Pyroptosis: the dawn of a new era in endometrial cancer treatment

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Endometrial cancer (EC) is a malignancy of the inner epithelial lining of the uterus. While early-stage EC is often curable through surgery, the management of advanced, recurrent and metastatic EC poses significant challenges and is associated with a poor prognosis. Pyroptosis, an emerging form of programmed cell death, is characterized by the cleavage of gasdermin proteins, inducing the formation of extensive gasdermin pores in the cell membrane and the leakage of interleukin-1β (IL-1β) and interleukin-18 (IL-18), consequently causing cell swelling, lysis and death. It has been found to be implicated in the occurrence and progression of almost all tumors. Recent studies have demonstrated that regulating tumor cells pyroptosis can exploit synergies function with traditional tumor treatments. This paper provides an overview of the research progress made in molecular mechanisms of pyroptosis. It then discusses the role of pyroptosis and its components in initiation and progression of endometrial cancer, emphasizing recent insights into the underlying mechanisms and highlighting unresolved questions. Furthermore, it explores the potential value of pyroptosis in the treatment of endometrial cancer, considering its current application in tumor radiotherapy, chemotherapy, targeted therapy and immunotherapy.

KEYWORDS

endometrial cancer, treatment, pyroptosis, molecular mechanism, gasdermins

1 Introduction

Endometrial cancer (EC) is the most common female reproductive system malignancy in developed countries (1). From 1990 to 2019, Overall incidence has risen by 132% (2). In 2020, there were 417,000 new cases and 97,000 deaths of EC globally, predominantly observed in women aged 65 to 75. Socioeconomic, racial disparities and geographic differences largely determine incidence and mortality of EC (1, 3). The high prevalence of EC is associated with several risk factors, including population aging, exposure to

endogenous or exogenous hormones, high body mass index (BMI), metabolic syndrome and epigenetic alterations (3, 4).

Abnormal uterine bleeding is the most common clinical symptom of EC (5), which ensures more than 60% of EC can be diagnosed at an early stage (6). For early-stage EC, the main treatment is surgery, and total hysterectomy with bilateral salpingo-oophorectomy (BSO) is standard of care. Depending on stage of disease and other risk factors, adjuvant radiotherapy and/or chemotherapy (carboplatin in combination with paclitaxel) can be used to reduce risk of recurrence (7). Over the past decade, four molecular subtypes have been identified through The Cancer Genome Atlas (TCGA)- polymerase ε ultramutated (POLEmut), mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H), copy number low(CNL)/no specific molecular profile (NSMP) and copy number high (CNH)/p53abn-which significantly improved the prognosis of EC with hormone therapy, immunotherapy and targeted therapy (8, 9). While the 5-year overall survival (OS) exceeds 80% in early stage EC (10), it is only 17% and 15% in patients of stage IVA and IVB EC (11), which pose a serious threat to women's health and well-being. Therefore, gaining a deeper understanding of the molecular changes occurring during the progression of EC and identifying potential biomarkers and therapeutic targets hold vital clinical significance. These endeavors can facilitate early screening and further enhance the prognosis of EC patients.

Pyroptosis is a recently discovered form of cell death that can be triggered by microbial infection and endogenous stimuli, which leads to the cleavage of gasdermins (GSDMs) and the formation of gasdermin pores on the cell membrane, resulting in cell lysis and death along with the leakage of intracellular content (12). Over the past 20 years, the interesting and important biological phenomenon of pyroptosis has attracted many scholars to investigate its corresponding molecular mechanisms. To date, not only in monocyte macrophages but also in neutrophils and dendritic cells (13), it has been discovered that pyroptosis can be induced by Salmonella (14), Shigella flexneri (15), Yersinia, Listeria (16), Vibrio cholerae and Pseudomonas aeruginosa (17). Pyroptosis plays a significant role in maintaining body homeostasis and certain

diseases, including infectious diseases (18, 19), neurodegenerative diseases (20, 21), and metabolic diseases (22, 23). Moreover, regulating pyroptosis has been found to promote cancer cell death (24) and inhibit tumor progression in various types of cancers such as hepatocellular carcinoma (25), lung cancer (26), breast cancer (27), and ovarian cancer (28). Currently, there is growing evidence for an association between pyroptosis and EC. Therefore, this article aims to summarize the mechanisms underlying the anti-tumor effects of pyroptosis, with a specific focus on its role in the initiation and progression of EC. Additionally, it explores the potential application of pyroptosis in the treatment of EC.

2 Overview of pyroptosis

2.1 pyroptosis and cell death

Cell death is a crucial process for maintaining body homeostasis and suppressing the uncontrolled growth of tumor cells. It can be classified into regulated cell death (RCD) and accidental cell death (ACD) (29). The fully physiological form of RCD is referred to as programmed cell death (PCD) that plays a significant role in homeostasis maintenance (29). Resistance to apoptosis is recognized as a contributor to chemotherapy resistance in tumors, thus, exploring strategies to induce non-apoptotic programmed cell death holds promise for cancer therapy. Common types of RCD include apoptosis (29, 30), necroptosis (31), ferroptosis (32), autophagy (33) and pyroptosis. A brief summary of the distinguishing features of these different forms of RCD is presented in Table 1.

2.2 Characteristics of Pyroptosis

(1) Molecular Characteristics: executive protein (gasdermin family members, N-terminal) move to and oligomerize on the cell membrane, forming membrane pores that facilitate the secretion of

TABLE 1 Comparison of common types regulated cell death.

	Pyroptosis	Apoptosis	Necroptosis	Ferroptosis	Autophagy
Morphology	Swell	Shrink	Swell	Swell	Crescent-shaped
Membrane	Pore formation	Intact	Pore formation	Pore formation	Intact
Organelle	Intact/deformed	Intact	Swell	Smaller mitochondria	Engulfed by autophagosome
Remark(s)	Inflammasome	Apoptotic body	Necrosome	Autophagosome	Autophagosome
DNA	Random degradation	Ladder degradation	Random degradation	Random degradation	Random degradation
Caspase-dependent	√	√	×	×	×
IL-18, IL-1β release	√	×	√	√	×
Pore-forming cause	Gasdermin protein	No	MLKL	Iron-dependent	No
Inflammation	√	×	√	√	×

MLKL, mixed lineage kinase domain-like.

mature interleukin (IL)-1β and IL-18. GSDMs exhibit a common autoinhibitory conformation in the inactive state, wherein gasdermins-C-terminal (GSDMs-CT, autoinhibition domain) binds to gasdermins-N-terminal (GSDMs-NT, pore-forming structure domain) (34). The GSDMs-NT which translocates on the cell membrane and forms extensive gasdermin pores on liposomes containing phosphoinositides, cardiolipin or natural polar lipid mixtures exhibit membrane-disrupting cytotoxicity (35, 36). Negatively charged conduits within the GSDM pores enable the discrimination between mature IL-1β and IL-18 and their precursors (37). Consequently, intracellular content including mature IL-1β, IL-18, ATP and high mobility group protein box 1 (HMGB1) are released extracellularly through GSDMs pores (38). These substances play a pivotal role in recruiting various cells, such as macrophages and neutrophils, and contribute significantly to promoting inflammatory antibacterial immune responses (39, 40). (2) Morphological Characteristics: Gasdermin forms non-selective pores that allow the passage of different ions and water influx, resulting in bubble-like protrusions on cell membrane, DNA fragmentation, chromatin condensation as well as cell swelling, lysis and death.
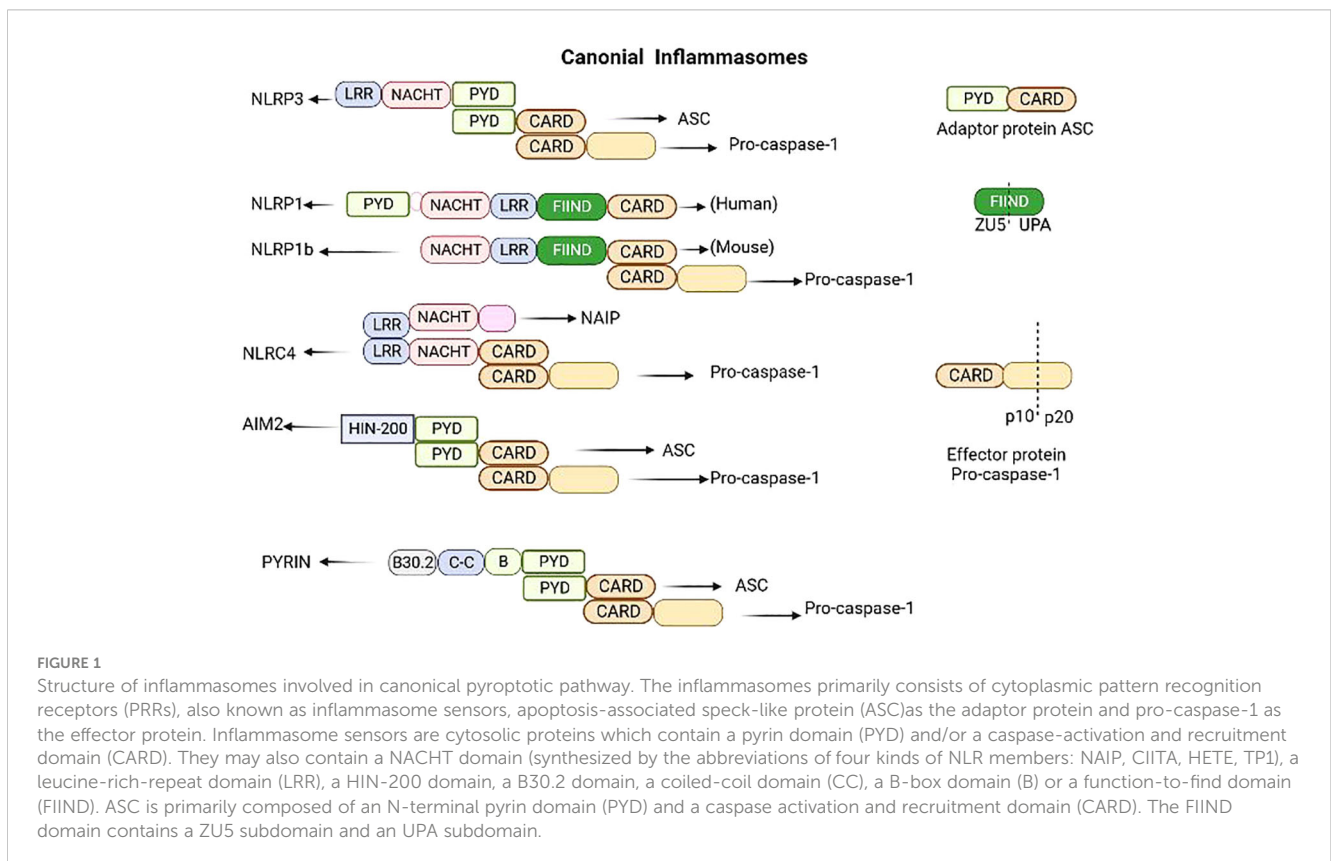
In the context of cancer, pyroptosis appears to be a double-edged sword, simultaneously inducing robust inflammation and immune responses during cell death processes. Inflammation has been implicated in promoting tumorigenesis across various cancer types, including endometrial cancer. Pyroptosis can either promote or inhibit tumorigenesis by shaping the tumor microenvironment (TME) or facilitating cancer cell death (41). Therefore, gaining a comprehensive understanding of the specific mechanisms underlying pyroptosis is crucial before exploring its role in endometrial cancer. Traditionally, the pyroptotic pathway can be categorized into the canonical pathway (involving the typical inflammasome and caspase-1), the noncanonical pathway (involving caspase-4/5/11), and other pathways. The detailed description of the pyroptotic pathway is presented below:

