



# Role of Pyroptosis in Endometrial Cancer and Its Therapeutic Regulation

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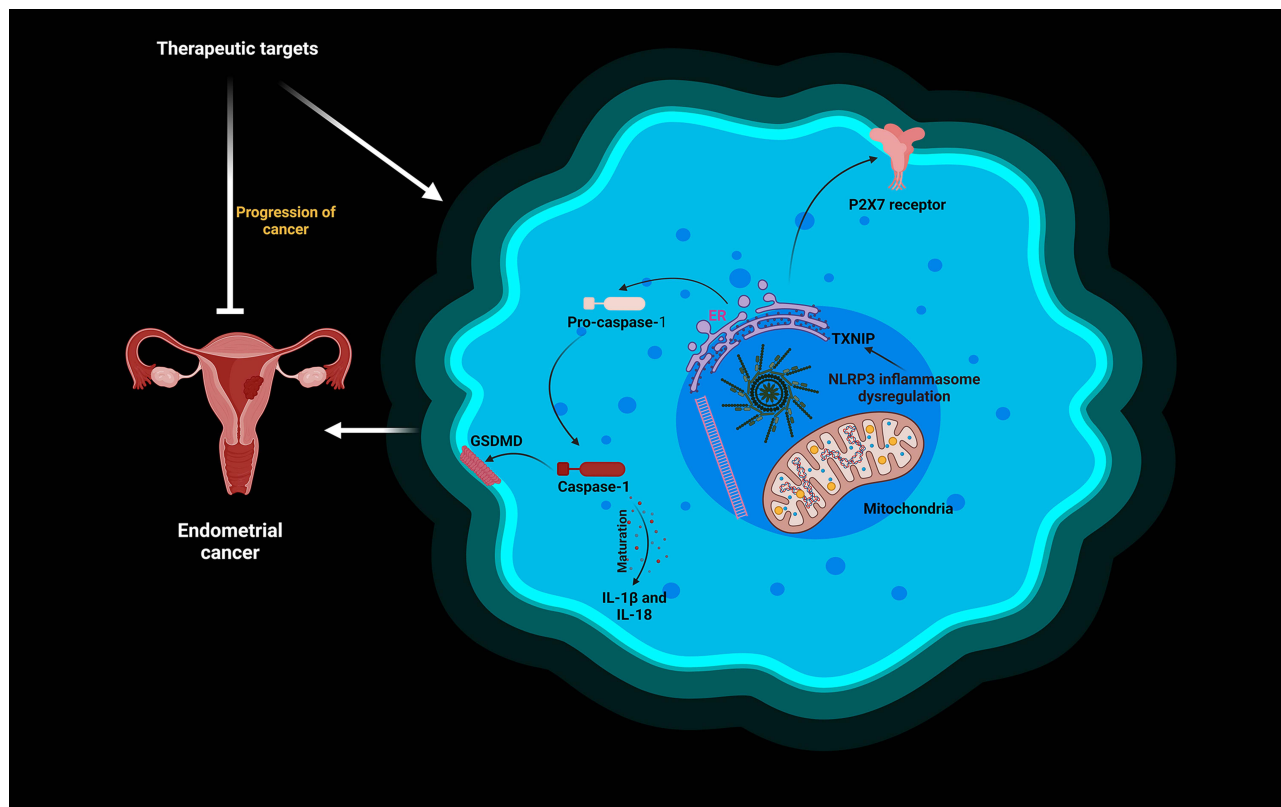
**Abstract:** Pyroptosis is an inflammatory cell death induced by inflammasomes that release several pro-inflammatory mediators such as interleukin-18 (IL-18) and interleukin-1 $\beta$  (IL-1 $\beta$ ). Pyroptosis, a type of programmed cell death, has recently received increased interest both as a therapeutic and immunological mechanism. Numerous studies have provided substantial evidence supporting the involvement of inflammasomes and pyroptosis in a variety of pathological conditions including cancers, nerve damage, inflammatory diseases and metabolic conditions. Researchers have demonstrated that dysregulation of pyroptosis and inflammasomes contribute to the progression of endometriosis and gynecological malignancies. Current research also indicates that inflammasome and pyroptosis-dependent signaling pathways may further induce the progression of endometrial cancer (EC). More specifically, dysregulation of NLR family pyrin domain 3 (NLRP3) and caspase-1-dependent pyroptosis play a contributory role in the pathogenesis and development of EC. Therefore, pyroptosis-regulated protein gasdermin D (GSDMD) may be an independent prognostic biomarker for the detection of EC. This review presents the molecular mechanisms of pyroptosis-dependent signaling pathways and their contributory role and function in advancing EC. Moreover, this review offers new insights into potential future applications and innovative approaches in utilizing pyroptosis to develop effective anti-cancer therapies.

**Keywords:** endometrial cancer, pyroptosis, NLRP3, caspase-1, GSDMD, IL-1 $\beta$ , IL-18

## Introduction

Endometrial cancer (EC) is the predominant form of gynecologic malignancy worldwide. The incidence of EC is approximately 142,000 women per year with an estimated 42,000 women dying from this disease.<sup>1</sup> There is currently a predominant role for surgical interventions in the management of patients without reproductive needs.<sup>2</sup> However, patients with elevated risk factors may require additional treatment techniques such as radiation and chemotherapy. These therapeutic approaches promote ROS-mediated stress and induce apoptosis in cancer cells. Cancer-related deficiencies in apoptosis initiation may occur, but there is also the possibility of an “oncogene addiction” phenomenon that can result in treatment ineffectiveness.<sup>3</sup> Cancer cells are exquisitely dependent upon a single oncogenic lesion through many genetic and epigenetic changes during the development of their neoplastic characteristics. It was found in a laboratory setting that tumor cells could depend on tumor cells when an oncogene was suppressed or tumor suppressor expression was restored, which led to the initial suggestion that the development of tumor cells could depend on tumor cells. These first discoveries suggested that therapeutic drugs aimed at the repair or regulation of these mutant gene products might have broad effectiveness in the treatment of EC. Apoptosis, necroptosis and pyroptosis are discrete cellular mechanisms of programmed cell death within host cells.<sup>4,5</sup> Recent data suggests a significant relationship between pyroptosis and the pathogenesis and progression of multiple diseases including cardiovascular diseases (CVDs),<sup>6–9</sup> cancer,<sup>10–12</sup> neurological diseases (NDs)<sup>13–15</sup> and metabolic diseases (MDs).<sup>16–18</sup> In addition, pyroptosis plays a key role in the onset and advancement of several inflammatory conditions, particularly in the conversion of organ or cell inflammation into cancer.

## Graphical Abstract



The purpose of this study was to find, screen and evaluate information on inflammasomes and pyroptosis-dependent cell death in EC including information obtained from Elsevier, Google Scholar, PubMed, Science Direct, Scirus, Sci Finder, Scopus, Springer and Web of Science. We also identified potential therapeutic compounds that may be used to suggest and control these mechanisms. Furthermore, we used local and international books and peer-reviewed journals to find relevant information. This review also discusses the molecular mechanisms of pyroptosis-related signaling pathways and their contributory roles in the pathogenesis and progression of EC.

