



# Pyroptosis: A Developing Foreland of Ovarian Cancer Treatment

Tianyi Liu<sup>1†</sup>, Min Hou<sup>2,3,4,5,6†</sup>, Manyu Li<sup>7</sup>, Cheng Qiu<sup>7,8</sup>, Lin Cheng<sup>8</sup>, Tianyu Zhu<sup>7</sup>, Jinfeng Qu<sup>9</sup> and Lanyu Li<sup>9\*</sup>

<sup>1</sup> Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, <sup>2</sup> Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University, Jinan, China, <sup>3</sup> Key Laboratory of Reproductive Endocrinology of Ministry of Education, Shandong University, Jinan, China, <sup>4</sup> Shandong Key Laboratory of Reproductive Medicine, Jinan, China, <sup>5</sup> Shandong Provincial Clinical Research Center for Reproductive Health, Jinan, China, <sup>6</sup> National Research Center for Assisted Reproductive Technology and Reproductive Genetics, Shandong University, Jinan, China, <sup>7</sup> Cheeloo College of Medicine, Shandong University, Jinan, China, <sup>8</sup> Department of Orthopaedic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China, <sup>9</sup> Department of Obstetrics and Gynecology, Central Hospital Affiliated to Shandong First Medical University, Jinan, China

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### \*Correspondence:

Lanyu Li  
ljjandlly@163.com

### †ORCID:

Tianyi Liu  
orcid.org/0000-0002-6308-8076

†These authors have contributed  
equally to this work and  
share first authorship

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Ovarian cancer (OVCA) has the second highest mortality among all gynecological cancers worldwide due to its complexity and difficulty in early-stage diagnosis and a lack of targeted therapy. Modern strategies of OVCA treatment involve debulking surgery combined with chemotherapy. Nonetheless, the current treatment is far from satisfactory sometimes and therefore the demand for novel therapeutic measures needs to be settled. Pyroptosis is a notable form of programmed cell death characterized by influx of sodium with water, swelling of cells, and finally osmotic lysis, which is distinctive from numerous classes of programmed cell death. So far, four major pathways underlying mechanisms of pyroptosis have been identified and pyroptosis is indicated to be connected with a variety of disorders including cancerous diseases. Interestingly enough, pyroptosis plays an important role in ovarian cancer with regard to long non-coding RNAs and several regulatory molecules, as is shown by previously published reports. In this review, we summarized major pathways of pyroptosis and the current research foundations of pyroptosis and ovarian cancer, anticipating enriching the thoughts for the treatment of ovarian cancer. What is more, some problems yet unsolved in this field were also raised to hopefully propose several potential threads of OVCA treatment and research directions in future.

**Keywords:** pyroptosis, ovarian cancer, gasdermin, inflammasome, caspase, cell death

## INTRODUCTION

Among all gynecological cancers, ovarian cancer (OVCA) does not represent the largest portion of new cases, but it is the cancer type with the second highest mortality worldwide (1, 2). Although the incidence has almost been stable for several years, OVCA is still estimated as the fifth cancer death reason for American women in 2021 due to its complexity and difficulty in early-stage diagnosis and a lack of targeted therapy (3). Moreover, the ovarian cancer patients usually show no evident

symptoms at the early stage. Even in advanced OVCA patients, some certain symptoms including back pain, fatigue, abdominal pain, bloating, constipation, and urinary symptoms cannot guarantee an accurate diagnosis, nor can the exploratory laparotomy (4, 5). Based on histopathological characteristics, ovarian cancers can be divided into three main types including epithelial, germ cell, and sex-cord-stromal types (6, 7). Surgery is undoubtedly the foundation of treating ovarian cancer. However, it is far from satisfactory and the traditional treatment of advanced ovarian cancer has become the combination of surgery and chemotherapy (7–9). Accordingly, many novel drugs selectively acting on specific targets such as prexasertib specifically inhibiting cell cycle checkpoint kinase (Chk) 1/2 have been developed for certain classifications of OVCA (10). Nevertheless, prexasertib acting as a Chk 1/2 inhibitor is now under investigation for the treatment of high-grade serous OVCA, whereas its promising efficacy has been preliminarily evidenced only in phase 1 studies on account of its moderate hematological toxicity (11). Therefore, larger confirmatory studies are required to evaluate these new drugs and innovative methods of treating other types of OVCA are needed as well.

Programmed cell death (PCD) is an essential biological process in all multicellular organisms, underlying many physiological progressions involving growth and development, anti-infection, and survival in extreme condition (12, 13), etc. Moreover, diseases comprising neoplasm, autoimmune diseases, infection, etc., could emerge when PCD is interrupted. Several famous forms of PCD have been well acknowledged so far, encompassing apoptosis, autophagy, necroptosis, ferroptosis, and pyroptosis (14). Apoptosis is characterized by cytoplasmic shrinkage, nuclear condensation, and the maintenance of completeness of membranes and organelles. Many molecules are involved in apoptosis, and the key initiators are caspase-2, -8, -9, and -10 while the main executioners are caspase-3, -6, and -7 (13, 15, 16). Autophagy is distinguished by the formation of autophagosomes, with the indispensable autophagy-related proteins. Moreover, caspase-2, -3, -6 and -8 are found to work as regulators (16–18). Necroptosis, a programmed cell death similar to necrosis, is realized by the activation of receptor-

interacting protein kinase 3 (RIPK3)-mixed lineage kinase domain-like pseudokinase (MLKL) pathway and the downregulation of caspase-8 simultaneously (14). As another newfound PCD, the physiological roles of ferroptosis remain intangible but it shows great potential in tumors. Therefore, it is a promising area of cancer treatment (18, 19).