3 Canonical pyroptotic pathway

The term "inflammasome" was introduced by Martinon et al. to describe a cytoplasmic multiprotein signal transducer found in activated immune cells that facilitates the activation of inflammatory caspases (42). The inflammasome primarily consists of cytoplasmic pattern recognition receptors (PRRs), apoptosis-associated speck-like protein (ASC) as the adaptor protein and pro-caspase-1 as the effector protein (43). PRRs, also known as inflammasome sensors, include members of the nucleotide-binding oligomerization domain (NOD) with leucine-rich repeat (LRR) protein family (NLR, NLRP1, NLRP3, and NLRC4), non-NLR receptors such as absent in melanoma 2 (AIM2) and pyrin (39) (Figure 1). NOD, also known as the NACHT domain, which is shared by the NLR family and play an important role in nucleic acid binding. ASC, a critical component, is primarily composed of an N-terminal pyrin domain (PYD) and a caspase activation and recruitment domain (CARD) (44).

In response to infection or specific immune diseases, inflammasome sensors activated by various upstream signals,

FIGURE 1

Structure of inflammasomes involved in canonical pyroptotic pathway. The inflammasomes primarily consists of cytoplasmic pattern recognition receptors (PRRs), also known as inflammasome sensors, apoptosis-associated speck-like protein (ASC)as the adaptor protein and pro-caspase-1 as the effector protein. Inflammasome sensors are cytosolic proteins which contain a pyrin domain (PYD) and/or a caspase-activation and recruitment domain (CARD). They may also contain a NACHT domain (synthesized by the abbreviations of four kinds of NLR members: NAIP, CIITA, HETE, TP1), a leucine-rich-repeat domain (LRR), a HIN-200 domain, a B30.2 domain, a coiled-coil domain (CC), a B-box domain (B) or a function-to-find domain (FIIND). ASC is primarily composed of an N-terminal pyrin domain (PYD) and a caspase activation and recruitment domain (CARD). The FIIND domain contains a ZU5 subdomain and an UPA subdomain.

including pathogen-associated molecular patterns (PAMPs) as well as host-derived danger-associated molecular patterns (DAMPs) (13), initiate the assembly of inflammasomes. PRRs like NLRP3, AIM2 and PYRIN contain a PYD may recruit ASC to mediate CARD–CARD interactions with pro-caspase-1. However, murine NLRP1b and NLRC4 contain a CARD and can interact directly with pro-caspase-1 without the need of ASC (39, 44). Active caspase-1, also known as interleukin-converting enzyme, cleaves pro-IL-1β and pro-IL-18 to promote the production of mature IL-1β and IL-18. Meanwhile, it specifically cleaves the GSDMD domain, resulting in the GSDMD-NT fragments oligomerize on the cell membrane, forming membrane pores that induce cytokine release and pyroptotic cell death (44, 45) (Figure 2). The canonical pathways involve five major types of inflammasomes: NLRP3 inflammasome, NLRP1 inflammasome, NLRC4 inflammasome, AIM2 inflammasome, and PYRIN inflammasome.

3.1 Activation mechanism of the NLRP3 Inflammasome

The NLRP3 inflammasome sensor, which is extensively studied as an intracellular sensor, consists of three domains: a LRR domain at the C-terminus, a central nucleotide-binding and oligomerization domain with ATPase activity called NACHT, and a PYD at the

N-terminus (44). The basal expression of NLRP3 is insufficient to activate the inflammasome, and its activation involves two major steps (Figure 3): initiation and activation. Firstly, initiation occurs through signaling from Toll-like receptors (TLRs) or cytokine receptors, which promotes the transcription and translation of NLRP3 and cytokines (46). Subsequently, the NLRP3 receptor proteins assemble and oligomerize upon exposure to inflammasome activating factors such as PAMPs or DAMPs, which recruits ASC and pro-caspase-1, resulting in the self-regulation and activation of caspase-1 (39). These PAMPs consist of components derived from Gram-positive bacteria (16, 47), Gram-negative bacteria (15), viruses (18, 48), fungi (49–51), and microbial activators of protozoan pathogens. Additionally, DAMPs involve extracellular ATP (16), calcium phosphate dihydrate (52), uric acid crystals and cholesterol crystals (53). NLRP3 sensors were activated by PAMPs and DAMPs through various processes, including K^+ efflux (54, 55), Ca^{2+} flux (56), Lysosomal damage (57), generation of mitochondrial reactive oxygen species (mtROS) (58, 59), release of oxidized mitochondrial DNA (Ox-mtDNA) (60).