## Historical and Biological Features and Functions of Pyroptosis

Pyroptosis originates primarily from the Greek words “pyro” and “ptosis”, which represent fever and falling, correspondingly.<sup>4,19</sup> This terminology is employed to describe a newly identified form of programmed cell death (PCD) that has inflammatory characteristics. In 1990, researchers discovered that *Shigella flexneri* and *Salmonella* infections remove mouse macrophages or human monocytes.<sup>20</sup> *Shigella dysenteriae* was reported to activate caspase-1 in host cells by Arturo Zychlinsky in 1997.<sup>21</sup> Hersh et al also showed that the inhibition of caspase-1 alleviated *Salmonella*-induced cell death.<sup>22</sup> Lawrence H. Boise and Brad Cookson reported in 2001 that microbial infection caused by bacteria led to the death of macrophages via the activation of caspase-1-dependent programmed necrosis.<sup>23,24</sup> Pyroptosis and apoptosis have comparable biological features and functions including DNA fragmentation and chromatin. Specifically, pyroptotic cells show denaturation and the development of spherical expansions on their cellular membranes.<sup>25</sup> The differences between pyroptosis and apoptosis can be distinguished based on a wide range of characteristics. Pyroptosis is mainly characterized by a rapid disruption of the plasma membrane, as opposed to the blebbing of the membrane that usually occurs during apoptosis. Pyroptosis results in rapid plasma membrane disintegration, whereas apoptosis is comparatively slow.<sup>26</sup> The degradation of the membrane structure leads to the infiltration of

water and ions into the cell, which ultimately causes the cell to enlarge and burst.<sup>27</sup> Pyroptosis also exhibits similar characteristics to apoptosis including caspase activation and PtdSer exposure.<sup>28</sup> Pyroptotic cells produce PtdSer, which attracts engulfing cells. However, this mechanism differs from the process of PtdSer exposure mediated by scramblase in apoptosis.<sup>29</sup> Studies have shown that pyroptosis results in the externalization of PtdSer through membrane disintegration.<sup>30</sup> Nuclear condensation and DNA damage are found in pyroptotic cells, but the nuclei remain undamaged compared to apoptosis. Apoptosis involves the caspase-3 enzyme. Pyroptosis exhibits distinct cellular properties that differentiate it from other types of cell death.<sup>31–33</sup> Pyroptosis induces low-grade inflammation, whereas apoptosis does not cause inflammation.<sup>34</sup> Pyroptosis is triggered by both external and internal signals such as viral and bacterial infections, being exposed to toxins and certain chemotherapeutic agents.<sup>35–37</sup> In contrast to necrosis, pyroptosis involves cytoplasmic damage caused by sudden plasma membrane rupture. Activation of caspases or release of granzymes leads to the oligomerization of gasdermin N-terminal and the development of pores (1–2  $\mu\text{m}$ ) in plasma membranes, which further promotes the matured form of IL-1 $\beta$ /IL-18 (4.5 nm) and caspase-1 (7.5 nm) permeability.<sup>38</sup> The ingress of water via holes stimulates cellular expansion, osmotic disintegration and plasma membrane rupture, resulting in the release of pro-inflammatory factors including IL-1 $\beta$  and IL-18.<sup>39,40</sup> Pyroptotic cell permeability is facilitated by the low molecular weight of 7-amino-actinomycin (7-AAD), phosphatidylinositol (PI) and ethidium bromide (EtBr). Pyroptotic cells eliminate these dyes by maintaining membrane integrity, whereas apoptotic cells destroy their membrane.<sup>41</sup> Annexin V is a marker for pyroptotic cells, which are similar to apoptotic cells. It forms a bond with phosphatidyl serine (PS). Consequently, Annexin V cannot distinguish between cells undergoing apoptosis and those undergoing pyroptosis. Apoptotic bodies are generated during the process of apoptosis, whereas pyroptotic bodies are generated during the process of pyroptosis.<sup>42</sup> Pyroptotic bodies have a diameter of 1–5  $\mu\text{m}$ , which is comparable to the size of apoptotic bodies.<sup>43</sup>

Ferroptosis causes a typical- morphological feature with intact cell membranes and nuclei devoid of chromatin condensation. However, mitochondria exhibit reduced cristae and membranes collapse and rupture.<sup>44</sup> It is triggered by disrupting the glutathione-dependent antioxidant defense using defects in system X<sub>C</sub><sup>-</sup> or glutathione peroxidase 4 (GPX4). Glutathione (GSH) is synthesized in the cell by converting extracellular cystine into cysteine.<sup>45</sup> GPX4 can swiftly facilitate the interaction between glutathione and lipid hydroperoxides, resulting in a decrease in the amount of lipid peroxidation inside cells. Inhibition of GPX4 or depletion of GSH leads to the accumulation of lipid hydroperoxides. It has been demonstrated that unbound iron reacts with lipid hydroperoxides via the Fenton reaction, which further produces reactive oxygen species (ROS) from lipids. The excessive production of ROS causes cell death. Ferroptosis activation may be verified by administering ferroptosis inhibitors (eg, liproxstatin-1 and ferrostatin-1) and by determining lipid peroxides (eg, malondialdehyde quantification and 4-hydroxynonenal quantification).<sup>46</sup>

Necroptosis, also called programmed necrosis, is featured by activating receptor-interacting protein kinases (RIPKs) via regulating a variety of signaling pathways.<sup>47</sup> RIPKs are triggered when they are brought into large molecular structures by several receptors on the cell surface including the T-cell receptor (TCR), toll-like receptors (TLRs) and the death receptors (DRs).<sup>48</sup> RIPK1 and RIPK3 are essential components of necrosomes.<sup>49</sup> The oligomerized mixed lineage kinase domain-like protein (MLKL) invades and permeates the cell membrane, resulting in the death of the cell.<sup>50</sup> Furthermore, the activation of RIP3-dependent necroptosis is also initiated by the cytosolic DNA sensor, which is a DNA-dependent activator of interferon (DAI) regulatory factors.<sup>51</sup> Necroptosis is a cell death process that exposes the necrotic characteristics including membrane rupture and the depletion of organelles. Necroptosis can be determined by evaluating the disruption of the plasma membrane using dyes that cannot enter the cell, the discharge of cellular components such as cyclophilin A, high mobility group box 1 (HMGB1) and lactate dehydrogenase (LDH) through Western blot analysis, the measurement of mitochondrial potential using fluorescent probes and the investigation of cellular morphology using electron microscopy. Several alternative approaches including blockers that inhibit necroptosis and measurement of key proteins in the pathway can be used.<sup>52</sup>

Nevertheless, a newly discovered GSDMD protein has been uncovered and thoroughly investigated. The protein is commonly observed in a condition of autoinhibition.<sup>53</sup> After caspase cleavage, GSDMD generates the N-terminal fragment (GSDMD-NT), which causes cells to swell and burst. Therefore, gasdermin D (GSDMD) acts as an effector molecule for pyroptosis-induced cell death. Comparable to the GSDMD pore-forming protein, DFNB59, DFNA5/

GSDME, GSDMC, GSDMB and GSDMA activate pyroptosis and induce the denaturation of cytoplasmic membrane.<sup>54,55</sup> Wang et al showed pyroptosis is triggered by GSDMD-NT and correlates with the interaction between 4 5-diphosphate phosphatidylinositol and the N-terminal domain of GSDME. This interaction leads to the creation of pores in liposomes and the removal of their phospholipid components.<sup>37</sup> The study by Shi et al renamed pyroptosis as a gasdermin family-dependent programmed necrosis.<sup>40</sup> Recently, Chauhan et al discovered that neutrophil elastase (NE) split GSDMD and caused neutrophil pyroptosis.<sup>56</sup> Pyroptosis is a type of regulated cell death (RCD) that relies heavily on the gasdermin protein family to form pores in the cell membrane. This process is usually triggered by the activation of inflammatory caspases, as stated by the Nomenclature Committee on Cell Death (NCCD) in 2018.<sup>57</sup>

## Molecular Mechanisms of Pyroptosis

Pyroptosis is induced by classic and non-classical inflammasome pathways, caspase-dependent apoptosis and granzymes-dependent signaling pathways.<sup>43</sup> Gasdermin proteins are essential mediators in various cellular signaling pathways and must undergo cleavage by granzymes or precursor caspases.<sup>58</sup> Caspases are classified into apoptotic and inflammatory caspases based on their distinct functions.<sup>59</sup> Caspases-1/4/5/11 are inflammatory caspases that further suppress pathogen proliferation, regulate pyroptosis and release inflammatory substances.<sup>60</sup> Caspases are primarily involved in protecting the body against infectious infections. Inflammasome is a multiprotein complex, which further activates the caspase-1 pathway. Caspase-1 is a member of the inflammatory caspase family, responsible for converting IL-18 into its fully developed state, which is a potent pro-inflammatory mediator. These pro-inflammatory variables distinguish pyroptosis from apoptosis, even though both processes rely on caspases.

