vicious cycle of oxidative stress damage, insulin resistance and hyperandrogenism [66,67]. In conclusion, the amassed evidence underscores the significance of autophagy in the disrupted physiology observed in PCOS conditions [Fig. 1].

2.3. Ferroptosis and PCOS

Research on ferroptosis has made significant progress since it was discovered in 2012. This unique cell death mode relies on iron-mediated lipid peroxidation, and its regulatory network involves multiple key metabolic links [68]. Iron plays a central role among the major drivers of ferroptosis. It can participate in Fenton reactions, generating ROS and initiating lipid peroxidation. Transferrin receptor 1 (TFRC) and divalent metal transporter 1 (DMT1) are involved in iron uptake, while ferroportin (FPN) exports iron out of the cell [69,70]. Once inside the cell, iron catalyzes the formation of lipid hydroperoxides from polyunsaturated fatty acids (PUFAs) in the cell membrane, leading to disruption of membrane integrity and eventual cell death [71]. Glutathione (GSH) is a key weapon for cells to fight oxidative damage, and it can effectively neutralize ROS. However, when GSH stocks are low, whether synthesis is reduced or consumption is increased, it will damage the ability of cells to resist lipid peroxidation, leading to ferroptosis [72]. Glutathione peroxidase 4 (GPX4) is an enzyme that utilizes GSH to detoxify lipid hydroperoxides. When GPX4 is inhibited, these lipid peroxides accumulate in the cell, eventually triggering ferroptosis [73]. A key upstream regulator of GSH synthesis is the xc-antiporter system, which transports cystine into the cell in exchange for glutamate. Once cystine enters the cell, it is reduced to cysteine, an important precursor for GSH biosynthesis. Dysfunction or inhibition of the xc-system limits the availability of cysteine, thereby hindering GSH production and making cells more sensitive to ferroptosis [74]. Beyond metabolic pathways, several redox signaling networks also influence ferroptosis susceptibility. For instance, the Nrf2-Keap1 pathway modulates the expression of antioxidant and iron-regulating genes. Similarly, the tumor suppressor protein p53 has emerged as a key player in ferroptosis regulation by altering the transcription of genes involved in iron metabolism and redox homeostasis [75,76].

The significance of ferroptosis extends beyond cell death, playing a pivotal role in disease contexts where OS is a contributing factor. This is particularly relevant in the female reproductive system, where maintaining a balance between ROS and antioxidants is crucial for normal physiological function. Disruption of this equilibrium either through excessive ROS generation or antioxidant depletion has been implicated in the pathogenesis of various obstetric and gynecological disorders [77,78]. A notable example is PCOS, where nearly half of patients are overweight and exhibit elevated levels of circulating free fatty acids, including arachidonic acid—a PUFA that alters mitochondrial distribution and increases ROS generation [41]. These metabolic imbalances heighten oxidative stress, thereby promoting lipid peroxidation. Under normal physiological conditions, the processes of oxygen radical reactions and lipid peroxidation are dynamically regulated, maintaining homeostasis in cellular, biochemical, and immune functions [79].