In recent years, research on NLRP3 has focused on understanding its activation mechanism and the state in which it is activated. NLRP3 is primarily present in an autoinhibited state in cells, mainly in the cytoplasm and trans-Golgi apparatus (TGN), forming monomeric or oligomeric cage structures (61, 62). Chen et al. reported for the first time that various NLRP3-activating
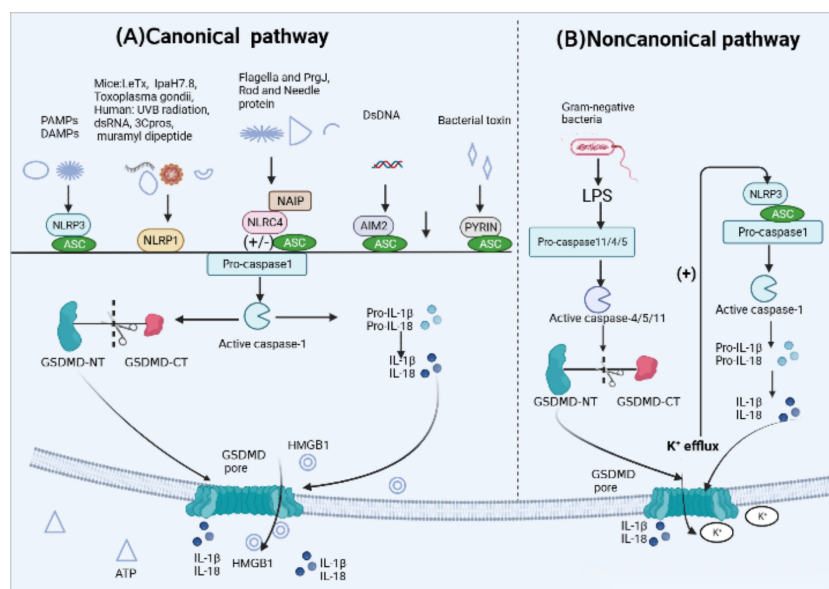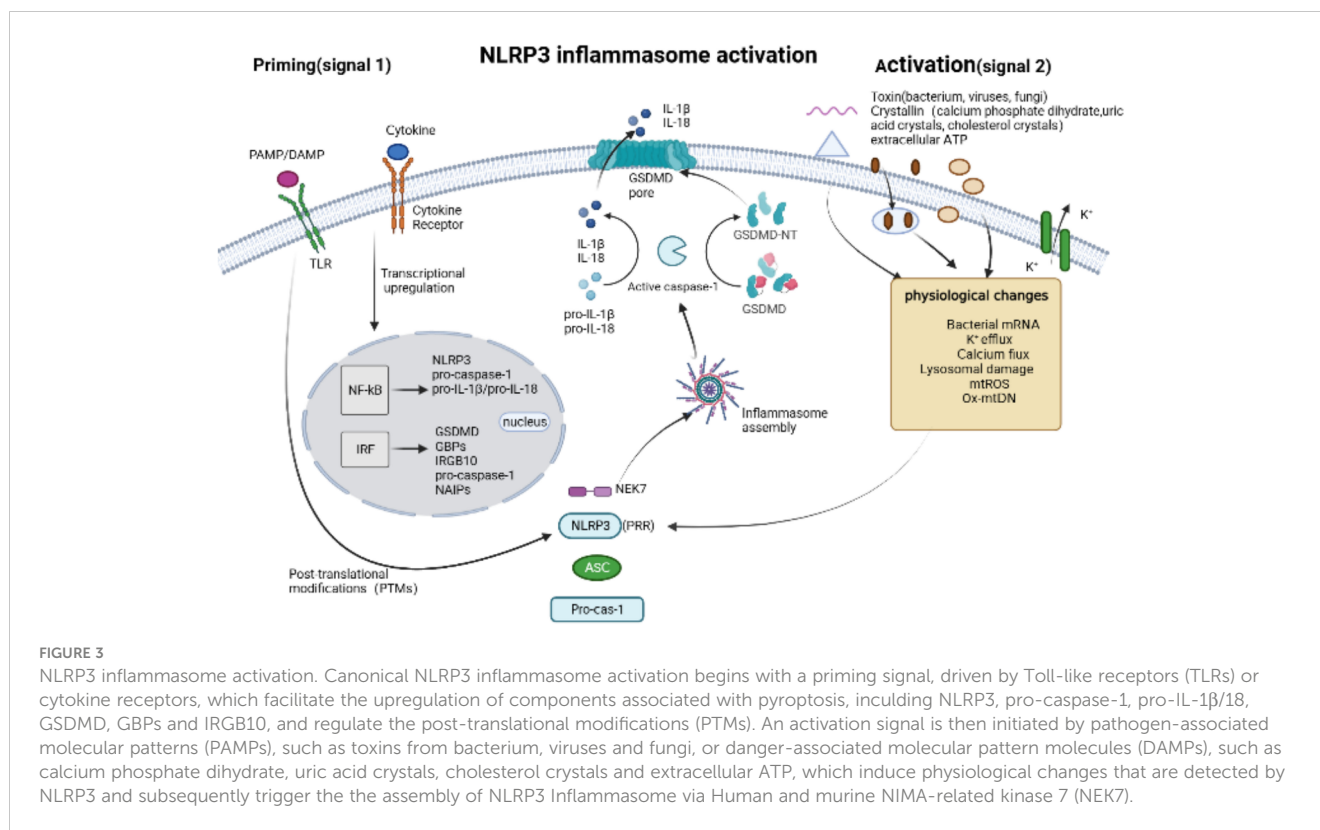

FIGURE 2
Activation mechanism of canonical and Noncanonical pyroptotic pathway. **(A)** Canonical inflammasome activation occurs in response to pathogen-associated molecular patterns (PAMPs) and host-derived danger-associated molecular pattern molecules (DAMPs). Responding to a variety of physiological or pathological changes, Inflammasome sensors, such as NLRP3, AIM2 and Pyrin, which contain a PYD may recruit adaptor protein apoptosis-associated speck-like protein (ASC) containing a caspase activation and recruitment domain (CARD) to mediate CARD−CARD interactions with effector protein pro-caspase-1. However, murine NLRP1b and NLRC4 contain a CARD and can interact directly with pro-caspase-1 without the ASC. After the above signal cascade response, inflammasomes activate pro-caspase-1 into active form. Activated caspase-1 cleaves pro-interleukin (IL)-1β and pro-IL-18 into their active forms. Caspase-1 also cleaves gasdermin D (GSDMD) to release the N-terminal domain (GSDMD-NT) which oligomerize on the cell membrane, forming membrane pores that induce the leakage of intracellular content including IL-1, IL-18, ATP and high mobility group protein box 1 (HMGB1) release and pyroptotic cell death. **(B)** Noncanonical pyroptotic pathway is mediated by human caspase-4/5 or murine caspase-11, which are activated by lipopolysaccharide (LPS) released from Gram-negative bacteria. Activated caspases cleave GSDMD into GSDMD-NT, leading to the formation of GSDMD pores. In addition, potassium(K+) efflux through those pores is enough to activate NLRP3 inflammasome, subsequently triggering caspase-1-dependent release of IL-1β and IL-18.

FIGURE 3
NLRP3 inflammasome activation. Canonical NLRP3 inflammasome activation begins with a priming signal, driven by Toll-like receptors (TLRs) or cytokine receptors, which facilitate the upregulation of components associated with pyroptosis, including NLRP3, pro-caspase-1, pro-IL-1β/18, GSDMD, GBPs and IRGB10, and regulate the post-translational modifications (PTMs). An activation signal is then initiated by pathogen-associated molecular patterns (PAMPs), such as toxins from bacterium, viruses and fungi, or danger-associated molecular pattern molecules (DAMPs), such as calcium phosphate dihydrate, uric acid crystals, cholesterol crystals and extracellular ATP, which induce physiological changes that are detected by NLRP3 and subsequently trigger the the assembly of NLRP3 Inflammasome via Human and murine NIMA-related kinase 7 (NEK7).

stimuli, regardless of their diverse sources, chemical compositions, and structural properties, can trigger a common cellular signal. Specifically, phosphatidylinositol 4-phosphate (PI4P) induces the transport and accumulation of NLRP3 to the specific disassembled trans-Golgi network structure (dTGN) (62). Zhang et al. further revealed that disruption of the endoplasmic reticulum-endosome membrane contact sites (EECS) leads to the accumulation of phosphatidylinositol 4-phosphate (PI4P) in lysosomes, which is crucial for NLRP3 inflammasome activation (63). However, the exact mechanism by which activators induce dTGN structure formation remains unclear. NEK7, a serine/threonine kinase localized in the microtubule organizing center, has been implicated in the assembly and activation of the NLRP3 inflammasome during mitotic interphase (64). Recently, Xiao et al. successfully reconstituted and stabilized the human NEK7-NLRP3-ASC inflammasome activated by nigericin both *in vivo* and *in vitro*. They analyzed the complex's high-resolution electron microscope structure and discovered that NEK7 interacts with and competes with LRR domain of NLRP3. It is speculated that NEK7 may play a role in opening the self-inhibitory cage structure of NLRP3 (65).

3.2 Activation mechanism of NLRP1 Inflammasome

NLRP1 is among the earliest discovered pattern recognition receptors. Human NLRP1 comprises five domains: a PYD, a NACHT domain, a LRR domain, the function-to-find domain (FIIND), and a CARD. The regulatory mechanism of human NLRP1 remains unclear. Recent studies have demonstrated that human NLRP1 is capable of sensing double-stranded viral RNA (66), Ultraviolet B (UVB) radiation and 3C protease (3Cpros) derived from enteroviruses like human rhinovirus (HRV) (67). However, none of these PAMPs can activate the rodent NLRP1 inflammasome. Interestingly, only inhibitors of dipeptidyl peptidase 8 (DPP8) and DPP9 have been identified as capable of activating both rodent and human endogenous NLRP1 inflammasomes (68).

Mice carry three NLRP1 analogues (NLRP1a-c) that lack the pyrin domain (66). The most representative NLRP1b is susceptible to Bacillus anthracis lethal toxin (LeTx), Toxoplasma gondii (69), IpaH7.8 secreted from Shigella flexneri ubiquitin ligase and inhibitors of cytoplasmic serine proteases DPP8 and DPP9 (70, 71). The FIIND domain contains a ZU5 subdomain and an UPA subdomain, whose auto-cleavage is required for NLPR1b inflammasome activation (72). Activation of NLRP1b via the N-end rule proteasomal degradation pathway represents a unified mechanism for its response to diverse activators (71, 73) (Figure 4). when NLRP1b is passed by LeTx, ubiquitination of NLRP1b induces proteasomal degradation of the NOD-LRR-ZU5 fragment, releasing the active UPA-CARD fragment that rapidly oligomerizes to engage downstream inflammasome effectors (74–76).

