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Mini Review

Mechanistic role of pyroptosis in tumor microenvironment and tumor immunotherapy

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Abstract

In recent decades, extraordinary attention has been devoted to cell death pathways principally because of multifaceted regulatory roles in normal developmental and pathophysiological processes. The removal of functionally defective, infected or potentially malignant cells is regulated by programmed cell death (PCD) cascades. Pyroptotic cell death is a highly complicated pro-inflammatory form of cell death. Pyroptosis is characterized by the formation of pores in the plasma membrane by oligomerization of the N-terminal fragment of gasdermins (gasdermin-NT) following the cleavage of gasdermin. Pyroptosis plays a pivotal role in the innate immune responses and mechanistically steered by inflammasome-mediated and inflammasome-independent cascades. In this review, we have comprehensively analyzed how different signaling pathways regulated pyroptosis in cancer inhibition and metastatic spread of cancer cells to the secondary sites. Comprehensive understanding of the interconnection between signaling pathways and pyroptosis will enable us to reap maximum benefits from the exciting mechanistic insights gained from pioneering studies related to pyroptosis.

Keywords: Cancer, Pyroptosis, Cell Signaling, Metastasis, PD-L1/PD-1 signaling

1. Introduction

With extraordinary breakthroughs brought by genetics, genomics and proteomics research, we now know that cancers are uniquely different, both in genetic alterations as well as origins. Our rapidly evolving understanding of the spatiotemporal regulation of carcinogenesis and metastasis has enabled comprehensive characterization of the heterogeneity and complexity of different subpopulations of cancer cells. Recent advancements in our knowledge related to oncogenic pathways underlying tumor growth, loss of apoptosis, drug resistance, metastatic colonization as well as immune-activating strategies have uncovered pharmacologically valuable targets (1-6).

The removal of potentially neoplastic and functionally defective cells is intricately regulated by programmed cell death (PCD) cascades, underlining their pivotal functions in homeostasis, host defense against pathogens and a range of different cancers (7-10). Unprecedented insights into PCD pathways have come from the breadth of cutting-edge research works and various types of PCD pathways have been characterized, including apoptosis, pyroptosis and necroptosis. We have structured this review into different sections for the analysis of mechanisms underlying pyroptosis and how GSDMD and GSDME reshape the tumor microenvironment to inhibit cancer progression. This review also gives an overview of the role of non-coding RNAs in the regulation of pyroptosis and how different pharmacologically precious natural products induce pyroptosis and consequent cancer inhibition.

2. Overview of GSDMD and GSDME

In 2015, Gasdermin D (GSDMD) was identified as an important target of caspase-1. It was shown that caspase-1-mediated cleavage of GSDMD promoted its insertion

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into cellular membranes to trigger pyroptosis. Cleaved amino-terminal GSDMD has a strong affiliation for the mammalian inner plasma membrane leaflets. These hallmark features enable insertion of amino-terminal GSDMD into the cell membrane and subsequent creation of pores to trigger pyroptotic death (Fig 1). Pore formation stimulates the release of active interleukin-1β and interleukin-18, which subsequently promotes the inflammatory responses (11,12).

TRIM21 physically interacts with GSDMD via its PRY-SPRY domain. Importantly, PRY-SPRY domain of TRIM21 stabilizes GSDMD. There is an evident increase in the concentration and size of GSDMD-N oligomers in TRIM21-expressing cells indicating that TRIM21 effectively promotes intricate formation of high-order oligomers of GSDMD-N (13).

GSDME, also known as (DFNA5, ICERE1), was earlier identified as a candidate gene for autosomal dominant non-syndromic hearing loss. However, in the later studies, it was found to be similar to gasdermins in context of sequence and structure (14). GSDME is cleaved specifically by caspase-3 at Asp^{270}. Accordingly, circumstantial evidence indicated that caspase-3 induced cleavage of GSDME generated a necrotic N-GSDME fragment that targeted the plasma membrane for the induction of pyroptosis (15). Chemotherapeutic drugs mediated activation of caspase-3 subsequently induced pyroptosis in GSDME-overexpressing cells but apoptosis in GSDME-negative cells (16).