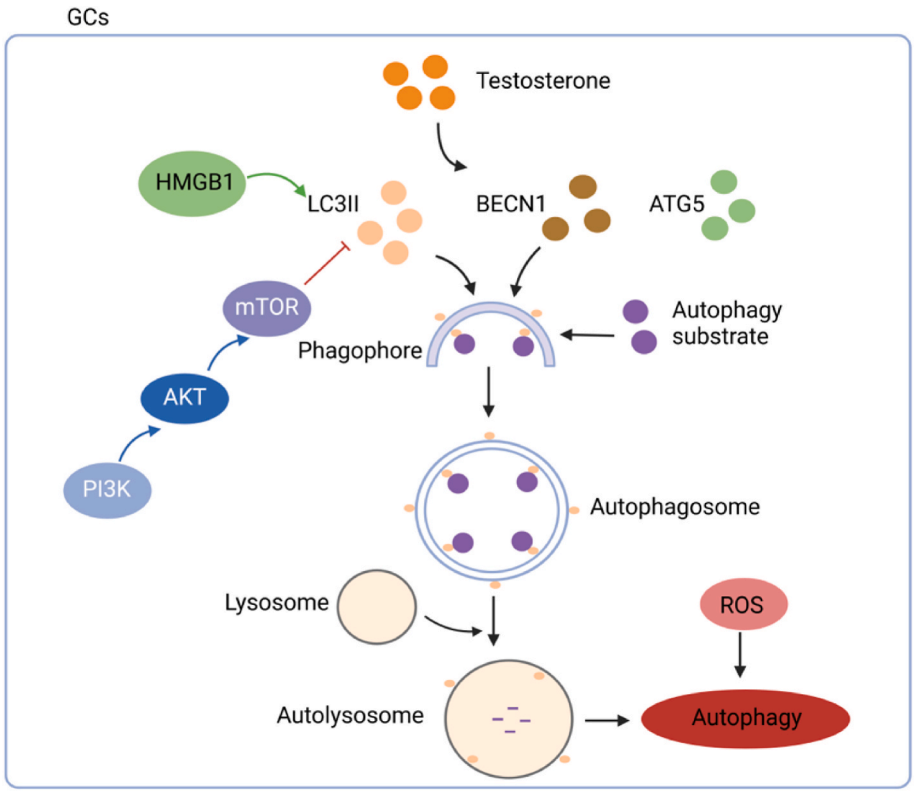

Fig. 1. Autophagy and PCOS
The levels of autophagy-related genes, such as ATG5, ATG7, and BECN1 mRNA, were significantly increased in granulosa cells of PCOS patients, as were the proportions of the autophagy marker protein light chain 3B II. The autophagosomes was formed with phagocytes and autophagy substrates.

However, excessive ROS can oxidize membrane-bound PUFAs and nucleic acids, producing lipid peroxidation byproducts such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE). These reactive species compromise membrane fluidity and permeability, eventually altering cell structure and function [80–82]. The quantity and location of polyunsaturated fatty acids (PUFAs) in PCOS determine the extent of lipid

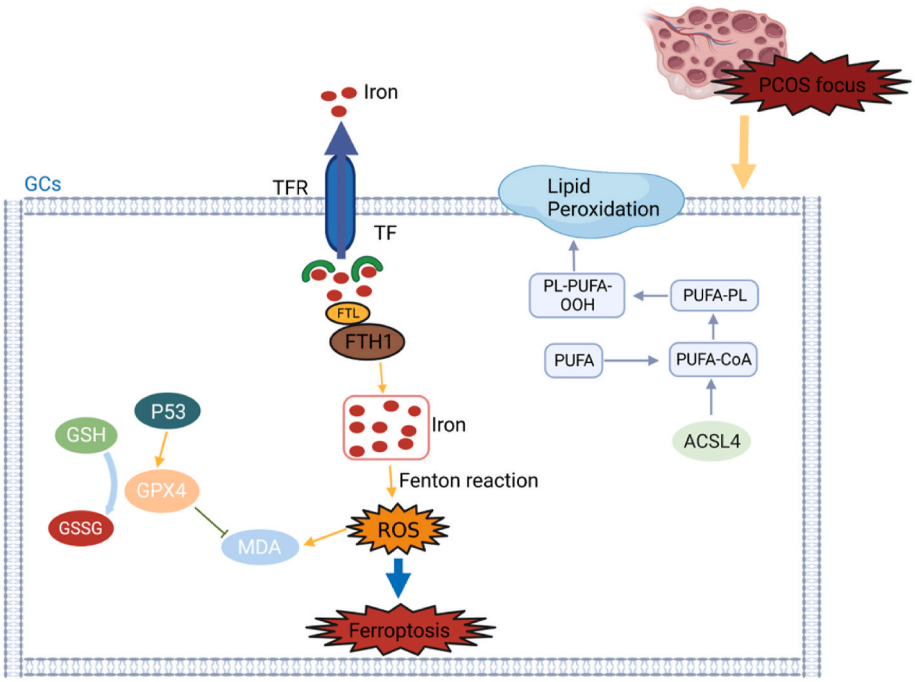

Fig. 2. Ferroptosis and PCOS
Total free fatty acid levels are elevated in PCOS patients, and the amount and location of polyunsaturated fatty acids (PUFA) determine the degree of intracellular lipid peroxidation and, to a certain extent, ferroptosis.