3.3 Activation mechanism of NLRC4 inflammasome

NLRC4 in human and mouse macrophages forms a NAIP-NLRC4 complex via the unique receptor NLR apoptosis inhibitory
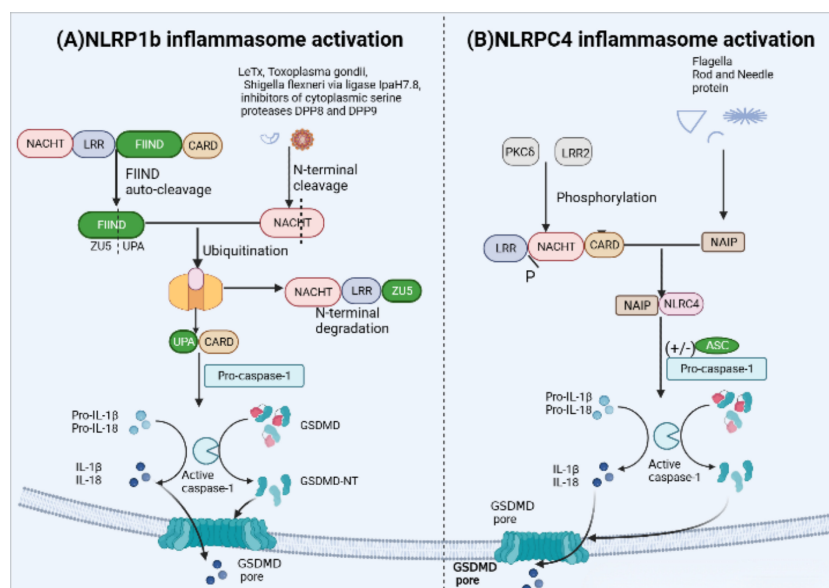
FIGURE 4

NLRP1b and NLRC4 inflammasome activation. **(A)** Activation of murine NLRP1b requires several steps of signal transmission. Firstly, the function-to-find domain (FIIND) containing a ZU5 subdomain and an UPA subdomain undergoes autoproteolytic cleavage, leading NLRP1b into two fragments in an autoinhibitory state until some specific stimuli, such asanthrax lethal toxin(LeTx), Toxoplasma gondii, IpaH7.8 inhibitors of DPP8 and DPP9, triggers inflammasome assembly. LeTx directly cleaves the N-terminal domain of the nucleotide-binding domain with ATPase activity(NACHT)−leucine-rich-repeat domain (LRR)−ZU5. Following cleavage, ubiquitination of NLRP1b marks it for proteasome degradation of the NACHT-LRR-ZU5 fragment and release of the active C-terminal fragment (UPA-CARD), which can initiate inflammasome assembly without ASC, leading to caspase-1-dependent release of IL-1b and IL-18 and pyroptosis. **(B)** The unique receptor NLR apoptosis inhibitory protein (NAIP) can detect bacterial flagellin, such as Salmonella typhi and Pseudomonas aeruginosa, and type III secretion system (T3SS) protein like the needle and rod protein components activation. Moreover, with or without ASC to form an inflammasome, phosphorylation of NLCR4 by PKCδ and leucine-rich repeat kinase 2 (LRRK2) triggers formation of an NAIP−NLRC4 complex and the recruitment of caspase-1.

protein (NAIP) (77, 78), which is recognized by bacterial flagellin, such as Salmonella typhi and Pseudomonas aeruginosa, and type III secretion system (T3SS) protein like the needle and rod protein components activation (77, 79). In addition, in mouse macrophages, the NLCR4 inflammasome also requires PKCδ and leucine-rich repeat kinase 2 (LRRK2) phosphorylation to function (80, 81) (Figure 4). NLRC4 structurally contains an N-terminal CARD and lacks PYD, therefore, the NAIP-NLRC4 complex can directly recruit and activate pro-caspase-1 to form inflammasomes. However, the presence of ASC can significantly enhance NLRC4-mediated pyroptosis (44).

3.4 Activation mechanism of AIM2 inflammasome

The AIM2 inflammasome in humans and mice is activated by microbial or self DNA (82) (Figure 5). Cytoplasmic bacteria induce the production of type I interferon (IFN), which leads to the collaboration of guanylate binding proteins (GBPs) and IRGB10, promoting the release of bacterial DNA into the cytoplasm and activating AM2 (83). On the other hand, DNA viruses such as mouse cytomegalovirus can activate AIM2 independently of type I IFN signaling (84). Additionally, the HIN-200 domain of AIM2 recognizes cytoplasmic double-stranded DNA (dSDNA) resulting from nuclear or mitochondrial damage, and then the pyrin domain

recruits ASC and caspase-1 to form an active inflammasome complex (85, 86).

3.5 Activation mechanism of pyrin inflammasome

Mutations in the MEFV gene which encodes pyrin inflammasome (not to be confused with the pyrin domain), are associated with autoinflammation in familial Mediterranean fever (FMF). The pyrin inflammasome can be activated by virogenic toxins (Figure 5), such as the major virulence factor TcdB of Clostridium difficile, toxins of Vibrio parahaemolyticus (VopS), the ADP-ribosylating C3 toxin of Clostridium botulinum (87, 88). In the case of Clostridium difficile toxin TcdB, it inactivates the Rho GTPase, leading to the activation of the Pyrin inflammasome. Active RhoA, in turn, activates the protein kinase N1/2 (PKN1/2), which bind and phosphorylate pyrin inflammasome sensors, resulting in the inhibition of pyrin inflammasome activation (89).

4 Noncanonical pyroptotic pathway

The noncanonical pathway involves the intracellular protease cascade triggered by lipopolysaccharide (LPS) through two human homologs, caspase-4/5 (caspase-11 in mice). This cascade results in
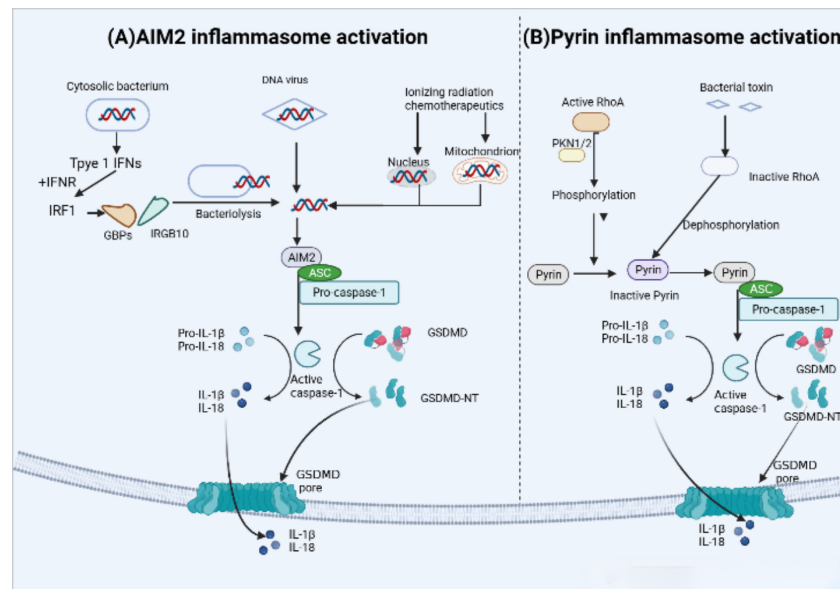
FIGURE 5

AIM2 and Pyrin inflammasome activation. **(A)** AIM2 inflammasome activation occurs in response to microbial or self-DNA. Cytosolic bacteria induce the production of type I IFNs which drive the expression of GBPs and IRGB10, targeting bacterial and vacuolar membranes for destruction. Bacterial DNA released into the cytoplasm to initiate AIM2 activation.In contrast, DNA viruses can activate AIM2 without type I IFN signaling. AIM2 also recognizes host cytoplasmic double-stranded DNA (dSDNA) leaked from nuclear or mitochondrial damage caused by Ionizing radiation chemotherapeutics. Upon binding to DNA, AIM2 participate in the following recruitment of ASC and pro-caspase-1,resulting in AIM2 inflammasome-caspase-1-mediated pyroptosis. **(B)** Under normal conditions, human and murine pyrin is phosphorylated by the Ras homolog family member A (RhoA) effector kinases, protein kinase N1/2 (PKN1/2) that keep pyrin in an inactive state. Bacterial toxins can inhibit RhoA activity and subsequent PKN1/2 phosphorylation, leading to the dephosphorylation of pyrin,which maintain it active status and recruits ASC and pro-caspase-1. Ultimately, active caspase-1 Inducts pyroptosis.

the processing and maturation of GSDMD, leading to the secretion of IL-1β and IL-18 (90, 91). In contrast to the typical inflammasome-mediated pyroptosis that requires various protein components for ligand sensing, assembly, and effector functions, caspase-4/5/11 possesses the ability to directly bind to cytoplasmic lipopolysaccharide (LPS) via its N-terminal CARD domain (92). It cleaves GSDMD, generating GSDMD-N, which translocates to the cell membrane and forms oligomers, creating membrane pores (93). It is important to note that the release of IL-1β and IL-18 occurs through secondary activation of the canonical pathway (17) (Figure 2). The noncanonical pathway-induced pore formation leads to potassium efflux, subsequently activating canonical pathway mediated by NLRP3 inflammasome and resulting in the secretion of IL-1β and IL-18 (94, 95). Furthermore, a recent study by Zhu et al. discovered a cytoplasmic lipopolysaccharide (LPS) sensor, an orphan nuclear receptor called Nur77, which binds to LPS and mitochondrial DNA and activates the atypical NLRP3 inflammasome (96). Extracellular LPS can enter the cytoplasm through endocytosis mediated by the Toll-like receptor 4 (TLR4) or bacterial outer membrane vesicles (OMVs) (96–98). It is reported that in interferon γ-stimulated cells the host guanylate binding protein (GBP) facilitates the surface of Gram-negative bacteria into a multivalent signaling platform required for caspase-4 activation (99).