More recently, pyroptosis, an inflammatory PCD, is made up of two Greek roots “pyro” and ‘ptosis’, which is presumed to happen in response to infection and is reported to be triggered by inflammasomes customarily. After the discovery of pyroptosis in the field of infection, the scope of research was gradually extended and pyroptosis has been revealed to be of vital importance in many other diseases, including metabolic diseases (20), cardiovascular diseases (21), neurological diseases (22). As inflammation is evidently one of the hallmarks of cancers (23), a strong association might exist between pyroptosis and malignant diseases. Importantly, in recent years, some chemotherapeutic agents have been found to stimulate the formation of inflammasomes, hinting that there may be a correlation between cancer treatment and pyroptosis (24, 25). Generally speaking, with activation of caspase-1, -4 (in human), -5 (in human), and -11 (in mice) and cleavage of gasdermins (GSDMs), plasma membrane pores subsequently form as a result of N-termini of GSDMs and cause membrane perforation, cell swelling, plasma membrane lysis, chromatin fragmentation, and release of intracellular proinflammatory contents, which distinguishes pyroptosis from apoptosis biochemically and morphologically (14, 17, 26, 27). Moreover, great strides have been made in detecting the underlying mechanisms of pyroptosis, broadening our understanding of cancers and providing new threads of cancer management.

Hereof, in this review, we mainly summarized some cardinal mechanisms of pyroptosis and discussed the relationship between pyroptosis and ovarian cancer with an emphasis on the current study foundations, hopefully to provide some potential perspectives in OVCA treatment.

## MAIN MECHANISMS OF PYROPTOSIS: SETTING THE CELLS ON FIRE

### The Gasdermin Family

The gasdermin family is a cluster of proteins encoded by GSDM family genes, including GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and PJVK. All the members share a similar structure containing a C-terminal repressor domain (RD) and an N-terminal pore-forming domain (PFD). Besides, there exists a linker region in all GSDMs except for PJVK. Significantly, the N-terminus and C-terminus are highly conserved in the GSDM family, while the linker regions are diverse (28), resulting in cleavage by different caspases or granzymes. Once the cleavage occurs, RD and PFD fall apart, and hence PFD could come into play. Then the PFD binds to membrane phospholipids and generates pores (29). The GSDM family possesses extensive functions and is widely expressed in human, although regrettably, a lot of detailed mechanisms are still unknown.

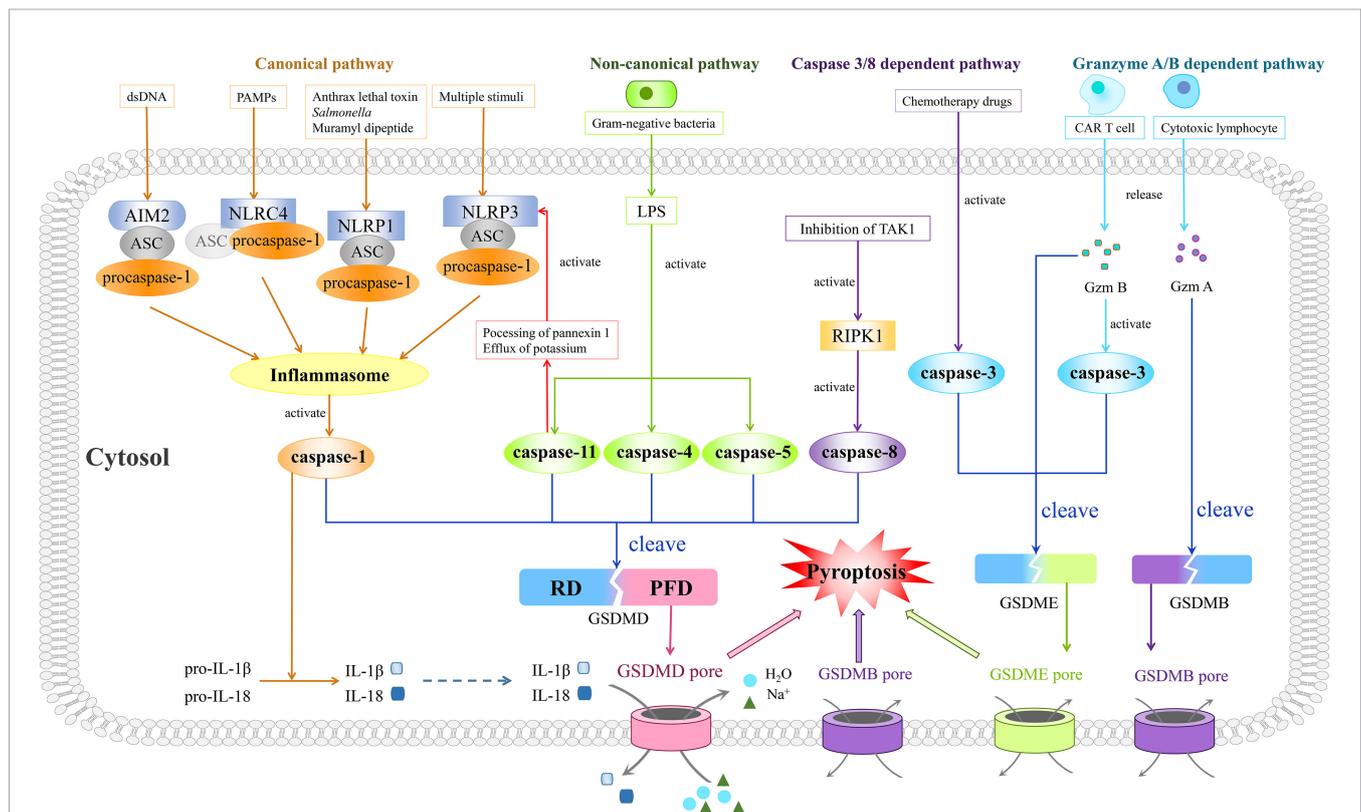
**Abbreviations:** OVCA, ovarian cancer; Chk, cell cycle checkpoint kinase; PCD, programmed cell death; RIPK3, receptor-interacting protein kinase 3; MLKL, mixed lineage kinase domain-like pseudokinase; GSDM, gasdermin; RD, repressor domain; PFD, pore-forming domain; PRR, pattern-recognition receptor; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; AIM2, absent in melanoma 2; NOD, nucleotide-binding oligomerization domain; NLR, NOD-like receptor; PYD, pyrin domain; CARD, caspase recruitment domain; PAMP, pathogen-associated molecular pattern; DAMP, damaged-associated molecular pattern; dsDNA, double-stranded DNA; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-18, interleukin-18; LPS, lipopolysaccharide; P2X7, purinergic receptor P2X, ligand-gated ion channel, 7; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; TNF, tumor necrosis factor; TAK1, TGF- $\beta$  activated kinase-1; Gzm, granzyme; CAR, chimeric antigen receptor; DEG, differentially expressed gene; lncRNA, long non-coding RNA; GAS5, growth arrest-specific transcript 5; HOTTIP, HOXA transcript at the distal tip; miRNA, microRNA; ASK1, apoptosis signal-regulating kinase1; JNK, c-Jun N-terminal kinase;  $\alpha$ -NETA, 2-(alpha-naphthoyl)ethyltrimethylammonium iodide; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; ICI, immune checkpoint inhibitor; NPC, nasopharyngeal carcinoma.