Therefore, pyroptosis is lytic and characterized by cell ruptures, swellings and many bubbles blowing on the plasma membrane.<sup>61</sup> Apoptotic caspases mainly induce and regulate the biological processes involved in programmed cell death, known as apoptosis. The cleavage of gasdermins by proteases leads to the activation of the pyroptosis-regulated cell death.<sup>62</sup>

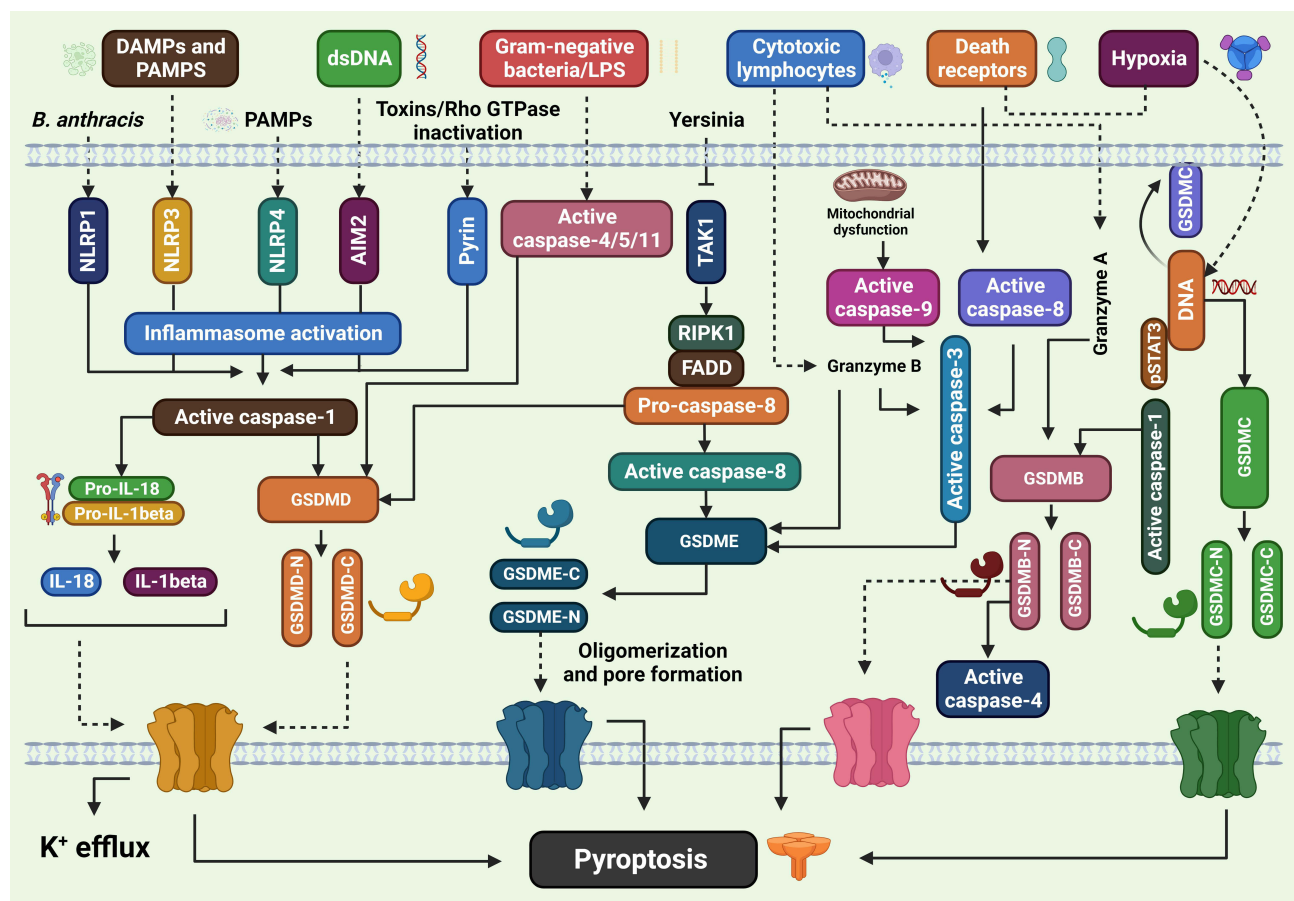
## Classical Signaling Pathways (Caspase-1-Dependent Pyroptosis)

The stimulation of inflammasomes may initiate classical pyroptotic cell death, which results in the fragmentation of GSDMD and the release of several pro-inflammatory molecules such as IL-18 and IL-1 $\beta$ .<sup>63,64</sup> Inflammasomes are intricate assemblies of several molecules that activate the adaptive immune response and act as a defense mechanism against microbial infections.<sup>65–69</sup> Inflammasomes can trigger illnesses that are not caused by microorganisms.<sup>70,71</sup> Accumulating evidence indicates that inflammasomes and their associated cytokines play an important role in the progression of cancer including processes such as cell proliferation, invasion and metastasis.<sup>72–75</sup> Cytosolic pattern recognition receptors (PRRs) that have been activated identify molecular patterns associated with pathogens and danger (DAMPs and PAMPs) to develop the inflammasome.<sup>76,77</sup> Activation of PRRs leads to the initiation of subsequent signaling pathways, resulting in the synthesis of type I interferons and several pro-inflammatory cytokines. PRRs bind to pro-caspase-1 and apoptosis-associated speck-like protein (ASC) to generate inflammasomes in response to cellular activation via signal molecules such as viruses and bacteria.<sup>78–80</sup> The most prevalent PRRs are nucleotide-binding oligomerization domain-like receptors (NLRs), which include NLRP1, NLRP3 and NLRC4, missing in melanoma 2 (AIM2) and pyrin.<sup>81,82</sup> The N-terminal pyrin domain (PYD), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR) and caspase recruitment domain (CARD) are constituents of NLRP1.<sup>83</sup> The PYD is crucial for engaging with the ASC protein. NOD stimulates the signal by controlling the production of ATP. LRR recognizes and automatically inhibits ligands. The CARD proteins then recruit pro-caspase-1. The presence of the anthrax lethal toxin, muramyl dipeptide and *Toxoplasma gondii* components might potentially stimulate the activation of NLRP1.<sup>84</sup> NLRP3 consists of N-terminal PYD, NOD and LRR domains but does not have a CRAD domain. The NLRP3 inflammasome signaling axis is activated by several stimuli comprising fungi, viruses, bacteria, ATP, ROS, uric acid and intrinsic damage signals.<sup>85,86</sup> The stimulation of the P2X7 receptor by extracellular ATP leads to the generation of IL-1 $\beta$  and the activation of the caspase-1 pathway. Thus, the outflow of K<sup>+</sup> ions is enhanced.<sup>87</sup> The NLRC4 protein consists of three domains: an N-terminal caspase activation and recruitment domain (CARD), a central nucleotide-binding domain (NBD) and a C-terminal leucine-rich repeat (LRR) domain. NLRC4 is upregulated by flagellin and proteins from type III secretion systems.<sup>88</sup> The PYD and HIN-200 domains present in AIM2 can identify double-stranded nucleotides that

originate from bacteria or viruses.<sup>89</sup> The Pyrin protein consists of a PYD domain, two B-box domains and a C-terminal SPRY/PRY region. Pyrin specifically designates the toxins of bacteria or effectors that deactivate host Rho guanosine triphosphatases.<sup>90</sup> PRRs either directly or passively attract pro-caspase-1 together with ASC to create the caspase-1-dependent inflammasome. This inflammasome then undergoes self-cleavage to activate caspase-1. The activation of the caspase-1 pathway results in the formation of the GSDMD-NT protein, which forms pores in the cytoplasm. Inflammation and pyroptosis are induced by this process (Figure 1).<sup>79</sup> Inflammasome-mediated pyroptosis significantly protects immune cells from microbial infections.