LPS-induced activation of noncanonical pathway triggers pyroptotic cell death and cytokine release through GSDMD pores, which is essential in the protection against cytoplasmic invading bacteria as well as in the induction of endotoxin shock. It is 1-

palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (oxPAPC) and its derivatives that show potential as therapeutic targets for noncanonical inflammasomes during Gram-negative bacterial sepsis. OxPAPC, an oxidized phospholipid derived from the host, competitively binds to LPS and inhibits the activation of the noncanonical inflammasome by caspase-4/11 in macrophages (100). However, this inhibition is not observed in dendritic cells (101). Furthermore, Li et al. revealed the immune escape mechanism of Shigella flexneri, which evades pyroptosis mediated by the atypical inflammasome caspase-4/11 through the secretion of inhibitory effectors or modification of its LPS structure (102).

5 Gasdermins-dependent pyroptosis

In recent years, there have been significant advancements in the understanding of pyroptotic underlying mechanisms, leading to the revision and redefinition of pyroptosis. Studies have increasingly reported that pyroptosis can occur without the activation of inflammasome and inflammatory caspases (103, 104). Instead, this cell death process relies on members of the gasdermin family. Some studies have proposed redefining "pyroptosis" as "call necrotic death induced by gasdermins" to better capture its characters of dependence on gasdermin family proteins (93, 105). The gasdermin protein family comprises six members: gasdermins A-E and deafness autosomal recessive type 59 (DFNB59 or pejvakin). Except for DFNB59, all other gasdermins have been implicated in the induction of

pyroptosis, as demonstrated in studies (35, 106). In the following sections, we will provide a brief overview of some research findings on the involvement of the five GSDMs in pyroptosis (Figure 6).

5.1 GSDMA

GSDMA, identified as a pyroptosis-triggering effector, whose activator bypasses inflammasomes and caspases has been reported recently (104, 107). GSDMA undergoes cleavage by the group A Streptococcal (GAS) cysteine protease SpeB, leading to the formation of pores in the cell membrane. This finding provide a piece of evidence that GSDMs can function as direct sensors of exogenous proteases, independent of host inflammasome sensors.

5.2 GSDMB

GSDMB plays a role in promoting the cleavage of GSDMD by enhancing the enzymatic activity of caspase-4, thereby participating in non-canonical pyroptosis (108). In 2020, it was found that lymphocyte-derived GzmA cleaves GSDMB, leading to pyroptosis in natural killer cells and cytotoxic T lymphocytes, indicating the activation of non-caspase factors (105). Similarly, GSDMB has recently been discovered to possess direct bactericidal activity

through its pore-forming capability (109). However, compared with other gasdermin s, the pyroptosis function of GSDMB has been questioned by some researchers (108, 109). Recently, Zhong et al. discovered the Shigella flexneri ubiquitin-ligase virulence factor IpaH7.8 can degrade GSDMB through a similar mechanism as target human GSDMD. Author considered the structure of GSDMB suggests stronger autoinhibition than other gasdermins, which is related to relatively poor pyroptosis function of GSDMB (110).

5.3 GSDMC

Caspase-8 has been reported to specifically cleave GSDMC to induce tumor cell scorch death (27, 111). Under hypoxia conditions, p-Stat3 physically interacts with programmed cell death ligand-1 (PD-L1), leading to its nuclear translocation and upregulation of GSDMC gene expression. Caspase-8 is specifically processed by macrophage-derived TNF-α to cleave GSDMC to induce scorch death (27). The function of PD-L1 beyond immune checkpoint regulation has been confirmed by these studies.

5.4 GSDMD

The innate immune system exhibits a complex interplay between cell death pathways and caspase-8 is extensively involved
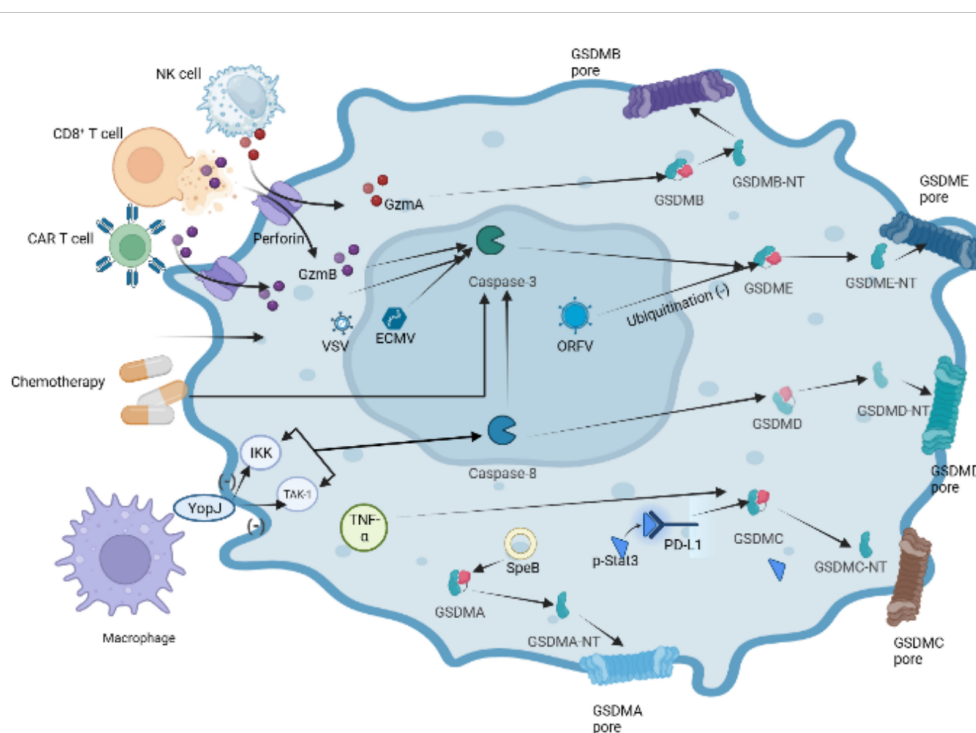

FIGURE 6
Other pathways of GSDMDs-dependent pyroptosis. In the granzyme-mediated pathway, GzmA secreted from NK cells and CD8+ T cells induces GSDMB-mediated pyroptosis. CAR-T cells can release a great deal of perforin and GzmB activating caspase-3,which cause GSDME cleaved by caspase-3 in target cells.Chemotherapeutic drugs could induce caspase-3-mediated GSDME cleavage with high GSDME expression and form GSDME-NT, causing pyroptosis of tumor cells. The inhibition of TAK1 and IKK activates caspase-8 via the lysosomal rag-ragulator complex, resulting in GSDMD cleavage and pyroptosis by Yersinia. Under hypoxia conditions, p-Stat3 interacts with PD-L1 and upregulates the transcription of GSDMC. Activated by TNF-α, caspase-8 cleaves GSDMC into GSDMC-NT, resulting in pyroptosis. Group A Streptococcal (GAS) cysteine protease SpeB cleaves directly to induce GSDMA-dependent pyroptosis.

in regulating pathways of apoptosis (112, 113). Studies have shown that Yersinia-infected mouse macrophages can inhibit kinase-1 (TAK1) or IκB kinase (IKK) through the effector protein YopJ, which results in caspase-8-dependent cleavage of GSDMD, subsequently triggering GSDMD-mediated pyroptosis (114, 115). Recently, it was demonstrated that the lysosomal membrane-anchored follicle protein (FlCN)-folliculin-interacting protein 2 (FNIP2)-Rag-Ragulator complex, which can recruit Fas-Associated protein with Death Domain (FADD), receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and caspase-8 and result in RIPK1 phosphorylation and caspase-8 activation, is necessary for RIPK1-caspase-8-dependent GSDMD-mediated pyroptosis (116).

5.5 GSDME

Active caspase-3 cleaves GSDME to generate an N-terminal fragment of GSDME and induces pyroptosis. Chemotherapeutic drugs can trigger caspase-3-gasdermin E mediated pyroptosis in tumor cells (117, 118). Interestingly, chemotherapeutic drugs induce caspase-3 mediated apoptosis in cells with low expression of GSDME, which indicates complex interactions between cell death Pathway in the immune system. In addition, recent reports have demonstrated that GSDME is cleaved by caspase-3 activated by granzyme B (GZMB) (119). GZMB, a serine protein highly expressed in cytotoxic lymphocytes, can augment the immune response of NK cells and CD8+ T cells. Chimeric antigen receptor (CAR) T cells can release more granzyme B which triggers the cleavage of GSDME to mediate B leukemic cells pyroptosis, and perforin than nontransduced natural T cells (119) (Figure 6). Several viruses have been found to induce pyroptosis through GSDME. For instance, Oncolytic parapoxvirus (ORFV) stabilizes GSDME by reducing its ubiquitination, leading to tumor cell pyroptosis (120). Additionally, infection with vesicular stomatitis virus (VSV) or encephalomyocarditis virus (ECMV) has been shown to trigger caspase-3/GSDME mediated pyroptosis in bone marrow-derived macrophages (BMDM) (118).