3. Role of GSDMD and GSDME in enhancing the accumulation of Tumor-infiltrating lymphocytes in Tumor-microenvironment

Studies show that functional organization of the tumor immune microenvironment requires complicated cross-talks and intricate roles of chemokines in the positioning and recruitment of its cellular constituents. Experimental verification and validation of scientific findings will not only generate highly valuable mechanistic insights related to the underlying antitumor immunological response as well as innovative opportunities to therapeutically engineer robust immunological responses in cancer patients.

Overexpression of GSDME in transplanted tumor cells caused tumor cell pyroptosis. Moreover, GSDME-overexpressing tumor cells enhanced the functions of tumor-infiltrating natural killer cells and CD8+ T lymphocytes (17).

GSDMD-NT-mediated pyroptosis effectively eliminated established tumors derived from the genetically modified tumor cells. Importantly, pyroptotic TC-1 tumor cell vaccine (GSDMD-NT-TC-1) considerably induced shrinkage of the tumors in mice xenografted with CT26 cells. There was a considerable increment in the levels of cytotoxic T lymphocytes and NK cells in the tumor tissues and spleen, while the activity of immunosuppressive cells MDSCs and regulatory T cells was noted to be reduced (18).

MDSCs accumulate in the tumor microenvironment and strongly inhibit anticancer effects of natural killer cells and T cells. Tumor microenvironment is a highly structured and complicated ecosystem and immunosuppressive activities promote cancer progression (19-23). Different mechanisms particularly, PD-L1/PD-1 signaling inactivated T cells and potentiated carcinogenesis (24-26). Therefore, concomitant use of chemotherapeutic drugs with PD-1/PD-L1 inhibitors induced tumor shrinkage in mice xenografted with small-cell lung cancer cells (27).

pH-activated supramolecular nanoprodrugs (PDNP) have also been found to induce pyroptosis. PDNP effec-