## Non-Classical Signaling Pathways (Caspase-4/5/11-Dependent Pyroptosis)

The non-classical pyroptotic signaling pathway does not include the association of human caspase-4/5 (or its mouse equivalent, caspase-11) with the downstream sensory complexes. Human caspase-4/5 (equivalent to mouse caspase-11) may be activated by straightaway binding to intracellular LPS via the N-terminal CARD in the non-classical pyroptotic route, which does not include upstream sensory complexes.<sup>91</sup> Unlike dendritic cells, macrophages are responsive to the oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (oxPAPC), which acts as a TLR4 agonist and suppresses the non-classical inflammasome.<sup>92</sup> Caspase-4/5/11 may cleave GSDMD, resulting in the formation of GSDMD-NT. GSDMD-NT undergoes polymerization and forms cytoplasmic pores.<sup>93,94</sup> The NLRP3/caspase-1



**Figure 1** Cellular and molecular mechanisms of pyroptosis-dependent signaling pathways. Pyroptotic signaling pathways are mainly triggered by the stimulation of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), leading to the activation of a variety of inflammasome components. The activated inflammasome proteins further activate the caspase-1 pathway. Then, the activated caspase-1 splits GSDMD to produce GSDMD N-fragment and plasma membrane pores, resulting in pyroptosis-dependent cell death. Furthermore, the caspase-1 pathway triggers the formation and release of IL-1 $\beta$  and IL-18 inflammatory factors. In addition, LPS binds to caspase-4/5/11 precursor, inducing pyroptosis. Caspase-3/GSDME can also cause pyroptosis-mediated cell death. Mitochondrial and death receptors can also trigger the caspase-3 pathway. The activated caspase-3 splits GSDME to produce GSDME N-fragment, creating plasma membrane pores, cell contraction and rupture and resulting in pyroptosis-mediated cell death.

pathway is necessary for maturing and releasing IL-1 $\beta$ /IL-18, but caspase-4/5/11 cannot mature pro-IL-1/pro-IL-18.<sup>95,96</sup> Furthermore, caspase-4/5/11 cleaves GSDMD, inducing the release of K<sup>+</sup> ions and initiating the activation of NLRP3 inflammasomes and pyroptosis in the cells.<sup>97,98</sup> Yang et al discovered that pannexin-1 is a crucial protein that triggers caspase-11-dependent non-classical pyroptotic cell death.<sup>97</sup> Lipopolysaccharide (LPS) triggers the activation of caspase-11, which leads to the cleavage and modification of Pannexin-1. This process further leads to the extensive release of cellular ATP and the subsequent activation of pyroptosis via activating the purinergic (P2X7) receptor.<sup>99</sup> In 2011, it was revealed that murine BMDMs lacking Pannexin-1 may cause the release of potassium ions and activate caspase-1 via the NLRP3 inflammasome without relying on P2X7.<sup>100</sup> In addition, the elimination of pannexin-1 in mice protects to counteract endotoxin shock, suggesting that particular potassium (K<sup>+</sup>) channels control the non-classical NLRP3 inflammasome signaling pathway.<sup>97</sup> Therefore, the stimulation of caspase-11 activates the NLRP3 inflammasome through non-classical pyroptotic signaling.<sup>101</sup>

## Alternative Signaling Pathways (Caspase-3/8-Dependent Pyroptosis)

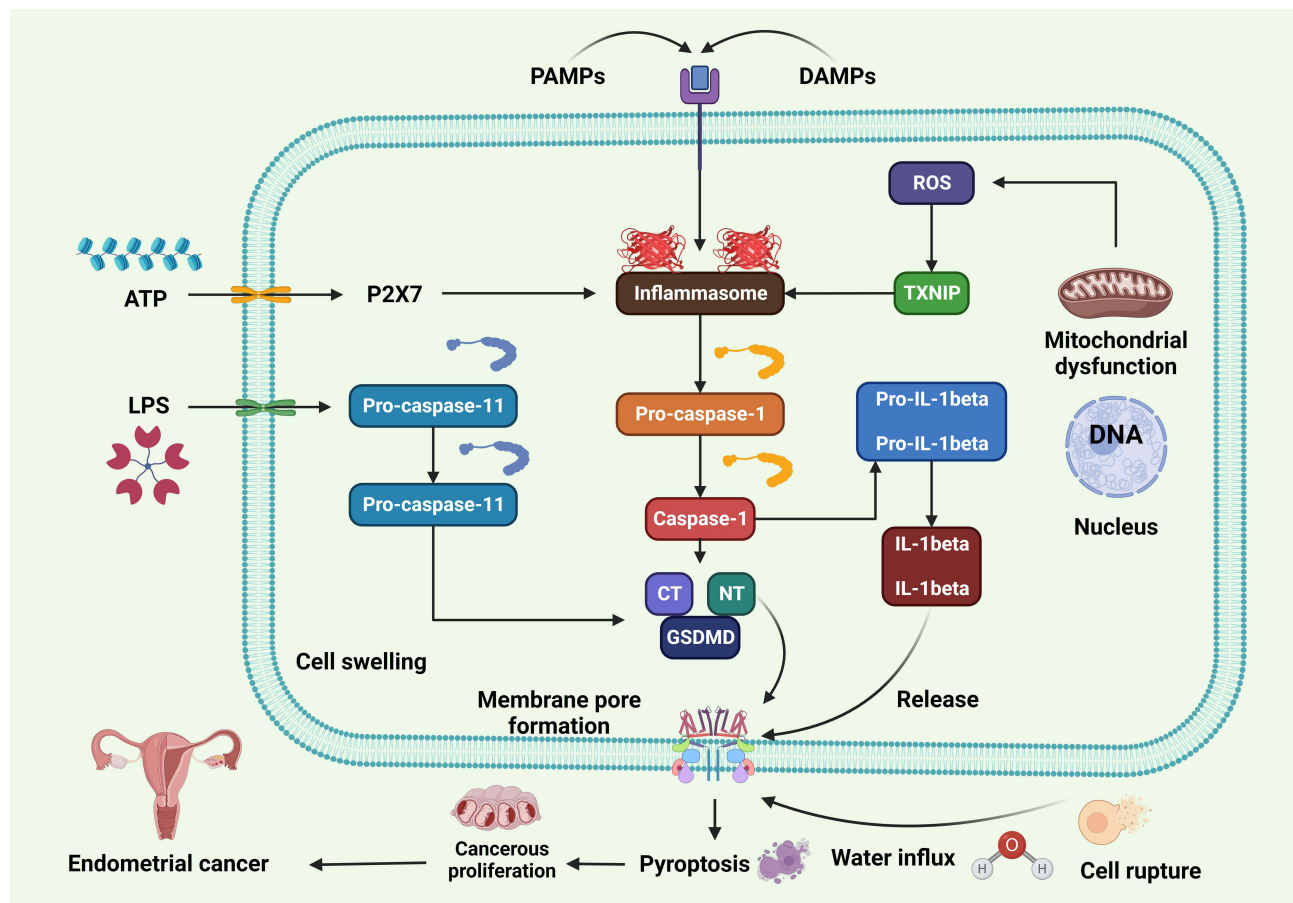
The composition of gasdermin proteins is highly conserved among members of the family. Gasdermins, except DFNB59, possess both C-terminal and N-terminal domains. Activation of the N-terminus results in pyroptosis.<sup>58</sup> Previous studies have shown that chemotherapeutic drugs may trigger the activation of caspase-3, leading to the cleavage of the gasdermin E (GSDME) protein. This process causes an increase in GSDME expression and results in the formation of N-GSDME termini in cancer cells.<sup>37,102</sup> Caspases involved in apoptosis *Yersinia* infection in mouse macrophages have been shown to hinder the activity of TGF- $\beta$ -activated kinase 1 (TAK1) and initiate the cleavage of GSDMD via the caspase-8 signaling pathway.<sup>103,104</sup> It was believed that caspases-3/8 could not generate gasdermin to induce pyroptosis. Further investigation revealed that *Yersinia* infection leads to the production of yersinia outer protein J (YopJ), a protein that hinders TAK1 and initiates the cleavage of GSDMD via caspase-8 in mouse macrophages.<sup>105</sup> Therefore, these results enhance the advancement and broadening of information about pyroptosis. Unexpectedly, Hou et al revealed that programmed cell death ligand (PD-L1) regulates the process of converting TNF-induced apoptosis to pyroptosis in breast cancer cells.<sup>106</sup> During hypoxia, the activation of p-Stat3 increases the movement of PD-L1 into the nucleus and the production of gasdermin C (GSDMC). LPS induces pyroptosis by the activation of caspase-4/5/11 signaling pathways.<sup>107</sup> Scientists have explored that LPS stimulates macrophages to initiate pyroptosis by activating the caspase-8 pathway.<sup>106</sup> The stimulation of TNF- $\alpha$  induces caspase-8 to lyse GSDMC, generate N-GSDMC and form membrane pores, resulting in pyroptosis.<sup>106</sup> TNF induces pyroptosis in macrophages by activating nuclear PD-L1, caspase-8 and GSDMC. Furthermore, Hou et al showed that chemotherapeutics and antibiotics can enhance pyroptotic cell death of BC cells by activating caspase-8/GSDMC-dependent pyroptosis.<sup>106</sup> Caspase-6 induces the NLRP3/caspase-1-dependent pyroptotic signaling axis by facilitating the connection among Z-DNA protein 1 and receptor-interacting serine/threonine protein kinase 3.<sup>108</sup> Further investigation is highly required to determine the precise roles and activities of the additional caspases implicated in pyroptosis.