Moreover, pyroptosis, as yet, is proved to be associated with GSDMB, GSDMD, and GSDME (30). GSDMA, related to mitochondrial homeostasis (31) and an increased apoptosis-inducing activity in human mucus-secreting pit cells, is found to be inhibited in gastric cancers (32). The biological functions of GSDMC and PJVK remain unknown, but it is reported that the expression level of GSDMC is positively correlated with the metastatic ability of melanoma cells (33), indicating the possible relationship between GSDMC and tumorigenesis.

## The Canonical Pathway

As pyroptosis was first coined in 2001, it is mostly concerned with inflammation (34) and largely depends on the assembly of a crucial component, the inflammasome complex, which is composed of pattern-recognition receptors (PRRs), procaspase-1, and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) (Figure 1). The activation of canonical inflammasomes mostly appears in macrophages and dendritic cells (35).

PRRs of canonical inflammasomes often cover NLRP1, NLRP3, and NLRC4, absent in melanoma 2 (AIM2), with these four proteins constituting four corresponding types of inflammasomes. The first three belong to the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family, with NLRP possessing a pyrin domain (PYD) and NLRC possessing an N-terminal caspase recruitment domain (CARD) (36). AIM2 is endowed with a PYD and a DNA-binding HIN-200 domain (37), and the latter decides the connection between AIM2 and endogenous or pathogen-derived DNA (38). PYD and CARD of these inflammasome receptors contribute to recognition of certain pathogen-associated molecular patterns (PAMPs) and damaged-associated molecular patterns (DAMPs) (36, 39). For example, the NLRP1 inflammasome mediates the recognition of lethal toxin from *Bacillus anthracis*, muramyl dipeptide, and *Salmonella* (40–42), whereas the NLRP3 inflammasome recognizes multiple stimuli, including PAMPs such as Sendai virus, influenza, and bacterial pore-forming toxins, as well as DAMPs such as extracellular ATP,



**FIGURE 1** | Four prestigious pathways indicated in mechanisms of pyroptosis. Of note is that the canonical pathway is composed of inflammasomes, caspase-1, and GSDMD. Moreover, the inflammasome complex consists of PRRs (NLRP1, NLRP3, NLRC4, and AIM2), procaspase-1, and ASC, with the last one being dispensable in NLRC4 inflammasome. Different PRRs constitute corresponding types of inflammasomes and recognize different types of PAMPs or DAMPs. After recognition of PAMPs or DAMPs, the assembled inflammasomes activate caspase-1, thus cleaving GSDMD. The gasdermin pore formed by N-terminus of GSDMD results in pyroptosis characterized by outlet for IL-1 $\beta$  and IL-18, influx of sodium with water, swelling of cells, and finally osmotic lysis. In the non-canonical pathway, LPS derived from gram-negative bacteria could trigger pyroptosis through activating caspase-4, -5, and -11 to cleave GSDMD. Besides, the activated caspase-11 could also inspire the activation of the NLRP3 inflammasome. As for the caspase 3/8-dependent pathway, activated RIPK1 by inhibition of TAK1 helps caspase-8 to cut GSDMD and to mediate pyroptosis while the activated caspase-3 by chemotherapeutic drugs could split GSDME, leading to pyroptosis as well. In the granzyme A/B-dependent pathway, Gzm B released by CAR T cells could induce GSDME-modulated pyroptosis by both direct cleavage of GSDME and indirect cleavage of GSDME via activation of caspase-3, while cytotoxic lymphocyte-released Gzm A cleaves GSDMB to induce pyroptosis.

hyaluronan, and glucose (35, 43–47). Additionally, the NLRC4 inflammasome recognizes PAMPs including flagellin and muramyl dipeptide (48, 49), while the AIM2 inflammasome only recognizes endogenous or pathogen-derived double-stranded DNA (dsDNA) (38).