peroxidation within cells, and to some extent, determine ferroptosis. The role of iron metabolism in regulating ferroptosis has gained significant attention in recent studies investigating ferroptosis-mediated therapy for PCOS. A clinical study involving 149 women with PCOS and 108 healthy controls demonstrated significantly higher serum ferritin levels in the PCOS group, independent of obesity status, indicating the presence of systemic iron overload in these patients. Ovulatory dysfunction, a hallmark of PCOS, often leads to delayed menstruation, light menstrual flow, or even amenorrhea. Since regular menstruation is one of the primary mechanisms for iron loss in women of reproductive age, disruptions in menstrual patterns may contribute to iron retention. Indeed, studies have shown a correlation between elevated serum ferritin levels and the severity of menstrual irregularities in PCOS, suggesting that impaired menstrual blood loss may be associated with increased iron stores [83,84]. Moreover, the compensatory hyperinsulinemia seen in insulin-resistant PCOS patients may enhance tissue iron uptake and inhibit iron release from macrophages [85], further contributing to systemic iron overload. Iron overload can further disrupt glucose metabolism, exacerbate metabolic disorders, and worsen insulin resistance or hyperinsulinemia. These effects enhance the sensitivity of ovarian cells to luteinizing hormone (LH), disrupt the normal ovulation process, and may affect embryo implantation [86,87]. These interrelated mechanisms not only reveal the potential role of ferroptosis in the pathogenesis of PCOS, but also provide new ideas for therapeutic intervention [Fig. 2].

2.4. Pyroptosis and PCOS

Pyroptosis is a form of RCD driven by the activation of inflammasome, which is morphologically distinct from apoptosis. It has attracted much attention due to its association with innate immunity and disease [88–91]. In response to infection, cellular stress, or activation by specific signaling pathways, inflammasomes are assembled within the cytoplasm. These complexes typically consist of sensor proteins such as NLRP3, adaptor proteins, and the effector enzyme caspase-1 [92–94]. Once the inflammasome is formed, caspase-1 becomes activated and begins cleaving several target proteins, including the inactive precursors of pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). Caspase-1 processes these precursors into their active forms, which are then released from the dying cell. These cytokines, in turn, initiate a strong inflammatory response and attract immune cells to the site of cell death [95,96]. Concomitantly, caspase-1 also cleaves gasdermin D (GSDMD), releasing its N-terminal domain, which oligomerizes to form pores in the plasma membrane. This pore formation causes rapid cell swelling, membrane rupture, and the release of intracellular contents into the extracellular space—hallmarks of pyroptosis that further amplify inflammation and signal immune cell recruitment [97]. In conclusion, cell pyroptosis is integral to host immunity against microbial infections, as it helps to eliminate infected cells and initiate an inflammatory response [98–100]. However, excessive or dysregulated pyroptosis can contribute to various inflammatory diseases, including sepsis, inflammatory bowel disease, and neurodegenerative disorders [101,102].