6 The relationship between pyroptosis and endometrial cancer

6.1 Inflammasome in endometrial cancer

The NLRP3 inflammasome is closely associated with the progression of various gynecological diseases., including polycystic ovary syndrome (121), cervical cancer (122, 123), ovarian cancer and endometriosis (EM) (124). EM is an inflammation-dependent disease with adhesive and invasive properties, sharing similarities with malignancies. NLRP3 inflammasome levels are relatively low in normal endometrium but significantly upregulated in EM and EC tissues (124–126). Zhou et al. demonstrated that NLRP3 activation in macrophages increased the secretion of IL-1β, promoting the migration and

invasion capabilities of endometrial stromal cells (ESCs) *in vitro*. Murakami et al. administered the NLRP3 inhibitor MCC950 to ovarian endometriosis (OE) mice and showed that inhibition of NLRP3 inflammasome activity reduced the expression of IL-1β and Ki67 in cyst-derived stromal cells (CSCs), leading to a significant inhibition of OE lesion size (127).

Estrogen receptors α (ERα) and ERβ play a crucial role in the development and malignant progression of type 1 endometrial cancer (128). 17β-estradiol (E2) binds to ERα and activates fibroblasts and myofibroblast cells, leading to the secretion of cell cycle proteins (MAD2L1, CDKN1A, and CEBPβ) and growth factors (IGF and TGF), which promotes epithelial-mesenchymal transition (EMT) and alters the expression levels of cell adhesion proteins, such as E-cadherin and β-catenin, enhancing resistance to apoptosis and promoting the activity of migration, and invasion (129). ERβ, which is less studied, is considered a gynecological tumor suppressor and plays an opposing role to ERα in EC development (130). Moreover, It can impair the transcriptional function of ERα (131). A study in 2019 found that E2 acts through ERβ, enhances the activation of NLRP3 inflammasome, and promotes the progression of endometrial cancer (132). These findings suggest that the abnormally expressed NLRP3 inflammasome in EC could be a specific target for clinical therapy. However, further research and exploration are needed to understand the impact of pyroptosis involving NLRP1, NLRC4, AIM2, and PYRIN inflammasome on the biological behavior of EC.

6.2 Gasdermins in endometrial cancer

GSDMD, GSDME, and GSDMB are the main pyroptosis-related GSDMs expressed in the endometrium (93). Yang et al. discovered that the expression of GSDMD was higher in EC and atypical hyperplastic endometrial tissues compared to benign endometrial tissues (126). Moreover, GSDMD serves as a prognostic marker and potential therapeutic target for endometrial cancer, considering GSDMD related to Wnt signaling and substance metabolism pathways.

Deafness autosomal dominant 5 (DFNA5), a potential tumor suppressor gene, has gained significant attention from researchers in recent years. Hu et al. discovered that DFNA5 expression was significantly lower in kidney chromosome (KICH), prostate adenocarcinoma (PRAD) and breast invasive carcinoma (BRCA) compared to adjacent normal tissues (133). In addition, methylation of the GSDME gene promoters in breast cancer has been associated with poor 5-year survival rate (134, 135). Several studies have reported downregulation of the GSDME gene in EC cells compared to surrounding normal tissues (133, 136). However, tumor microenvironment (TME) with low GSDME expression has been found to have reduced tumor-infiltrating lymphocytes (TIL, CD8+ T and NK), GzmB, and perforin (PFN), potentially leading to an immunotherapy-unfavorable microenvironment in EC (137). The mechanism by which GSDMB affects EC is currently unclear, and there is limited research on the role of GSDMB in EC. Pyroptosis mediated by GSDMs is emerging as a novel antitumor

therapy (119), and further studies are needed to elucidate the mechanistic role of GSDMs in EC.

6.3 Dual roles of pyroptosis in endometrial cancer

Tumor cells, stromal cells, immune cells, and extracellular matrix (ECM) components in the tumor microenvironment (TME) form a complex network (138), which collectively regulates tumor cell proliferation and metastasis under hypoxic and inflammatory conditions. Pyroptosis plays a dual role in the occurrence and progression of EC. On one hand, the inflammatory response amplified by pyroptosis promotes the formation of an inflammatory microenvironment conducive to the growth of EC cells. On the other hand, inducing pyroptosis may inhibit the malignant progression of EC (Table 2).

6.3.1 Pyroptosis-mediated inflammatory microenvironment promotes endometrial cancer progression

Numerous cohort studies and meta-analyses have confirmed a positive correlation between obesity, insulin resistance, diabetes, and endometrial cancer (139–142). This association is linked to systemic or endometrium local chronic inflammatory conditions of obese and diabetic patients (143, 144). The imbalance of adipokines and cytokines in obese women creates TME conducive to the development and progression of endometrial cancer. Obese individuals exhibit reduced secretion of the anti-inflammatory adipokine adiponectin and increased secretion of inflammatory adipokines, such as leptin, which promote EC proliferation and metastasis. Inflammatory cells in adipose tissue show elevated secretion of IL-6, IL-11 and tumor necrosis factor-α (TNF-α). Poor blood glucose regulation in diabetic patients is often associated with increased levels of IL-1β and TNF-α (58).In vitro studies have demonstrated the ability of IL-1β to promote the proliferation and metastasis of human endometrial stromal cells (HESCs) (145).

Pyroptosis, as a pro-inflammatory form of cell death, is characterized by the secretion of IL-1β and IL-18. Its role in diabetes mellitus (DM)-associated EC has attracted scholarly attention. Guo et al. discovered that under hyperglycemia (HG)

conditions, hexokinase domain protein 1 (HKDC1) activates canonical NLRP3 inflammasome-mediated pyroptosis through mitochondrial ROS. This process creates a pro-inflammatory and acidic TME that promotes the malignant progression of EC (125). *In vitro* experiments further demonstrated that lncRNA-HOXC-AS2 acts as a competing endogenous RNA (ceRNA) to potentially inhibit miR-876-5p, resulting in the upregulation of HKDC1. These findings reveal the potential therapeutic significance of targeting the lncRNA-HOXC-AS2/miR-876-5p/HKDC1 axis as a treatment approach for HG-associated EC (125).

6.3.2 Inducing pyroptosis of EC cells to exert anti-endometrial cancer effect

In recent years, the regulation of tumor cell pyroptosis as an anti-endometrial cancer treatment strategy has gained confirmation. Yang et al. confirmed through *in vivo* and *in vitro* experiments that molecular hydrogen can activate ROS and mtROS production in endometrial cancer cells. This activation triggers the ROS-NLRP3-caspase-1-GSDMD pathway, leading to pyroptosis and influencing the biological behavior of endometrial cancer cells. In mouse models transplanted with EC tissue, this intervention resulted in reduced tumor volume and weight (126). Hydrogen molecules, known as natural antioxidants, selectively reduce hydroxyl radicals, the most cytotoxic ROS, without affecting other physiological ROS (146). The anti-oxidative stress, anti-inflammatory, and anti-apoptotic effects of hydrogen have been confirmed in animal models of cardiovascular and cerebrovascular diseases, chronic liver disease, pancreatitis, and other conditions (146–148). In clinical trials, hydrogen inhalation has shown the ability to reduce airway inflammation in patients with asthma and COPD (149).

In a hypoxic environment, tumour cells activate hypoxia-inducible factor 1α (HIF-1α) to reprogramme their energy metabolism pathways to maintain high proliferation rates and promote tumour growth, invasion and neointima formation. Studies have shown that over expression of HIF-1α in EC promotes lymph node metastasis and myometrial invasion of tumour cells, which is significantly associated with poor prognosis of EC (150). It is known that hypoxia up-regulates cyclin-dependent kinase inhibitors p27 and p53, causing cell cycle arrest and thus favoring the survival of endometrial cancer cells (151, 152). Notably it has recently been proposed that high expression of HIF-1α in EC tissues also enhances the anti-pyroptosis characteristics of tumour cells (153). However, this hypothesis awaits further scientific proof in the form of experiments.

7 Prospects of pyroptosis in anti-endometrial cancer therapy

Recent studies have demonstrated the feasibility and clinical potential of using pyroptosis as an anticancer therapy mechanism. Many researchers are attempting to treat cancer by modulating pyroptosis with other oncology treatments to inhibit tumor cell proliferation, migration and invasion.

TABLE 2 The regulatory role of pyroptosis-related targets in endometrial cancer progression.

Target	Mechanism	Function	Reference
E2	Activates ERβ-NLRP3-caspase-1-GSDMD	Induce pyroptosis and promote endometrial cancer	(132)
HKDC1	Activates ROS-NLRP3-caspase-1-GSDMD	Induce pyroptosis and promote endometrial cancer	(125)
Hydrogen	Activates ROS-NLRP3-caspase-1-GSDMD	Induce pyroptosis and suppress endometrial cancer	(126)

7.1 Radiotherapy

Postoperative radiation therapy (RT), comprising total pelvic external beam radiation therapy (EBRT) and intracavity vaginal brachytherapy (VBT), is a crucial adjuvant treatment for women with intermediate-risk and high-risk EC. It effectively decreases the risk of local EC recurrence (154, 155). The challenge in radiotherapy for human tumors has always been to achieve maximal tumor cell eradication while minimizing radiotoxicity to adjacent normal organs.