PAMPs and DAMPs are activated to recruit inflammasome adaptors ASC after recognition by PRRs. PYD and CARD are contained in ASC as well, similar to that of PRRs and participating in a homotypic interaction. The PYD–PYD interaction helps PRRs to summon ASC, and in the meantime CARD of ASC is indispensable for recruiting procaspase-1 into the inflammasome complex *via* CARD–CARD interaction (50). Apart from recruiting procaspase-1, ASC is indispensable in the maturation of IL-1 $\beta$  (51). Besides, NLRP1B and NLRC4 probably recruit procaspase-1 directly as they have CARD themselves (52). Moreover, the self-cleavage of procaspase-1 could give rise to caspase-1 activation primarily in macrophages and dendritic cells (53–55) (**Figure 1**).

Caspase-1, also referred to as interleukin-1-beta-converting enzyme, is another pivotal core in this pathway, distinguishing pyroptosis from apoptosis (56). It was first described as an inflammatory cysteine protease by Thornberry et al. in 1995 (57). After being recruited to inflammasomes, the concentration of regional caspase-1 monomers increases and consequently the dimerization might be accelerated (58), since the dimeric form of caspase-1 has protease activity. In caspase-1, there exists a CARD domain linker between the CARD domain and C-terminus, along with an interdomain linker inside the C-terminus which separates it into a larger subunit (p20) and a smaller one (p10) (59). As these two linkers could be self-cleaved by caspase-1 at diverse sites (60), the p20 subunit and p10 subunit are separated to reunite the active tetramer which is composed of two p20 subunits and two p10 subunits (61). Also, following research revealed that active caspase-1 could transform precursors of IL-1 $\beta$  and IL-18 into mature forms (62), while cleaving GSDMD into two termini as well (53). Then, the N-terminus of GSDMD, PFD, could generate a gasdermin pore in the plasma membrane when the inhibitory RD is cleaved apart. These pores bring about the outlet for IL-1 $\beta$  and IL-18, the influx of sodium with water, the swelling of cells, and finally the osmotic lysis (29, 63–65) (**Figure 1**). Intriguingly, in gastric cancer cells, the expression of GSDMD is downregulated according to a previously published article, which results in abnormal proliferation of cancer cells (66), indicating that elevating the expression of GSDMD might inhibit the progression of gastric cancer.

## Non-Canonical Pathway

Unlike that of the canonical pathway, the non-canonical pathway requires caspase-4 and -5 in human and ortholog caspase-11 in mice (67, 68). In the 1990s, the study by Li found that caspase-1 knockout mice showed high resistance to the injection of lipopolysaccharide (LPS) (69). Moreover, following articles described possible mechanisms. It was found that caspase-11 is expressed in a great quantity due to the stimulation of LPS (70). This expression causes the induction of pyroptosis in macrophages, which possibly depends on the ATP-mediated P2X7 signaling pathway according to Yang et al. They observed the instantly fast

release of extracellular ATP after transfection of LPS in bone marrow-derived macrophages, mediated by the cleavage of pannexin-1 depending on caspase-11 (71). ATP finally triggered the activation of P2X7, leading to its opening with ion movement, formation of larger pores on the membrane, and following pyroptosis (72, 73). Besides, the stimulation of LPS results in potassium's efflux, in which pannexin-1 is indispensable. Caspase-11 somehow could activate NLRP3 inflammasome mentioned in the canonical pathway, for the efflux of potassium plays a critical part in this procession (67, 71, 74). The direct combination of LPS and orthologs of caspase-11, caspase-4, and caspase-5 could induce the activation of caspases themselves (68, 75, 76). All these activated caspases engender the cleavage of GSDMD resembling that of caspase-1 and ensuing pyroptosis as mentioned above (53, 77, 78) (**Figure 1**). In a study conducted by Yokoyama et al., it was revealed that secretoglobin 3A2 was capable of inhibiting growth of human non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) cells in the mouse metastasis model by means of the caspase-4-mediated non-canonical pyroptosis pathway (79).

According to a study analyzing the caspase-1, -4, and -5 gene mutations in cancers, it is indicated that inhibition of caspase-5 probably contributes to carcinogenesis in microsatellite instability-positive tumor entities (80). Terlizzi et al. also found that in patients with NSCLC, the circulating level of caspase-4 is raised compared with those without (81). With further diligent work, their recent study clearly declared that caspase-4 is highly expressed in NSCLC compared to normal lung tissues, while caspase-11 motivates the development of lung cancer in mice. Notably, this high expression of caspase-4 is associated with a poor survival rate in NSCLC patients (82).

## Caspase 3/8-Dependent Pathway

In 2017, Feng and colleagues firstly demonstrated the novel function of caspase-3 in pyroptosis, breaking the stereotype that pyroptosis could be induced only by inflammatory caspases. In their experiment, chemotherapy drugs could mediate the caspase-3-governed cleavage of GSDME, exposing its gasdermin N-terminal domain and executing pyroptosis as well (**Figure 1**). Moreover, TNF-induced apoptosis was also found to be switched to pyroptosis by GSDME1 (83). Their results were later reconfirmed in various sorts of cancers, including gastric cancer (84), lung cancer (85), and colon cancer (86). Besides, in murine macrophages, it was indicated that when the traditional canonical NLRP3-inflammasome pathway is blocked, its activators like ATP could induce pyroptosis through the caspase-3/GSDME pathway, a switch between apoptosis and pyroptosis in cancers (87), instead of the caspase-1/GSDMD pathway (88). Briefly, the switch between pyroptosis and apoptosis is primarily determined by the expression level of GSDME, and both the PCD pathways are caspase-dependent. When GSDME is highly expressed, active caspase-3 cleaves it in two termini with the N-terminal domains punching holes on the cell membrane and causing pyroptosis. Conversely, apoptosis will occur if there is a low expression level of GSDME. However, more studies are needed to reconfirm the mechanisms underlying this switch (87).