Recent research has highlighted the relevance of pyroptosis in reproductive disorders, particularly in PCOS. Persistent hyperandrogenemia of PCOS promotes local inflammatory activation of the ovary, and the imbalanced inflammatory microenvironment leads to pyroptosis of GCs, further including a series of pathologies including follicular dysfunction and ovarian interstitial cell fibrosis [103]. These findings establish a potential mechanistic link between chronic inflammation and reproductive impairment in PCOS. Further supporting this connection, numerous studies have demonstrated elevated levels of inflammatory markers and mediators-such as CRP, TNF-α, IL-6, IL-8 and IL-18 in patients with PCOS. These cytokines are key mediators of the inflammatory response, and their elevated levels further support the involvement of systemic inflammation in the pathogenesis of PCOS [104]. Under normal physiological conditions, tissue remodeling and controlled inflammation are essential for ovarian folliculogenesis. However, excessive or dysregulated inflammation can disrupt normal follicular development [105]. Notably, previous studies have observed significantly elevated expression of pyroptosis-related genes and proteins—such as caspase-1, NLRP3, and the cleaved form of gasdermin D (GSDMD-N)—in granulosa cells from PCOS patients. These molecular signatures confirm the activation of the NLRP3 inflammasome in PCOS and its central role in triggering pyroptotic cell death. Once activated, the NLRP3 inflammasome facilitates cleavage of pro-caspase-1 into its active form, leading to the maturation and release of IL-1β and IL-18, as well as the cleavage of GSDMD and subsequent pore formation in the cell membrane [106]. Although NLRP3 serves physiological roles in normal follicular development, its chronic or excessive activation has been implicated in the development of polycystic ovaries and the deterioration of ovarian function [107]. For instance, a study by Cai et al. reported significantly elevated levels of GSDMD and caspase-1 in the ovaries of PCOS model mice, along with evident pyroptosis of granulosa cells cultured in vitro—a process initiated by caspase-1 activation [108]. Building upon this, Wang et al. were the first to demonstrate that pyroptosis mediated via the NLRP3/GSDMD/caspase-1 axis leads to substantial granulosa cell loss in PCOS [103]. This finding underscores the pathological importance of inflammasome-induced pyroptosis in the depletion of functional ovarian cells. Importantly, inflammasome activation and the ensuing pyroptotic cascade not only damage local ovarian tissue but also amplify systemic inflammation. When sustained over time, this creates a vicious cycle: inflammation promotes pyroptosis, which further exacerbates the inflammatory response, ultimately impairing ovarian function and accelerating the progression of PCOS. Therefore, targeting the pyroptosis pathway may hold therapeutic potential for breaking this cycle and restoring reproductive health in affected individuals.

2.5. NETosis and PCOS

NETosis constitutes a regulated cell death mechanism noted for the liberation of neutrophil extracellular traps (NETs)by neutrophils, which are a type of white blood cell [109]. Neutrophils serve as integral elements of the immune system, pivotal in safeguarding the body against microbial infections. As a defense mechanism, NETosis is initiated when neutrophils encounter certain stimuli, such as pathogens, inflammatory signals, or immune complexes. When stimulated by external factors, neutrophils are activated and undergo a series of significant morphological changes: first, the DNA in the nucleus depolymerizes, and the nuclear membrane disintegrates, causing the nuclear contents to mix with the cytoplasm; then, these depolymerized chromatin binds to a variety of antimicrobial proteins such as histones, neutrophil elastase, and myeloperoxidase, eventually forming a mesh of neutrophil extracellular traps (NETs). After these special mesh structures are released outside the cells, they can not only serve as a physical barrier to capture pathogenic microorganisms, but also directly kill pathogens through a variety of antimicrobial proteins attached to their surface, showing a unique dual defense mechanism [110–113]. Therefore, NETs have a dual role: they can both remove pathogens and regulate inflammatory responses. However, NETosis is actually a double-edged sword - although NETs play a protective role in anti-infection, excessive or uncontrolled NETs formation may cause tissue damage and aggravate the inflammatory response [114,115].