Researchers in 2020 discovered that chimeric antigen receptor (CAR) T cells secrete granzyme B (GzmB), which activates caspase-3.<sup>109</sup> The activation of caspases-3 and GSDME pathways induces pyroptosis. Studies have shown that GzmB directly cleaves GSDME and triggers pyroptosis, which promotes the anti-tumor immune response and inhibits the growth of tumors.<sup>110</sup> Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells were found to eliminate GSDMB-positive cells by triggering the process of pyroptosis. A recent study by Zhong et al reports that GSDMB is highly expressed in specific tissues, particularly inside the gastrointestinal system epithelium and tumors originated in this region.<sup>111</sup> Zhou et al showed that gasdermin might go through hydrolysis at a site besides aspartic acid, leading to the formation of cytoplasmic pores.<sup>112</sup> These results contradict the widely accepted belief that caspases may only trigger pyroptosis.

## Role of Pyroptosis-Regulated Signaling Pathways in the Pathogenesis and Progression of EC

Inflammasomes are important components of the innate immune response to PAMPs and DAMPs.<sup>65</sup> The NLRP3 inflammasome can react to a broad spectrum of stimuli. NLRP3 binds pro-caspase-1 through the pyrin domain of the adaptor protein of ASC, which promotes pro-IL-1 $\beta$  and pro-IL-18 to accelerate their maturation. Recent studies suggest

that the NLRP3 inflammasome plays a significant role in the progression of several types of cancer including gastric cancer, breast cancer, colorectal cancer and liver cancer.<sup>74,113–115</sup> Therefore, the prognosis for patients with EC is enhanced by investigating alternative cell death mechanisms. Patients diagnosed with EC exhibit elevated levels of oxidative stress (OS) and systemic inflammatory conditions, which can be attributed to the presence of metabolic syndrome. The significant role of inflammatory pathways in estrogen metabolism in EC is noteworthy.<sup>116,117</sup> Radiotherapy and chemotherapy may not be effective in the treatment of serous carcinomas and tumors with high-risk characteristics such as distant metastases or deep myometrial invasion, as they are resistant to necrosis and apoptosis.<sup>118</sup> Therefore, targeting pyroptotic cancerous cell death might be considered an alternative therapeutic avenue for the treatment and management of EC in the near future. However, it was found that the protein expression level of GSDMD varies significantly between EC cells and normal endometrial tissues, according to the data obtained from the TCGA database. Furthermore, this discrepancy was shown to be associated with the pathological type, stage and patient weight. Contemporary studies indicate that pyroptosis is a distinguishing feature of autoinflammatory and autoimmune disorders.<sup>117,119</sup> Yang et al found that EC lesions exhibit pyroptotic events, as indicated by the presence of increased NLRP3, caspase-1 and GSDMD concentrations.<sup>120</sup> The GSDMD-NT portion facilitates the formation of cytoplasmic pores that function as “hydrogen channels” for hydrogen efflux. Chang et al discovered that patients with EC had elevated expression of inflammasomes such as AIM2 and NLRP3 compared to the control group.<sup>121</sup> The protein expression levels of GSDMD, NLRP3, caspase-1 and IL-1 $\beta$  were markedly elevated in atypical hyperplasia and cancer tissues compared to benign endometrial tissues. Therefore, GSDMD may play a significant role in the progression of EC by regulating pyroptosis (Figure 2).



**Figure 2** The pathophysiological mechanisms of pyroptosis-related signaling pathways in the progression of EC.

The precise biochemical pathways implicated in tumor-associated macrophages (TAMs) polarization in extracellular matrix cancer (EMC) are not fully defined. It is widely believed that IL-1 $\beta$  modulates the immune response against tumors and triggers an inflammatory response.<sup>122,123</sup> Immune cells such as lymphocytes, antigen-presenting cells, macrophages and neutrophils release several pro-inflammatory mediators such as IL-1 $\beta$  and IL-18.<sup>123</sup> The activation of IL-1 $\beta$  is regulated by inflammasomes such as NLRP3, which further facilitate the conversion of pro-IL-1 $\beta$  into its active form.<sup>124</sup> Abais et al indicated that the activation of OS can activate the NLRP3 inflammasome axis, resulting in the overproduction of ROS, specifically in macrophages.<sup>125</sup>