Only 1 year later in 2018, two back-to-back studies revealed that inhibition of TGF- $\beta$ -activated kinase-1 (TAK1) by *Yersinia*

YopJ has the ability to provoke pyroptotic cell death in murine macrophages during *Yersinia* infection (89, 90). They uniformly agreed that during the aforementioned process, TAK1 blockade by *Yersinia* bacteria could lead to activation of RIPK1, together with the subsequent activation of caspase-8, and caspase-8 could chop GSDMD, finally unleashing IL-1 $\beta$  as a result of the pores formed by N-termini of GSDMDs (89, 90) (**Figure 1**). This process was then reassured by Schwarzer et al. in intestinal epithelial cells in a gut inflammation model (91). Moreover, intriguingly, in two recent works, caspase-8 was regarded as the pivot of the apoptosis–necroptosis–pyroptosis network (92, 93), exhibiting its shining role in cell death.

### Granzyme A/B-Dependent Pathway

So far, five subtypes of human granzymes (Gzms) have been described in natural killer cells and cytotoxic T lymphocytes whereas eleven subtypes of murine granzymes are now known to us (94). Among all, Gzm A and B are of vital importance, which also function in cell death, inflammation, infection, and tumor immunity (95). Over the years, much attention has been given to Gzm A and B in cell death, where their roles in either caspase-dependent or caspase-independent cell death are well explained. Moreover, perforin, a 67-kDa protein guarding the entrance of granzymes, is widely expressed in immune cells and could induce cell apoptosis in synergy with granzymes (96).

In January of last year, Liu et al. described their conclusion that chimeric antigen receptor (CAR) T cells stimulate caspase-3 to cut GSDME through unleashing granzyme B, the function of which is to cleave and activate caspase-3 in cooperation with perforin, and thus pyroptosis happens in target cells (97). Shortly afterward, Zhang et al. reported that Gzm B could split GSDME without the existence of caspase-3. In other words, Gzm B could induce GSDME-modulated target tumor cell pyroptosis by both direct cleavage of GSDME and indirect cleavage of GSDME *via* activation of caspase-3 (98) (**Figure 1**). Additionally in the same year, it was demonstrated that other than Gzm B, Gzm A also takes effect as a pyroptosis executioner. In GSDMB-positive cells, natural killer cells and cytotoxic T lymphocytes cause cell death through pyroptosis. What is more, cytotoxic lymphocytes are confirmed to release Gzm A, which then specifically cuts GSDMB through the interdomain with the help of perforin as well, resulting in pyroptosis (**Figure 1**). Furthermore, this remarkable pathway could successfully promote tumor clearance in mice (99), providing a new paradigm for pyroptosis and cancer treatment.

## CURRENT RESEARCH FOUNDATIONS OF PYROPTOSIS AND OVARIAN CANCER

### Genes That Might Regulate Pyroptosis in OVCA

With more studies focusing on pyroptosis and ovarian cancer, it was not so long ago that Berkel et al. published their paper comparing differential expression and copy number variations of certain GSDM family members in normal ovarian tissues with those of malignant serous ovarian tissues (100). They firstly

pointed out that the expression of GSDME is downregulated whereas GSDMD and GSDMC are expressed at a high level in serous OVCA, which is associated with a poor prognosis of TP53-mutated OVCA patients. Likewise, as executioners of GSDMs, the expression of caspase-1, -3, -4, -5, and -8 is decreased at the mRNA level in serous ovarian cancer. Also, the copy number variation events happen more frequently in genes encoding GSDMD and GSDMC, in accordance with their expression. Additionally, various histological subtypes of epithelial ovarian cancer express GSDMB and GSDME differently (100) (**Table 1**).

Secondly yet importantly, not long ago Qi and colleagues identified 31 differentially expressed genes (DEGs) that might regulate pyroptosis between OVCA and normal ovarian tissues, based on which the OVCA cases were classified. Among the 31 DEGs, 13 genes were downregulated while the remaining 18 genes were enriched in the tumor tissues. Moreover, a total of 7 DEGs including 3 downregulated (PLCG1, ELANE, and PJVK) and 4 upregulated (AIM2, CASP3, CASP6, and GSDMA) genes were retained for generating a prognostic model and a risk model because of their significant *p*-values, where 3 genes (PLCG1, ELANE, and GSDMA) were shown to be risk factors, while the other 4 genes (AIM2, PJVK, CASP3, and CASP6) were protective in the TCGA cohort. Thereafter, prognostic value was evaluated and pyroptosis-related genes were ascertained to play a key role in tumor immunity and predicting the prognosis of OVCA (101) (**Table 1**).

### LncRNAs and Pyroptosis in OVCA

Alternatively, two studies revealed that two long non-coding RNAs (lncRNAs), lncRNA growth arrest-specific transcript 5 (GAS5) and lncRNA HOXA transcript at the distal tip (HOTTIP), could regulate the pyroptosis process in OVCA, serving as a good cop and a bad cop, respectively (102, 103). Li et al. determined the positive effect of lncRNA GAS5 on pyroptosis in OVCA. Not only did they determine the repressed expression of lncRNA GAS5 in ovarian cancer tissues, but also they used lncRNA GAS5 overexpression and depletion models to identify that lncRNA GAS5 triggers the formation of inflammasome, thus leading to pyroptosis both *in vivo* and *in vitro* (102). The work done by Tan et al. was more complicated, with several downstream effectors discovered. In ovarian cancer tissues and cell lines, lncRNA HOTTIP is upregulated, the knockdown of which could lead to pyroptosis, hampering the progression of OVCA. Mechanistically, silencing lncRNA HOTTIP brings about upregulation of its downstream target gene microRNA (miRNA)-148a-3p, low AKT2 expression, positive modulation of the ASK1/JNK signaling pathway, and elevated formation of NLRP1-inflammasome (103) (**Figure 2, Table 1**). In view of the broad research prospects of pyroptosis in OVCA, more potential lncRNAs that could modulate pyroptosis are yet to be unearthed.