Currently, pyroptosis has been implicated in radiation-induced damage to normal tissues. For instance, Li et al. demonstrated that high-dose X-ray irradiation triggered pyroptosis in human umbilical vein endothelial cells (HUVECs) (156). The activation of caspase-1 and release of IL-1β are influenced by Panx1, an important factor in pyroptosis (157). Hu et al. reported that ionizing radiation and chemotherapeutics-induced DNA damage in the nucleus can activate the AIM2 inflammasome, leading to caspase-1-mediated pyroptosis in intestinal epithelial cells and myeloid cells (85). Hence, targeting the AIM2 inflammasome could potentially alleviate myelodysplastic syndrome or gastrointestinal toxicity in cancer patients undergoing radiation or chemotherapy. Wu et al. found that radiation-induced pyroptosis in small intestinal cells involves the activation of the NLRP3 inflammasome/caspase-1 pathway through ROS generation (158). Notably, FlaAN/C, a flagellin derivative, was shown to inhibit radiation-induced ROS production and protect small intestinal tissue (158). Although the clinical application of pyroptosis blockade to mitigate the toxic side effects of radiotherapy requires extensive preclinical validation, these findings offer valuable insights into the mechanisms underlying radiation-induced cytotoxicity.

7.2 Chemotherapy

Cancer chemotherapy is a rapidly evolving field faced with challenges of drug resistance and adverse reactions. Precise regulation of pyroptosis has emerged as a potential solution to address tumor chemotherapy resistance and adverse events (AEs) (117, 159). Platinum- and paclitaxel-based chemotherapy resistance and toxic side effects pose significant challenges in the treatment of advanced, recurrent and metastatic EC (160). A multicenter retrospective cohort study analyzing 262 patients with recurrent endometrial cancer who had a history of receiving first-line platinum-based chemotherapy, found the response rates at second-line chemotherapy for patients with platinum-free intervals of <6 months, 6-11 months, 12-23 months and ≥24 months were 25%, 38%, 61% and 65%, respectively (161). It has been demonstrated that a ruthenium(II) polypyridine complex, Δ-Ru1, in combination with paclitaxel, can enhance the anticancer effect on paclitaxel-resistant cancer cells through caspase-1/GSDMD-mediated pyroptosis (162). Differential expression of GSDME in tumor cells versus normal cells has been associated with chemotherapy sensitivity and AE (137). Cancer cells with low GSDME expression undergo caspase-3-mediated apoptosis upon

chemotherapy, while those with high GSDME expression shift towards pyroptosis (117). Decitabine and azacitidine have been shown to reverse GSDME silencing, increasing tumor cell sensitivity to chemotherapeutic drugs (117). These drugs are used in the treatment of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (163, 164). Compared with GSDME-/- mice, wild-type mice exhibited increased severity of cisplatin-induced weight loss and spleen size reduction. Meanwhile, intraperitoneal injection of 5-FU exacerbated intestinal bleeding, inflammatory cell infiltration and crypt loss in wild-type mice (117). Reversing the expression level of GSDME in cancer cells may hold the key to leveraging pyroptosis therapy for EC treatment in the coming years.

In recent years, pyroptosis has emerged as a distinct form of cell death that can be triggered by exogenous drugs in various cancers, offering a unique anti-tumor mechanism different from apoptosis or autophagy. For instance, cisplatin and paclitaxel have been shown to induce pyroptosis in lung cancer A549 cells through caspase-3/GSDME activation (165). Lobaplatin was proven to induces ROS/JNK (c-Jun N-terminal kinase) signalling to induce the pyroptosis via a novel Bax-caspase-GSDME pathway in colon cancer cells (166). Similarly, 2-(α-naphthoyl) ethyltrimethylammonium iodide (α-NETA) was found to inhibit epithelialization and induce caspase-4-triggered pyroptosis in epithelial ovarian cancer, restraining the proliferation of it (167). Tanshinone IIA has demonstrated anticancer activity against cervical cancer cells by upregulating miR-145/GSDMD signaling (168). The underlying mechanisms of these compounds regulating pyroptosis pathway are summarized in Table 3.

7.3 Targeted therapy

Since the identification of 4 distinct EC subgroups associated with differential survival by The Cancer Genome Atlas (TCGA), clinical trials investigating targeted therapies for EC have been expanding and showing promise. For instance, the combination of TC (carboplatin and paclitaxel) plus trastuzumab has demonstrated increased progression-free survival (PFS) (HR = 0.46; 90% CI, 0.28-0.76) and overall survival (OS) (HR=0.58; 90% CI, 0.34–0.99) in patients with advanced or recurrent uterine-serous-carcinoma (USC) exhibiting human epidermal growth factor receptor 2 (HER2) overexpression (175). Vascular endothelial growth factor (VEGF) is considered a crucial factor in tumor angiogenesis, regulating tumor proliferation, invasion, migration, and neovascularization (176–178). Combining anti-angiogenic drugs, such as bevacizumab, with carboplatin and paclitaxel has significantly prolonged OS of EC (OS HR=0.28; 95% CI, 0.14-0.59), particularly those with TP53 mutations, compared to paclitaxel and carboplatin regimens (179, 180). Lenvatinib combined with pembrolizumab has shown significant improvements in PFS and OS for EC patients and has received FDA approval for second-line treatment of recurrent or metastatic endometrial cancer (181). However, lenvatinib is associated with common adverse reactions in clinical applications, including

TABLE 3 Compounds inducing pyroptosis signal pathways in cancers.

Classifcation	Compounds	Cancer types	Mechanisms of pyroptosis induction	References
Chemotherapy drugs	Decitabine/Azacitidine	MDS/AML	Caspase3/GSDME	(117)
	Topotecan/Etoposide/Cisplatin	neuroblastoma	Caspase3/GSDME	(117)
	Cisplatin/PTX	Lung cancer	Caspase-3/GSDME	(165)
	Lobaplatin	CRC	ROS/JNK/Caspase-3/GSDME	(166)
	DOX	breast cancer	ROS/JNK/Caspase-3/GSDME	(159)
Natural products	Dioscin	OS	Caspase-3/GSDME	(169)
	DHA	ESCC	PKM2-Caspase-8/3-GSDME	(170)
	CME	Lung cancer	Caspase-3/GSDME	(170, 171)
	CBD	HCC	Caspase-3/GSDME	(25)
	Tanshinone IIA	Cervical cancer	miR-145/Caspase-1/GSDMD	(168)
	Berberine	HCC	Caspase-1	(172)
Reagents	C10	Prostate cancer	PKCδ/JNK/Caspase-3/GSDME	(173)
	BI 2536	OC	Caspase-3/GSDME	(28)
	α-NETA	OC	Caspase-4/GSDMD	(167)
	13d	Lung Cancer	inhibit NF-kB pathway	(174)

PTX, paclitaxel; DOX, doxorubicin; DHA, Dihydroartemisinin; CME, Cordyceps militaris extract. CBD, Cannabidiol; C10, 3',5'-diprenylated chalcone; α-NETA, 2-(α-naphthoyl) ethyltrimethylammonium iodide; 13d, low toxicity NF-kB inhibitor; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; CRC, colorectal cancer; OS, osteosarcoma; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; OC, ovarian cancer; GSDME, gasdermin E; GSDMD, gasdermin D; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; PKM2, pyruvate kinase isoform M2; miR-145, microRNA-145; PKCδ, protein kinase C delta; NF-kB, Nuclear factor kB.

fatigue, fever, nausea, vomiting, hypertension, diarrhea, and more severe events like liver injury and intracranial hemorrhage (182, 183). Grade 3 or higher AEs often impact the tolerability of recurrent EC patients.

Anti-angiogenic drugs exhibit anti-tumor effects by triggering pyroptosis, which is associated with an amplified inflammatory response leading to adverse drug events. Sorafenib, a broad-spectrum kinase inhibitor used for hepatocellular carcinoma (HCC) treatment, induces macrophage pyroptosis by activating caspase 1. The released cytokines synergistically enhance NK cell effector functions, resulting in effective tumor cell killing (184). Lenvatinib, on the other hand, induces ROS-caspase 3-GSDME-dependent pyroptosis in GSDME-expressing cells through the loss of mitochondrial membrane potential (185). However, ZLF-095, a novel VEGFR inhibitor, effectively inhibits liver and colorectal cancer proliferation without inducing pyroptosis, thus reducing the adverse effects associated with lenvatinib (185). This study highlights the potential association between pyroptotic amplified inflammatory response and adverse reactions caused by systemic treatment of lenvatinib. In the treatment of anaplastic thyroid cancer (ATC), the combination of apatinib, an anti-angiogenic targeted drug, with melittin activates caspase-1/GSDMD and caspase-3/GSDME-mediated pyroptosis. This combination reduces the incidence of adverse events by decreasing the therapeutic dose of apatinib alone. Furthermore, positive feedback interaction was observed between the two GSDM-mediated pyroptotic pathways (186). Currently, there is limited research on whether anti-angiogenic drugs activate pyroptosis in EC to exert

anti-tumor effects. Understanding the biological effects of pyroptosis factors in EC targeted therapy is crucial for optimizing treatment strategies and improving prognosis in the future.

7.4 Immunotherapy

Pyroptosis plays a crucial role in converting "cold" tumors into "hot" ones and exhibits a synergistic effect when combined with immune checkpoint blockade (ICB) therapy. The exploration and analysis of molecular subtypes have become significant aspects of anti-tumor drug research in EC. While Immune checkpoint inhibitor shows positive responses in patients with microsatellite instability-high (MSI-H) and mismatch repair deficient (MMRd) EC (187, 188), the overall response rate remains low due to ineffective infiltration or activation of T lymphocytes and NK cells within the tumor microenvironment. Notably, despite being of the mismatch repair deficient (MMRd) subtype, 22% of the cases still exhibit low levels of TIL-Low, with such matters being more prevalent in p53 abnormal type (p53abn) and p53 wild type (p53wt) (189).