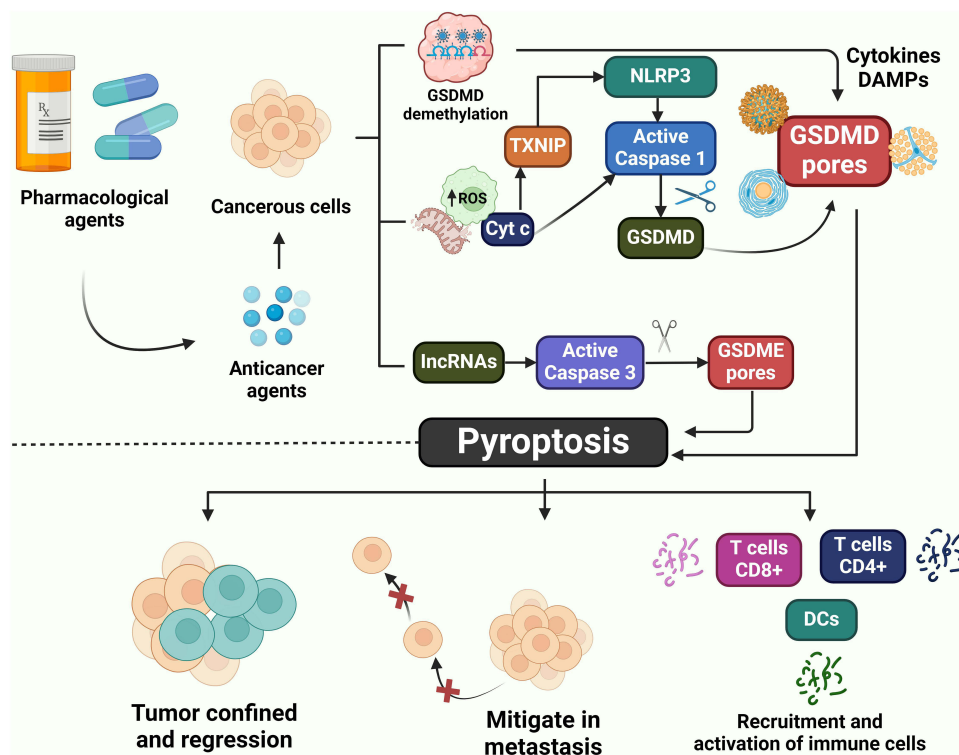
The identification of safe and effective treatments for activating pyroptosis in EC is of paramount importance. ROS is an upstream mechanism that mediates cellular pyroptosis.<sup>126</sup> The production levels of ROS are drastically elevated in EC compared to normal endometrial tissue. Elevated ROS can further induce cell death by stimulating signaling pathways associated with pyroptosis in EC cells.<sup>127</sup> The NLRP3 inflammasome induces damage to the host by inflammatory events including TNF- $\alpha$  exposure, NF- $\kappa$ B pathway activation and ROS accumulation.<sup>125</sup> The expression of inflammasome components including NLRP3 and caspase-1 was significantly augmented in EC tumor tissues compared to benign tissues. ROS are bioproduct molecules characterized by their high reactivity, which can further induce OS and damage several physiological constituents.<sup>128</sup> In addition, ROS activate intracellular signaling pathways, which promote cell proliferation, survival and migration.<sup>129</sup> Accumulating evidence indicates that the excessive accumulation of ROS within cells can induce cell damage, cellular dysfunction and cell death.<sup>130–132</sup> Several lines of studies have revealed that NLRP3 inflammasomes regulate ROS production through different regulatory mechanisms. This can either inhibit tumor growth by activating cellular stress and death or increase angiogenesis, inflammation and immune suppression, which can advance tumors.<sup>133–135</sup> Recently, Zhu et al revealed that macrophage NLRP3 deletion reduced cytotoxic T cells in EM tumors, possibly due to altered TAM-lymphocyte interactions.<sup>136</sup> The study confirms prior findings that macrophage NLRP3 signaling regulates the differentiation of T cells.

The immune-regulating thioredoxin interacting protein (TXNIP) has been associated with cardiovascular and neurological disorders.<sup>137–140</sup> Studies have consistently indicated that TXNIP is downregulated in a variety of cancers.<sup>141</sup> Several lines of studies also suggest that TXNIP expression is decreased in tumors.<sup>142–144</sup> An innovative investigation carried out by Kim et al revealed that downregulation of TXNIP may further accelerate the progression of EC.<sup>145</sup> Therefore, the TXNIP gene is considered a potential tumor suppressor.<sup>146</sup> Growing evidence indicates that the expression of TXNIP is markedly downregulated in several cancers including lung, liver and breast cancers.<sup>147–149</sup> The upregulation of TXNIP has been demonstrated to hinder the proliferation of cancerous cells.<sup>150</sup> TXNIP has profound pathogenic significance and is interconnected with the cellular response to ROS. Normal cells typically produce low and stable levels of ROS, which are naturally occurring byproducts of oxygen metabolism. Therefore, the ROS/TXNIP signaling axis may play a contributory role in the progression of EC.

Several mechanisms have been implicated in the loss of viability of cells including autophagy and pyroptosis.<sup>151</sup> Multiple pathological mechanisms are involved in the activation of pyroptosis.<sup>152</sup> Researchers have discovered that pyroptosis can be used as a biomarker for diagnostic and predictive purposes in uterine corpus endometrial carcinoma (UCEC).<sup>153,154</sup> Previous studies have linked pyroptosis to the advancement of cancer.<sup>116</sup> Yu et al found a correlation between the glutamyl hydrolase (GGH) expression level of T helper type 2 (Th2) cells and the low infiltration of cell adhesion molecule 56 (CD56) killer cells.<sup>155</sup> This association suggests a mechanism for driving the progression of UCEC. Zheng and his colleagues report that neural PAS domain protein 2 (NPAS2) can further induce UCEC by infiltrating immune cells into tumors.<sup>156</sup> Liu et al designed and validated a Treg-related risk signature (TRRS) for predicting the outcome of UCEC and immune status.<sup>157</sup> TRRS could be used to provide personalized treatment for UCEC patients based on their prognosis. A comprehensive review of the references revealed that pyroptosis is a significant factor in the advancement of inflammatory or malignant tumors. Intriguingly, Huang et al identified 47 genes that contribute to the progression of UCEC by regulating pyroptosis-related signaling pathways.<sup>154</sup> Furthermore, 42 genes associated with pyroptosis were validated for their essential role in the development and progression of UCEC. Eight pyroptosis-related genes were used to develop pyroptosis-mediated gene models to predict the survival of patients with UCEC.

Research has shown that interferon regulatory factor 2 (IRF2) promotes the stimulation of GSDMD by inducing pyroptosis.<sup>158</sup> Inflammatory vesicles activate the caspase-1 pathway, which further leads to focal death. It is believed that pyroptosis is caused by caspase-11 substrates that generate non-selective pores in the cytoplasmic membrane region, resulting in cell enlargement, ruptures and the release of proinflammatory mediators.<sup>25,159,160</sup> A growing body of evidence indicates that GSDMD and GSDMB play a key role in the activation of pyroptosis in cancer, which enhances the preventative potential of UCEC.<sup>161,162</sup> Selenoprotein GPX4 is a glutathione peroxidase with inhibitory properties for lipid peroxidation.<sup>163</sup> It has been proven that GPX4 activates cancerous cells to initiate apoptosis.<sup>164–166</sup> Guerriero et al demonstrated that GPX4 suppressed macrophage pyroptosis in mice model.<sup>167</sup> The augmented level of GPX4 could efficaciously suppress pyroptosis in UCEC. Targeting the GPX4 inducers may alleviate the symptoms of UCEC associated with pyroptosis and improve patient survival. Previous studies have demonstrated that charged multivesicular body protein 2A (CHMP2A) deficiencies can promote the formation of autophagic vesicles and activate pyroptosis.<sup>168</sup> The actual role and function of CHMP2A in EC remains unclear. Current studies have revealed that the identification of low levels of CHMP2A expression in UCEC patients is associated with poor survival, suggesting that inhibiting CHMP2A could serve as a therapeutic target in this disease.<sup>154</sup> Therefore, pyroptosis-related genes have a significant role in the pathogenesis and advancement of UCEC.

The innate immune response to bacterial LPS relies on toll-like receptor 4 (TLR4) and nuclear factor kappa B (NF- $\kappa$ B) pathways.<sup>169,170</sup> TLR4 senses LPS and activates the NF- $\kappa$ B signaling pathway, which modulates the creation of several pro-inflammatory mediators and immune response genes through the NLRP3 inflammasome domain.<sup>171</sup> In addition, macrophages activate the TLR4/NF- $\kappa$ B pathway via NLRP3 inflammasome, which may alter pro-inflammatory molecules and other immune-regulating genes.<sup>172</sup> EMC cells co-cultured with NLRP3-depleted macrophages exhibit increased growth, invasion, and migration potential.<sup>136</sup> It was observed that the expression level of NLRP3 was downregulated in EMC macrophages. NLRP3 depletion might be a key molecular mechanism responsible for the impact of cancer biology on macrophages.