### Several Regulatory Molecules of Pyroptosis in OVCA

Meanwhile, some reports showed that apart from lncRNAs, pyroptosis in OVCA could also be induced by various molecules comprising osthole, nobiletin, and 2-( $\alpha$ -naphthoyl)

**TABLE 1** | Current research foundations of pyroptosis and ovarian cancer.

Year	Authors	Research object	Ovarian cancer cell lines	Gate molecules	Signaling pathways	Additional information
2021	Berkel et al. (100)	Differential expression and copy number variations of GSDMs	/	/	/	In epithelial ovarian cancer, the expression of GSDMB is increased in mucinous histotype compared to endometrioid and serous histotypes. Also, the expression of GSDMD is elevated in clear cell and serous histotypes compared to endometrioid histotype.
2021	Ye et al. (101)	Pyroptosis-related genes	/	/	/	The 13 downregulated genes include PRKACA, GSDMB, SCAF11, PJKV, CASP9, NOD1, PLCG1, NLRP1, GSDME, ELANE, TIRAP, CASP4, and GSDMD while the 18 upregulated genes are GPX4, NLRP7, NLRP2, CASP3, CASP6, TNF, IL1B, IL18, CASP8, NLRP6, GSDMA, GSDMC, PYCARD, CASP5, AIM2, NOD2, NLR4, and NLRP3.
2018	Li et al. (102)	LncRNA GAS5	SKOV3, OVCAR-3, A2780, and 3AO	GSDMD	The canonical pathway	Depletion of lncRNA GAS5 promotes viability of OVCA cells, while the overexpression of lncRNA GAS5 inhibits proliferation and colony formation in OVCA cells.
2021	Tan et al. (103)	LncRNA HOTTIP	CAOV-3, A2780, SKOV3, and OVCAR3	GSDMD	ASK1/JNK signaling pathway	LncRNA HOTTIP is upregulated in ovarian cancer tissues, and microRNA-148a-3p was a downstream target gene of HOTTIP, exerting negative effects on the regulatory functions of HOTTIP.
2020	Liang et al. (104)	Osthole	A2780 and OVCAR3	GSDME	/	Osthole could mediate GSDME-dependent pyroptosis while suppressing cell death by mitochondria-mediated apoptosis and causing cell autophagy in OVCA.
2020	Zhang et al. (105)	Nobiletin	A2780 and OVCAR3	GSDMD, GSDME	/	Nobiletin could inhibit cell proliferation, induce apoptosis via DNA damage in a dose-dependent way, and mediate pyroptosis through induction of autophagy in OVCA cells.
2019	Qiao et al. (106)	$\alpha$ -NETA	Ho8910, Ho8910PM, Hey, SKOV3, and A2780	GSDMD	GSDMD/caspase-4 pathway	$\alpha$ -NETA treatment causes epithelial ovarian cancer cell membrane blistering and cytoplasm leakage, typical manifestations of cells undergoing pyroptosis, which could be arrested by $\beta$ -arrestin-2.

ethyltrimethylammonium iodide ( $\alpha$ -NETA) (104–106). Osthole, a natural compound found in several medicinal plants such as *Cnidium monnieri* and *Angelica pubescens*, is reported to show potential anticancer, antioxidant, antimicrobial, and anti-inflammatory activities (107, 108). Similarly, nobiletin is another plant-derived natural compound targeting various oncogene and onco-suppressor pathways, thus showing great anticancer activity (109, 110). Moreover,  $\alpha$ -NETA is a stable, non-competitive, slowly reversible choline acetylcholine transferase inhibitor (106).