NETs released during NETosis are known to have both beneficial and detrimental effects. This dual nature of NETosis has drawn attention in the context of chronic inflammatory diseases. Studies have observed increased NETosis and NET formation in various inflammatory conditions, including autoimmune disorders [116,117]. One such condition potentially influenced by NETosis is PCOS, which is linked to chronic low-grade inflammation, marked by heightened concentrations of inflammatory markers circulating in the blood. Indeed, inflammation

contributes significantly to the onset and advancement of PCOS along with its related symptoms [118,119]. Emerging evidence suggests that NETosis may be involved in the underlying inflammatory processes of PCOS. Studies have indicated elevated concentrations of neutrophils and inflammatory cytokines in women with PCOS, implicating their involvement in the process of NETosis. Some studies have proposed that NETosis may contribute to the inflammatory environment observed in PCOS. Specifically, the heightened NETosis observed in women with PCOS is speculated to correlate with activated neutrophils and the consequent release of NETs. This process potentially contributes to inflammation and insulin resistance, mutual traits of PCOS [120,121]. Nevertheless, it is crucial to emphasize that the connection between PCOS and NETosis remains an active area of investigation. The precise mechanisms and direct relationships are not yet fully comprehended. Thus, ongoing studies are essential to clarify the exact role of NETosis in the advancement of PCOS and its potential clinical implications.

2.6. Necroptosis and PCOS

Necroptosis is a regulated form of necrotic cell death that serves as an alternative to apoptosis, particularly when apoptotic pathways are inhibited. Unlike apoptosis, which is typically immunologically silent, necroptosis is pro-inflammatory, as it disrupts the integrity of the plasma membrane and leads to the release of damage-associated molecular patterns (DAMPs) that activate the innate immune system [9]. Mechanistically, this form of cell death is primarily mediated through a signaling cascade initiated by tumor necrosis factor receptor 1 (TNFR1) or other death receptors such as TLR3 and TLR4 under specific conditions. Upon binding of TNF-α to TNFR1, a multiprotein signaling complex—Complex I—is formed, comprising TRADD, TRAF2/5, RIPK1, cIAP1/2, and LUBAC. Under normal circumstances, this pathway may lead to apoptosis; however, if apoptosis is inhibited, often due to caspase-8 suppression, RIPK1 interacts with RIPK3 to form a functional unit known as the necrosome. Within this complex, RIPK3 phosphorylates MLKL (mixed lineage kinase domain-like protein), which then oligomerizes and translocates to the plasma membrane. There, MLKL forms disruptive pores, leading to loss of cellular homeostasis, cell lysis, and inflammatory cell death [122–124]. Beyond its role in host defense—where necroptosis eliminates pathogen-infected cells that evade apoptosis—this mechanism has broader biological significance. In particular, it contributes to inflammatory processes by releasing DAMPs and amplifying immune responses. Interestingly, recent studies have highlighted the importance of necroptosis in reproductive biology, especially in regulating follicular cell death, which is essential for proper follicle development, growth, and ovulation.

In this reproductive context, necroptosis has emerged as a potential pathological mechanism in PCOS. Increasing evidence indicates that GC necroptosis may play a pivotal role in the onset and progression of PCOS [125]. One key factor contributing to this process is oxidative stress, a known driver of GC apoptosis and follicular atresia. Sustained overproduction of reactive oxygen species (ROS) activates inflammatory signaling pathways, which, in turn, promote necroptosis in granulosa cells, potentially disrupting the follicular microenvironment. As necroptotic GCs perish, they deprive adjacent oocytes of vital nutrients, growth factors, and survival signals, rendering the oocytes more susceptible to further damage or even follicular system–mediated necroptosis [126]. As a result, the simultaneous necroptosis of GCs and oocytes contributes to follicular atresia, a hallmark of PCOS-related ovarian dysfunction. Moreover, elevated levels of ROS and pro-inflammatory cytokines have been shown to upregulate RIPK1 and RIPK3 expression in GCs, further amplifying necroptotic signaling pathways [127]. This suggests the presence of a self-reinforcing loop between oxidative stress, inflammation, and necroptosis, which may underlie the persistent follicular dysregulation observed in PCOS. Notably, a study by Wang et al. identified several genes—IL33, BCL2, PYGM, and TNFSF10—as potential diagnostic markers associated with necroptosis in PCOS, highlighting the potential for targeting this pathway in future therapeutic strategies [125].