**Figure 3** The schematic strategy for the pharmacological induction of pyroptosis-mediated cancer cell death for the therapeutic regulation of EC.

Caspases 11 is one of the exciting members of the Caspases family. Nobuhiko et al confirmed that Caspases sense bacterial LPS, mediate immune responses and trigger pyroptosis.<sup>173</sup> LPS and caspase-11 bind to lipid A in gram-negative bacteria with their caspase-activated recruitment domain (CARD).<sup>174</sup> LPS and TLR4-MD2 display a similar affinity through electrostatic adsorption to most of the positive charges found in the CARD domain.<sup>175</sup> Caspases-11 can recognize LPS directly without an NRL-like scaffold. Caspase-11 fragments when LPS interacts with its CARD domain.<sup>176</sup> TLRs are activated in inflammatory tissues, which further induces cell death by activating caspase-11.<sup>177</sup> The strong association between gram-negative anaerobes and periodontitis indicates that caspase-11-dependent pyroptosis plays a significant part in the advancement of EC. Therefore, caspase-11 has excellent potential as a focus for therapeutic intervention in the treatment and management of EC (Figure 3). Nevertheless, the actual function of caspase-11-dependent pyroptosis in the development of EC remains unknown. The significance of caspase-11 in EC needs to be further investigated and confirmed.

Endogenous ATP binds to P2X7 receptors, which are present at high nanomolar and low micromolar levels in the extracellular fluid of epithelial cells.<sup>178</sup> P2X7 is a receptor for P2 nucleotides located on the cell membrane and is activated by ligands. Extracellular ATP activates the P2X7 receptor, which creates channels in the plasma membrane that allow the passage of cations up to 900 kDa. Multiple evidence indicates that stimulation P2X7R facilitates the formation of NLRP3, which is an intracellular multimeric protein complex that triggers inflammatory responses and cell death (pyroptosis and apoptosis) by activating caspase-1.<sup>36,179–182</sup> Caspase-1 pathway activation fosters GSDMD-mediated pyroptosis, leading to the production of pro-inflammatory mediators including IL-1 $\beta$  and IL-18.<sup>183</sup> Li et al have shown that the expression of the P2X7 receptor is downregulated in epithelial cancer cells of the ectodermal, urinary sinus, and distal paramesonephric duct.<sup>184</sup> Kim et al demonstrated that epithelial cancer cells from the ectodermal, urogenital sinus, and distal paramesonephric ducts express reduced P2X7 level.<sup>185</sup> Therefore, the downregulation of P2X7-dependent pyroptosis contributes to the progression of EC.

The endometriosis syndrome is a chronic inflammatory condition associated with a mechanism reliant on estrogen that affects approximately 10% of pregnant women.<sup>186</sup> Endometriosis of the ovary is the predominant manifestation of endometriosis and can induce sterility and dysmenorrhea.<sup>187</sup> The inflammasome is a complex composed of several proteins including Nod-like receptors (NLRs). These proteins are responsible for detecting pathogen-associated molecular patterns and molecular processes that disrupt homeostasis. Inflammasomes such as NLRP3, which contain nucleotide-binding oligomerization domains, leucine-rich repeats and pyrin domains, have been implicated in the development of endometriosis.<sup>188–191</sup> Recently, Zhang et al showed that NLRP3 inflammasome-mediated pyroptosis induces Notch signal activation in endometriosis.<sup>192</sup> In addition, Hang et al have reported that E3 ubiquitin ligase tripartite motif-containing 24 protein (TRIM24) deficiency promotes NLRP3/caspase-1/IL-1 $\beta$ -mediated pyroptosis in endometriosis.<sup>193</sup> Intriguingly, Zhao et al suggest that astrocyte elevated gene-1 (AEG-1) exacerbates inflammation by facilitating the development of NLRP3 inflammasome in endometrial lesions in mice.<sup>194</sup> The NLRP3 receptor is an intracellular receptor that detects both external and internal stimuli. The NLRP3 inflammasome complex is formed by the interaction of this substance with ASC and caspase-1. The combination stimulates the secretion of pro-inflammatory cytokines IL-1 $\beta$  and IL-18, enhancing the immune response and pyroptosis.<sup>35</sup> Prior research has shown the distinct function of NLRP3 inflammasome in triggering the activation of mast cells (MCs) during the autoinflammatory response.<sup>195</sup> Anti-cytokine therapy targets NLRP3 inflammasome activation and IL-1 $\beta$  production.<sup>196</sup> Nevertheless, the precise processes by which the NLRP3 inflammasome influences the formation of ectopic endometrium remain unclear. The groundbreaking research of Guo et al has shown that endometriosis is associated with the activation of the NLRP3 inflammasome by estrogen via a nuclear-initiated signaling pathway.<sup>197</sup> In summary, inflammasome and pyroptosis contribute to the development and advancement of endometriosis.

Molecular and genomic profiling in EC is becoming increasingly popular.<sup>198–200</sup> The L1 cell adhesion molecule (L1CAM) is frequently mutated in endometrial cancer.<sup>201</sup> Kommos et al have demonstrated L1CAM to be a significant indicator of high-risk disease in EC.<sup>202</sup> Recently, Giannini et al reported that L1CAM has a prognostic role in stage EC, thus providing a potentially useful tool for tailoring the need for adjuvant therapy.<sup>203</sup> L1CAM expression influences survival outcomes in stage-I EC. Recently, it has been shown that specific genetic markers L1CAM, Annexin 2, insulin-like growth factor receptor, epidermal growth factor receptor, etc) and aberrant molecular signaling pathways could be key players in metastatic processes in EC cells, although further clinical trials are required to confirm their prognostic value of EC in clinical practice.<sup>204,205</sup> It was found that high L1CAM expression correlated with worse disease-free survival (HR 4.11, 95% CI 1.02–16.59,  $p = 0.047$ ) and

overall survival (HR 3.62, 95% CI 1.32–9.31,  $p = 0.012$ ). High LICAM level was also associated with a more aggressive FIGO grade and with older age. However, the role and significant relationship of LICAM with pyroptosis is still unclear. The published paper indicates that LICAM-regulated inflammasome or pyroptosis may play a possible role in EC progression. However, further studies are highly required to elucidate the contributory role of LICAM-regulated pyroptosis in the pathogenesis and progression of EC.

## Therapeutic Regulation of EC via Pyroptosis-Dependent Signaling Pathways

Hydrogen ( $H_2$ ) may suppress tumor formation and protect normal healthy cells. Recent studies have shown that  $H_2$  can be applied in the treatment of a variety of diseases including cancer, metabolic diseases and organ ischemia/reperfusion injury.<sup>206–208</sup> Numerous studies also suggest that  $H_2$  impedes tumor cell activity, proliferation, invasion and migration dose- and time-dependently and promotes apoptosis in cervical, breast and cutaneous melanoma.<sup>209–211</sup> Further evidence also indicates that  $H_2$  can significantly alleviate the progression of lung cancer, colon cancer, ovarian cancer, thymic lymphoma, Ehrlich ascites tumor cells, oral squamous cell carcinoma (OSCC) and fibrosarcoma cells, reduce tumor volume and weight and suppress tumor growth in xenografted mice.<sup>209,212–215</sup> In addition,  $H_2$  has been shown to mitigate radiotherapy and chemotherapy-induced renal toxicity.<sup>216</sup> The published work of Liu et al showed that  $H_2$  stimulates pyroptosis by activating the ROS-NLRP3-caspase-1 signaling pathways in the EC.<sup>120</sup> Thus,  $H_2$  induces GSDMD-dependent pyroptosis, which may enhance the effectiveness of cancer therapies that target GSDMD. The pharmacological efficacy of  $H_2$  in inducing pyroptosis-dependent cancer cell death for therapeutic regulation of EC requires further study.