However, GSDME expression can modulate the quantity and function of tumor-infiltrating natural killer (NK) cells and CD8+ T lymphocytes, which triggers cytotoxic granule-mediated PFN-dependent killing and cytokine secretion, thereby enhancing the patients' anti-tumor immunity (137, 190). Cancer cells have developed two strategies to evade GSDME-mediated tumor suppression: epigenetic suppression and mutation of GSDME

(135). Consequently, upregulating GSDME expression in EC, potentially through the use of DNA methylation inhibitors, is expected to improve the response rates to ICB therapy of all molecular subtypes.

In addition, statins have been reported to enhance antitumor immunity by promoting caspase-1/GSDMD-induced pyroptosis and synergistically inhibiting ARID1A-mutated clear cell ovarian cancer (OCCC) when combined with ICB therapy (191). These findings provide valuable insights for the development of drugs targeting pyroptosis-related pathways to activate anti-tumor immunity in endometrial cancer.

8 Pyroptosis in diagnosis and prognosis of endometrial cancer

Molecular typing of EC has become widely used for prognostic assessment and treatment guidance. Currently, the activation of signaling pathways including PI3K/Akt, P53, mitogen-activated protein kinase, and Wnt/β-catenin is known to be closely associated with the pathogenesis of EC (10). Mutations in genes such as PTEN, PI3KCA, POLE, CTNNB1, and TP53, loss of DNA mismatch repair proteins, expression of estrogen receptors and progesterone receptors, and overexpression of HER2 are involved in the diagnosis and prognosis of EC (6, 10). Additionally, several studies have explored the expression levels of pyroptosis-related genes and proteins in EC patients, along with their correlation with patient prognosis, through bioinformatics analysis (Table 4). These studies aim to identify more effective therapeutic targets and diagnostic biomarkers associated with prognosis.

TABLE 4 Pyroptosis-related genes in patients with endometrial cancer.

Related genes	Diagnostic potential	Prognostic potential	Reference
CASP3, GPX4, GSDMD, NOD2, PYCARD and TIRAP		√	(192)
BAK1, CHMP2A, GSDMD, IRF2, GPX4, GSDMB, TIRAP and TNF		√	(193)
HM13-IT1, FIRRE, NNT-AS1, ATP6V0E2-AS1, AL353622.1 and POC1B-AS1		√	(194)
NLRP1, NLRP6, TNF, NOD2, IL18, ELANE, CASP5, NLRP3, AIM2 and IL-6		√	(195)
NFKB1, EEF2K, CTSV, MDM2, GZMB, PANX1 and PTEN		√	(196)
AC087491.1, AL353622.1, AL035530.2, LINC02036, AL021578.1, AL390195.2, AC009097.2, AC004585.1 andAC244517.7		√	(197)

9 Discussion and outlook

The understanding of the regulatory mechanisms and key regulators of pyroptosis, an emerging form of cell death, has rapidly advanced since its discovery. The precise regulation of pyroptosis in EC cells *in vivo* may offer a new treatment strategy for those patients who are ineligible for surgery, radiotherapy or chemotherapy. Pyroptosis, as a proinflammatory form of cell death, exhibits a dual role in the occurrence and development of EC. On one hand, the inflammatory environment induced by pyroptosis can promote the growth of EC cells and contribute to tumor formation, invasion, and metastasis. On the other hand, the induction of pyroptosis in EC cells can exert anti-tumor activity. This dual role, possibly attributed to the complexity of the pyroptosis pathway and its components, poses significant challenges for the clinical regulation of EC cell pyroptosis as a treatment. Numerous studies have demonstrated that conventional tumor treatments not only induce cancer cells apoptosis, but also trigger pyroptosis. It seems feasible and promising that combining pyroptosis with other tumor treatments, such as radiotherapy, chemotherapy and immunotherapy, to treat EC by regulating pyroptosis to suppress the proliferation, migration, and invasion of tumor cells.

This article provides a comprehensive review of physiological and pathological effects as well as the molecular mechanism of pyroptosis, with a specific focus on its research progress in the development, prognosis, and treatment of EC. However, these studies represent only a fraction of the research conducted thus far. Pyroptosis is expected to play a central role in EC therapy in the coming years. For instance, precise regulation of EC pyroptosis to directly exert anti-tumour activity, in addition, induction of EC pyroptosis can increase the response rates of first-line chemotherapy and immunotherapy for advanced and recurrent EC, and lessen the AEs of radiotherapy, chemotherapy and targeted therapy. Currently, numerous unanswered questions remain. EC is characterized by highly heterogeneous and it is not clear how sensitive different molecular subtypes of EC are to pyroptosis. Additionally, it is important to explore the regulators and mechanisms that influence the sensitivity of EC cells to pyroptosis. Furthermore, apart from NLRP3 inflammasome activation, there may be other pathways that induce pyroptosis and trigger distinct biological effects. The functional implications of different gasdermins and, in particular, the roles of GSDMB and GSDME in EC remain largely unknown. Addressing these issues will require further comprehensive investigations through massive preclinical and clinical studies.

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Conflict of interest

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Glossary

BMI	body mass index
FIGO	The International Federation of Gynecology and Obstetrics
TCGA	The Cancer Genome Atlas
OS	overall survival
GSDMs	gasdermins
GSDMs-CT	gasdermins-N terminal
GSDMs-NT	gasdermins-C terminal
IL-1β	interleukin-1β
IL-18	interleukin-18
ATP	adenosine triphosphate
HMGB1	high mobility group protein box 1
RCD	regulated cell death
ACD	accidental cell death
PCD	programmed cell death
GSDMD	gasdermin D
GzmB	Granzyme B
GzmA	Granzyme A
TME	tumor microenvironment
ASC	apoptosis-associated speck-like protein
PRRs	pattern recognition receptors
NOD	nucleotide-binding oligomerization domain
LRR	leucine-rich repeat
AIM2	absent in melanoma 2
PYD	pyrin domain
CARD	recruitment domain
PAMPs	pathogen-associated molecular patterns
DAMPs	danger-associated molecular patterns
NACHT	oligomerization domain with ATPase activity
mtROS	mitochondrial reactive oxygen species
Ox-mtDNA	oxidized mitochondrial DNA
TGN	trans-Golgi apparatus
dTGN	disassembled trans-Golgi network structure
PI4P	phosphatidylinositol 4-phosphate
EECS	endoplasmic reticulum-endosome membrane contact sites
HRV	human rhinovirus
UVB	Ultraviolet B
DPP8	dipeptidyl peptidase 8

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DPP9	dipeptidyl peptidase 9
LeTx	lethal toxin
NAIP	NLR apoptosis inhibitory protein
LRRK2	leucine-rich repeat kinase 2
PKCδ	protein kinase Cδ
IFN	type I interferon
GBPs	guanylate binding proteins
IRGB10	
FMF	Mediterranean fever
PKN1	protein kinase N1
PKN2	protein kinase N2
oxPAPC	1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine
DFNB59 or pejvakin	deafness autosomal recessive type 59
GAS	group A Streptococcal
PD-L1	Programmed cell death ligand 1
FlCN	follicle protein
FNIP2	folliculin-interacting protein 2
FADD	Fas-Associated protein with Death Domain
RIPK1	receptor-interacting serine/threonine-protein kinase 1
CAR-T	Chimeric antigen receptor T
ORFV	Oncolytic parapoxvirus
ECMV	encephalomyocarditis virus
NK	natural killer
BMDM	bone marrow-derived macrophages
EM	endometriosis
ESCs	endometrial stromal cells
OE	ovarian endometriosis
CSCs	cyst-derived stromal cells
ERα	estrogen receptors α
ERβ	estrogen receptors α
E2	17β-estradiol
MAD2L1	mitotic arrest deficient 2 like 1
CDKN1A	Cyclin-Dependent Kinase Inhibitor 1A
CEBPβ	CCAAT enhancer binding protein beta
IGF	Insulin-Like Growth Factor
TGF	transforming growth factor
EMT	epithelial-mesenchymal transition
DFNA5	Deafness autosomal dominant 5
BRCA	breast invasive carcinoma

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KICH	kidney chromosome
IL	tumor-infiltrating lymphocytes
TME	tumor microenvironment
PFN	perforin
ECM	extracellular matrix
TNF-α	tumor necrosis factor-α
HESCs	human endometrial stromal cells
DM	diabetes mellitus
HG	hyperglycemia
HKDC1	hexokinase domain protein 1
LncRNA	Long noncoding RNA
ceRNA	competing endogenous RNA
HIF-1α	hypoxia-inducible factor-1α
RT	radiation therapy
EBRT	external beam radiation therapy
VBT	vaginal brachytherapy
HUVECs	human umbilical vein endothelial cells
AEs	adverse events
MDS	myelodysplastic syndrome
AML	acute myeloid leukemia
JNK	c-Jun N-terminal kinase
α-NETA	2-(α-naphthoyl) ethyltrimethylammonium iodide
USC	Uterine-serous-carcinoma
HCC	hepatocellular carcinoma
ATC	anaplastic thyroid cancer
MMRd: MSI-H	mismatch repair deficient
p53abn	p53 abnormal type
p53wt	p53 wild type
HER2	human epidermal growth factor receptor 2