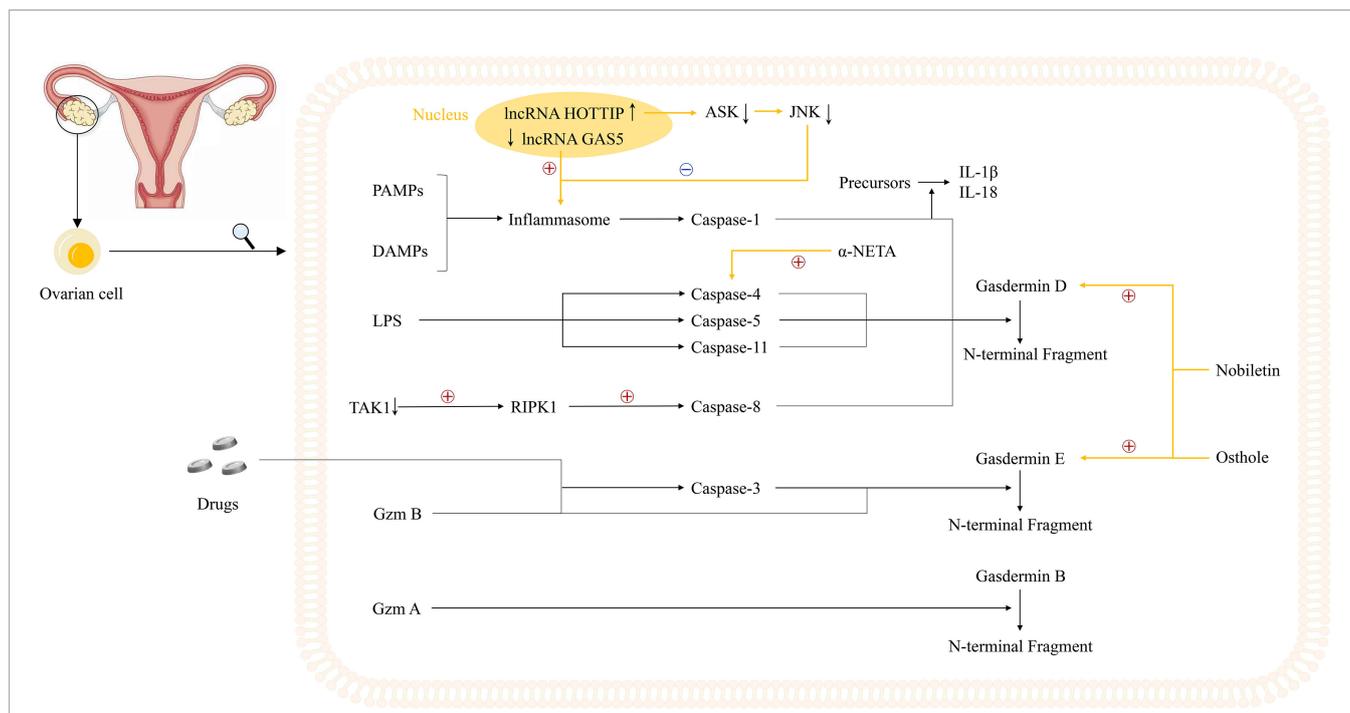
Recently, Liang et al. have found that osthole could mediate GSDME-dependent pyroptosis while eliciting reactive oxygen species (ROS) generation, decreasing mitochondrial membrane potential (MMP), and inducing LC3-mediated autophagy. In their study, the level of cleavage of GSDME was raised by osthole, exerting tremendous influence on the occurrence of pyroptosis (104). Remarkably, and perhaps not coincidentally, Zhang et al. uncovered the new identity of nobiletin as the pyroptosis trigger in OVCA in the same year. Highly similar to osthole, nobiletin could also stimulate ROS production, decrease MMP, and promote the evocation of classical autophagy in connection with LC3. Besides, nobiletin was verified to evoke the pyroptosis process in an autophagy-related, ROS-mediated, GSDMD- and GSDME-dependent way, slightly different from that of osthole (105). What is more, a later published paper further convinced that  $\alpha$ -NETA treatment causes epithelial ovarian cancer cell death through pyroptosis, with a dramatically augmented level of GSDMD, caspase-4, LC3B, and IL-18 secretion (106) (**Figure 2, Table 1**).

## Characteristics of Pyroptosis in OVCA and Other Types of Cancer Cells

The pyroptosis process happens not only in OVCA cells but also in many other types of tumor cells. For example, in NSCLC patients, GSDMD is highly expressed, the same as that in malignant serous ovarian tissues, and indicates a poor prognosis as well. Moreover, in digestive system carcinomas, caspase-1 is demonstrated to be low-expressed in hepatocellular carcinoma and colorectal cancer (111). Surprisingly in colorectal cancer, lncRNA RP1-85F18.6 is reported to promote proliferation and invasion as well as suppress pyroptosis (112) whereas lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) could mediate ionizing radiation-induced pyroptosis relying on upregulation of GSDME expression (113). Besides, as a platinum antitumor agent, lobaplatin could remarkably elevate the level of ROS in CRC cells and phosphorylate JNK. Then activated JNK could cause mitochondrial damage and release of cytochrome C, promoting caspase-3 and -9 cleavage and GSDME-dependent pyroptosis, which shows a moderate overlap between OVCA and CRC (86).

## DISCUSSION

Taken together, as a notable style of lately identified programmed cell death, pyroptosis displays a significant role in multitudinous diseases embodying cancerous ailments (84, 86, 104), infectious



**FIGURE 2** | Potential mechanisms underlying pyroptosis in ovarian cancer cells and current study foundations. Notably, two lncRNAs, GAS5 and HOTTIP, play an important role in the regulation of inflammasomes. The inhibited expression of lncRNA GAS5 in ovarian cancer could trigger the formation of inflammasome while lncRNA HOTTIP is highly expressed in ovarian cancer, the knockdown of which leads to upregulation of ASK1/JNK signaling, elevated formation of NLRP1-inflammasome, and pyroptosis. Moreover, three novel small molecules including osthole, nobiletin, and  $\alpha$ -NETA are reported to regulate the pyroptosis process in ovarian cancer cells. Osthole and nobiletin are of high similarity since they both have an effect on ROS production, MMP, and LC3-related autophagy. However, osthole could mediate GSDME-dependent pyroptosis while nobiletin could mediate pyroptosis through GSDMD- and GSDME-dependent ways. Moreover,  $\alpha$ -NETA treatment causes epithelial ovarian cancer cell death through pyroptosis, with dramatically augmented level of GSDMD and caspase-4.

diseases (90, 114), neurological diseases (115, 116) and cardiovascular events (117, 118). Among them, nevertheless, carcinomas are emerging as one of the auspicious prospects. Moreover, as is conspicuously stated above, compelling evidence denotes a close relation between pyroptosis and ovarian cancer. With four major pathways of pyroptosis being discovered one after another, the gasdermin family becomes the kernel of pyroptosis induction, and caspases that have the capacity to mediate pyroptosis are no longer confined to inflammatory ones. Therefore, questions are gradually starting to surface. Are the existing pathways complete mechanisms of pyroptosis? We now know that caspases triggering pyroptosis, for example caspase-3 and -8, could also participate in apoptosis. Particularly, caspase-8 serves as hub of the apoptosis–necroptosis–pyroptosis network, whose bigger potential needs to be tapped. So is there a chance that other apoptosis-related caspases, such as caspase-2, -6, -7, -9, and -10, could also function in pyroptosis? For this reason, a grand network involving apoptosis-related caspases and yet undetected further GSDMs is worth looking forward to.