Inflammasomes consist of NLR family proteins, leucine-rich repeat and pyrin domain-containing (NLRP) 1b, NLRP9b, NLRP6, NLRP3, or NLR family caspase recruitment domain (CARD)-containing protein (NLRC) 4, which sense danger-related, pathogen-related and homeostasis-altering molecular patterns.<sup>217,218</sup> Prior research has uncovered that the NLRP3 inflammasome contributes to the development of endometriosis.<sup>219</sup> Several lines of studies have indicated that prolonged endometriosis can further result in the advancement of EC.<sup>220,221</sup> The NLR NLRP7 is associated with myometrial invasion in human endometrial cancerous tissues and with endometriosis. Furthermore, endometrial cyst contents stimulate NLRP3 inflammasome in a stressful environment more strongly than cultured cells. The pharmacological strategy of suppressing the overactivation of NLRP3 inflammasome may be more effective in the management of EC. MCC950 can not hinder the major anti-microbial inflammasome components including NLRC4 and NLRP1. Osoku et al showed that the expression level of NLRP3 was significantly augmented compared to other NLRs in OE samples and CSCs.<sup>121</sup> Researchers have discovered that overactivation of the inflammasome and proteins involved in pyroptosis leads to cell death, alleviates the development of EC and offers potential therapeutic targets. Furthermore, the researchers discovered that MCC950 effectively suppressed the activation of oxidative stress in granulosa cells of the mouse model with endometriosis. However, the exact pharmacological effects and underlying molecular mechanisms of NLRP3 inflammasome blocker MCC950 in alleviating the progression of EC remains unclear. Therefore, extensive research is strongly required to explore the pharmacological actions of MCC950 to discover promising anti-cancer drugs for the treatment and management of EC.

Long non-coding RNA (lncRNA) refers to RNA fragments longer than 200 nucleotides that are not genetically coded for protein synthesis.<sup>222,223</sup> The significant role and function of lncRNA in biology was previously thought to be undefined. It has recently been demonstrated that lncRNA plays an important role in the regulation of cancer. Current studies indicate that lncRNA may also serve as a biomarker for the detection and prediction of a variety of cancers including EC.<sup>224,225</sup> Studies have revealed that the long non-coding RNA small nucleolar RNA host gene 4 (SNHG4) regulates the epithelial-mesenchymal transition (EMT) signal and exhibits antitumor properties in esophageal cancer by acting on specificity protein 1 (SP-1) transcription factor.<sup>226</sup> It has been demonstrated that long non-coding RNA SLERT controls the BDNF/TRKB pathway to facilitate the spread of EC cells.<sup>227</sup> Further research into lncRNAs will provide new insight into the potential role of new lncRNAs in EC. Recently, Shan et al reported that ENST00000534735 suppresses the proliferation and migration of EC cells and promotes programmed cell death and inflammatory cell death by the OSBPL3 protein via regulating the APMK/SIRT1/NF- $\kappa$ B signaling pathway.<sup>228</sup> It was found that the high ENST00000534735 expression resulted in a considerable

elevation in levels of cleaved caspase-1, GSDME-N and NLRP3. Conversely, the reduction of ENST00000534735 led to a decrease in the expression of cleaved caspase-1, GSDME-N and NLRP3 in HEC-1A and Ishikawa cells.

Previously, Mao et al revealed that the TFE3-ERR $\alpha$  pathway stimulates the alteration of lipid composition and promotes the development of pseudopodia in EC cells, resulting in enhanced cell membrane fluidity. This process facilitates the invasion and metastasis of EC.<sup>229</sup> Further studies are required to fully understand the process by which ERR $\alpha$  promotes resistance to chemotherapy. Tumor cells have an enhanced glycolytic capacity in order to meet their higher energy requirements. Furthermore, there is a correlation between the rate of aerobic glycolysis and the development, advancement and resistance to drugs in cancer.<sup>230</sup> Zeng et al found that miR-211-5p promotes cancerous effects in low-metastatic melanoma tumor cells by inhibiting pyroptosis and increasing glycolysis. This is achieved by modulating the expression of the targeted gene guanine nucleotide-binding protein subunit  $\alpha$ -15 (GNA15).<sup>231</sup> ERR $\alpha$  plays an important role in regulating energy metabolism. Analysis of the cancer genome atlas (TCGA) dataset revealed that genes associated with ERR $\alpha$  are engaged in the process of glucose metabolism and regulated cell death. The data clearly suggested that the excessive production of ERR $\alpha$  may stimulate glycolysis, elevate the ECAR in EC cells and promote pyroptotic resistance. This may indicate the primary interaction between the metabolic shift towards glycolysis and the activation of pyroptosis in endothelial cells triggered by chemotherapy. ERR+ cells exhibited a high IC<sub>50</sub> for cisplatin (DDP) compared to EC cells lacking ERR+. It has been shown that the overexpression of ERR $\alpha$  causes resistance to DDP by suppressing pyroptosis and inducing glycolytic reprogramming in EC cells. It was discovered by Daniela et al that ovarian cancer cells that are resistant to chemotherapy showed increased sensitivity to glucose deprivation. The drug-resistant cells also rely heavily on glucose to maintain their viability.<sup>232</sup> A study revealed that hepatocellular carcinoma cells exhibited an increase in glycolytic metabolism, which is associated with resistance to sorafenib.<sup>233</sup> He and his colleagues examined the possible involvement of metabolic reprogramming in the development of drug resistance in osteosarcoma and the specific molecular mechanisms that regulate this phenomenon. The scientists demonstrated a correlation between elevated ERR $\alpha$  expression and the metabolic reprogramming of osteosarcoma cells that are resistant to treatment. Targeted suppression of ERR $\alpha$  expression reverses the metabolic mode transformation.<sup>234</sup> Thus, the overexpression of ERR in patient-derived EC increases resistance to pyroptosis and upregulates glycolysis-related genes in tumor cells.

## Conclusion, Limitations and Future Directions

Pyroptosis induced by caspases involves cytoplasmic pore formation, cell lysis, membrane denaturation and secretion of several intracellular components. Multiple diseases have been associated with pyroptotic cell death, which has attracted considerable attraction from researchers and clinicians. Recent studies have increasingly concentrated on the contributing roles and functions of inflammasome and pyroptosis-regulated cell death in EC tumors. Our study provided an understanding of the intricate molecular processes of pyroptosis-related signaling pathways, which may offer new therapeutic approaches for the treatment and management of EC. Thus, targeting pyroptosis can deliver an innovative strategy for the treatment and regulation of a variety of cancers including EC. Current researches suggest that pharmacologically inducing pyroptosis-dependent cancer cell death can efficaciously suppress the formation of malignant tumors and provide a new treatment option for EC. Currently, research focuses primarily on compounds that activate inflammasomes such as NLRP3 and caspase-1 and promote pyroptosis, which could be useful for the treatment of EC. There are still many unresolved issues in the study of pyroptosis. The present and future implications of pyroptosis-mediated cell death in EC research are only beginning to be explored. A limited body of research has specifically investigated the molecular regulator of GSDMD, a key pyroptosis executor in EC. Furthermore, the precious function and role of non-canonical inflammasome and GSDME-dependent pyroptotic signaling pathways in the development of EC have not yet been explored. Therefore, more research is highly required to understand and clarify the contributory role and function of molecular mechanisms of non-canonical inflammasome and apoptotic-mediated pyroptosis in the progression of EC. In addition, extensive research on pyroptosis should also be conducted to uncover new possibilities and avenues for the therapeutic regulation of EC. Specific potential candidates have shown promise as prospective therapeutic agents for the induction of pyroptosis-mediated cancerous cell death in the therapy and control of EC. However, additional investigation is required to comprehend the processes better and develop targeted therapies for inflammasome activation and pyroptosis in EC.

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## Disclosure

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