3. Conclusions

The key takeaway from these studies is the substantial contribution of regulatory forms of cell death to the development of PCOS. In PCOS, ovarian granulosa cell death is a central event in the pathogenesis. In PCOS, apoptotic and autophagic cell death programs appear to be particularly significant. These studies highlight their prevalence and suggest potential therapeutic avenues by targeting these specific cell death pathways. The latest data are encouraging a reevaluation of the significance of apoptosis and ferroptosis in PCOS, prompting a reconsideration of their respective roles in contributing to the syndrome [37–40,59–61]. Several studies have shown aletrations in apoptotic pathways in the ovaries of women with PCOS. These changes can affect follicular development, ovulation, and the overall balance of hormone production. Specifically, increased apoptosis has been observed in the granulosa cells, which surround and support the developing egg within the ovarian follicles. Granulosa cell apoptosis disrupts the normal development of follicles and promotes the formation of ovarian cysts in PCOS patients [128]. Studies have also found that women with PCOS often have abnormal lipid metabolism, manifested as disorders in specific lipid and fatty acid levels [129,130]. These lipid abnormalities may lead to lipid peroxidation, which may promote ferroptosis [5]. In addition, iron dysregulation has been observed in PCOS, which can increase the susceptibility to ferroptosis [87]. The above data suggest that preferentially targeting death receptors and apoptosis in the mitochondrial pathway is expected to be key to treating PCOS. However, considering the potential benefits, inhibition of ferroptosis may also be a promising complementary approach to treat this syndrome. In summary, in-depth study of the molecular complexity and physiological impact of apoptosis, autophagy, ferroptosis, pyroptosis, and NETosis is essential to understand their roles in PCOS. Designing targeted drug therapies against these specific cell death and immune processes is expected to more effectively treat this syndrome.

4. Prospect

Emerging evidence suggests that inflammation, oxidative stress, and regulated cell death pathways are intricately linked to the pathophysiology of PCOS, beyond the classic features of androgen excess and insulin resistance. Women with PCOS have persistent chronic low-grade inflammation, characterized by elevated levels of cytokines such as TNF-α, IL-6, and CRP, and are closely associated with metabolic and reproductive dysfunction [131,132]. At the same time, enhanced oxidative stress, manifested by increased ROS production and impaired antioxidant defenses, further amplifies inflammatory signaling and contributes to ovarian dysfunction, follicular atresia, and insulin resistance [133,134].

It is worth noting that this oxidative stress-inflammatory microenvironment in PCOS patients may have an important impact on the activation and cross-regulation of multiple programmed cell death modes, including apoptosis, ferroptosis and pyroptosis. For instance, excessive ROS and lipid peroxidation may drive ferroptosis in granulosa cells, impairing follicular development [135], while inflammasome activation may trigger pyroptosis, exacerbating local ovarian inflammation [136]. Dysregulated apoptosis of granulosa or theca cells may also contribute to anovulation and the formation of cystic follicles [40]. Moreover, emerging studies suggest that metabolic stress and hyperandrogenemia may modulate the sensitivity of ovarian cells to different death modalities, further linking systemic metabolic disturbances with cellular homeostasis [137].

A deeper understanding of how oxidative stress and inflammation converge to regulate cell death pathways in PCOS may open new therapeutic avenues. Targeting this cross-talk—through antioxidants, anti-

inflammatory agents, or modulators of cell death—holds promise for restoring ovarian function and improving systemic metabolic outcomes. Future research should focus on delineating the molecular mechanisms underlying this interplay and identifying cell-type-specific vulnerabilities within the ovary and peripheral tissues.

CRediT authorship contribution statement

Ying-ying Li: Writing – original draft. **Yi-qiu Peng:** Investigation. **Yu-xi Yang:** Investigation. **Ning Xu:** Investigation. **Ting-juan Shi:** Investigation. **Rui-xia Liu:** Writing – review & editing. **Ying-yi Luan:** Writing – review & editing. **Cheng-hong Yin:** Writing – review & editing.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Not applicable.

Appendix A. Supplementary data

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Data availability

No data was used for the research described in the article.

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