What is more, since mounting studies demonstrated an association between pyroptosis and tumor immunotherapy, it might be possible to treat cancer patients with immunotherapy assisted by pyroptosis-inducing nanoparticles (119–121) in the future. It was reported that one of those nanoparticles could mediate tumor cell pyroptosis in a mouse colon carcinoma

model, and the pyroptotic tumor cells could release DAMPs, thus initiating adaptive immunity and boosting the efficacy of immune checkpoint inhibitors (ICIs) (120). However, the safety of those nanoparticles should be taken into consideration when applied. Additionally, it was also reported that ICIs could kill resistant tumors only in the context of the concomitant induction of pyroptosis (122), highlighting the importance of the combination of pyroptosis inducers and ICIs in treating ICI-resistant tumors. Nevertheless, since the occurrence of pyroptosis brings about the release of inflammatory components, which might promote the development of tumors (123, 124), pyroptosis, as a double-edged sword, should be carefully harnessed, either shutting a door or opening a window for a great deal of cancer patients.

Aside from the aforementioned issues and back to OVCA, pyroptosis in cancer treatment and cancer patients is another thing to be addressed. Since distinct chemotherapy drugs are of benefit with respect to ovarian cancer *via* stimulation of pyroptosis, along with generation of ROS and decrease of mitochondrial membrane potential, many other precisely targeting pyroptosis medications intended for diverse specific subtypes of ovarian cancer are urgently needed to be developed, as well as more *in vivo* experiments. Besides, the possibility of treating OVCA patients with immunotherapy in conjunction with pyroptosis is worth exploring. Moreover, as mechanisms of pyroptosis in OVCA are

still poorly studied, whether unsuspected mechanisms could solve problems related to drug resistance, progression, or recurrence in OVCA patients is yet unknown.

Moreover, there might be a subtle correlation of pyroptosis with ferroptosis and mitochondrial autophagy, which awaits further elucidation. So is it possible to treat OVCA patients with medications that could mediate ovarian cancer cell death through induction of pyroptosis, ferroptosis, necroptosis, and autophagy so as to kill target cells to the greatest degree? Now that a few lncRNAs are reported to regulate pyroptosis in OVCA, chances are that ovarian cancer could be treated at a genetic level. Back to patients themselves, when the pyroptosis progress occurs, a variety of immune components partake including cytotoxic lymphocytes, CAR T cells, IL-1 $\beta$ , and IL-18. Cytotoxic lymphocytes could kill tumor cells by transferring granzymes into target cells. During this process, GSDMB activated by Gzm A or GSDME activated by Gzm B and caspase-3 induces pyroptosis, which probably reinforces the cytotoxicity (125). CAR T cells are supposed to experience a similar course to launch attack, and Gzm B plays a significant role in activating GSDME and caspase-3, as well as inducing pyroptosis. Besides, due to a high affinity between CAR T cells and their ligands, it is more efficient for those cells to induce pyroptosis (126). Moreover, although the cytokines could be properly utilized to assist in fighting against malignancies, for cancer patients, the possibly forthcoming inflammatory cytokine storm under infectious conditions might make things worse. Besides, the newly discovered pyroptosis-related DEGs between OVCA and normal tissues, along with the prognostic and risk models derived from DEGs, might play a critical role in predicting the prognosis of OVCA patients in the future.

Last but not least, there are many FDA-approved drugs in clinical practice that could induce pyroptosis (122). These drugs involve antidiabetes drug metformin, anticancer drugs paclitaxel and doxorubicin, and nutrients anthocyanin and DHA, which show great antitumor activity. In particular, paclitaxel and doxorubicin exhibit enormous potential owing to their dual effects including treating cancers and inducing pyroptosis, but cancer cells could still quickly develop resistance against them, which remains an unsolved but interesting problem. In a study focusing on nasopharyngeal carcinoma (NPC), it was discovered that caspase-1 inhibition and

GSDMD knockout could induce a Taxol-resistant phenotype *in vitro* and *in vivo* and that autophagy could negatively regulate the canonical pathway of pyroptosis in NPC cells (127). Additionally, it was also found that the knockdown of USP47, a cysteine protease, could increase doxorubicin-induced pyroptosis in CRC while the ectopic expression of USP47 leads to doxorubicin resistance in CRC cells (128). Thus, we speculate the fact that patients taking particular drugs with dual effects experience drug resistance or tumor relapse might possibly result from the fine regulation of the intricate PCD pathway network. Moreover, although the induction of pyroptosis by these drugs might not directly follow the aforementioned four pathways, the preclinical studies did bring hope to us. Consequently, developing drugs targeting pyroptosis in tumor cells is a promising area. Furthermore, clinical trials regarding pyroptosis do exist, with one focusing on diabetes (129) and the other on leukemia (130). In B cell acute lymphoblastic leukemia patients, B leukemic cell pyroptosis was stimulated through the Gzm B pathway triggered by CAR T cells. However, target cell pyroptosis stimulates macrophages to cause cytokine release syndrome (130), which might be detrimental to patients and become a flaw in pyroptosis, limiting its development. Similarly in patients with type 2 diabetes, alleviation of diabetes *via* inhibiting pyroptosis was observed (129), further confirming the negative inflammatory process during pyroptosis. Therefore, it is inevitable to take the concomitant inflammatory process during pyroptosis into account.

By and large, the continuous exploration centering upon pyroptosis and ovarian cancer provides clinicians with more choices from a genetic level to a chemotherapeutic or an immunotherapeutic level, enriching the thoughts for the treatment of ovarian cancer. Despite some problems to be settled, the significant and promising prospect of pyroptosis is worthy of the wait.

## AUTHOR CONTRIBUTIONS

TL, MH, and LL had the idea for the article. TL, MH, ML, and LL were the major contributors in the drafting of the work. CQ, LC, TZ, and JQ critically revised the work. All authors contributed to the article and approved the submitted version.

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