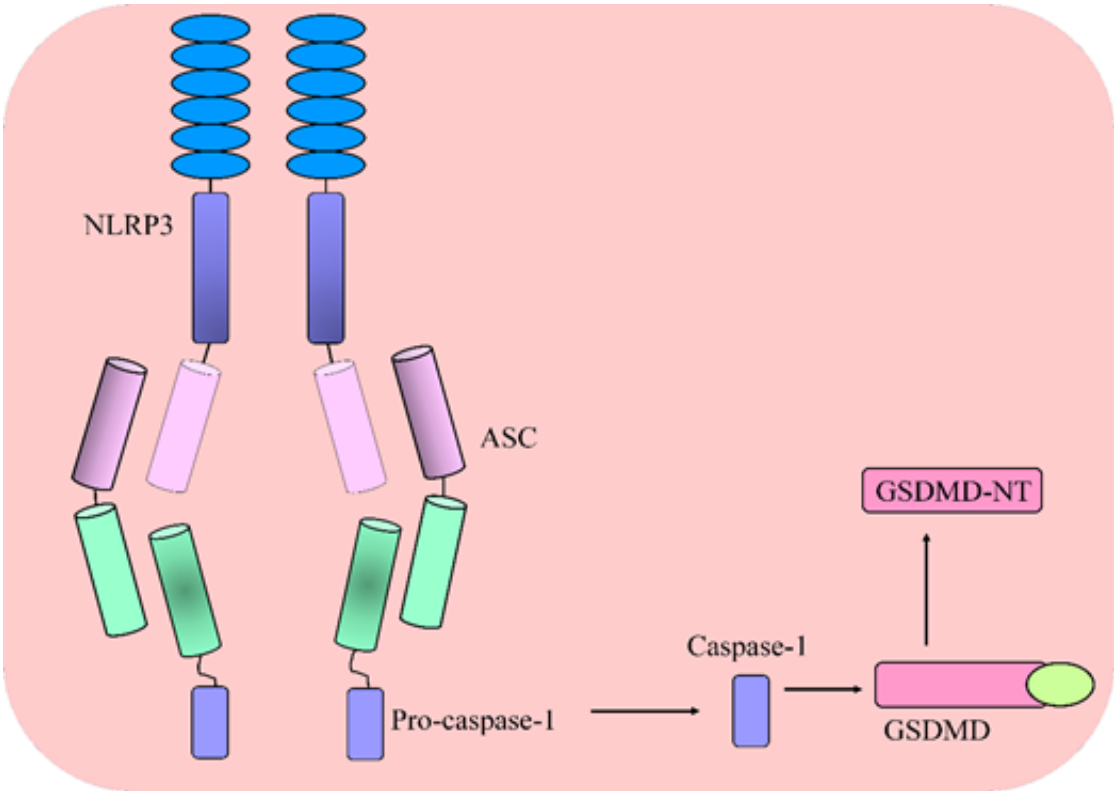

Fig. 1. NLRP3 inflammasome-mediated activation of caspase-1 inhibits cancer progression. Caspase-1-mediated cleavage of GSDMD induced the formation of pores in cell membranes, resulting in pyroptosis. Pore formation also enhanced the extracellular release of active IL-1β and IL-18.

tively reduced the percentage of MDSCs and inhibited carcinogenesis. PDNPs induced the infiltration of $CD8^+$ $PD\text{-}1^+$ T cells in tumors and impeded the exhaustion of CD8+ T cells. PDNPs were administrated preferentially for the rejuvenation of CD8+ T cells and anti-PD-1 was intraperitoneally injected to block PD-1 in mice bearing tumor xenografts (28).

4. Regulation of non-coding RNAs by Pyroptosis

Phenomenal findings distilled from decades of research have revolutionized our classical view about non-coding RNAs. Evolution of the non-coding RNA concept from 'junk' transcriptional products to functional regulatory molecules that mediate cellular processes has opened new horizons for the identification of different mechanisms. Discovery and characterization of microRNAs (miRNAs) (29-36), long non-coding RNAs (lncRNAs) (37-41) and circular RNAs have revealed the diversity of their regulatory roles.

Different long non-coding RNAs have been shown to inhibit pyroptosis and promote tumorigenesis. Gain of H3K4me1 and H3K27Ac can lead to the activation of LINC00969. NLRP3 inflammasomes convert procaspase-1 to functionally active caspase-1 and promote caspase-1-mediated cleavage of GSDMD, leading to pyroptosis. METTL3 (methyltransferase-like 3) catalyzes m6A modifications. YTHDF2 is a "reader" protein and recognizes m6A-modified sites. Importantly, half-life of NLRP3 transcripts was found to be increased in YTHDF2-silenced cells. Furthermore, silencing of LINC00969 led to a significant reduction in the binding of YTHDF2 to NLRP3 mRNA. These findings provided evidence that LINC00969 interacted with METTL3 and reduced the expression of NLRP3 in an m6A-YTHDF2-dependent manner. LINC00969 promoted the binding of EZH2 to the promoter of NLRP3 and increased the levels of H3K27me3. Intratumoral administration of si-LINC00969 reduced gefitinib resistance and caused shrinkage of the tumors. Additionally, combinatorial treatment with si-LINC00969 and gefitinib synergistically reduced tumorigenesis in xenografted mice (42).

Cisplatin activated NLRP3/caspase-1/GSDMD pathway in MDA-MB-231 breast cancer cells. MEG3 (Maternally expressed gene-3), an lncRNA promoted the activation of caspase-1/GSDMD pathway (Fig.2). Essentially, the levels of IL-18 and IL-1β were found to be reduced in MEG3-silenced cancer cells. Cisplatin-mediated pyroptotic cell death was blocked by knockdown of MEG3. Cisplatin did not cause regression of the tumors in mice xenografted with MEG3-silenced- MDA-MB-231 cancer cells (43).

Sodium new houttuyfonate (SNH) is a ramification of Sodium houttuyfonate (SH) derived from *Houttuynia cordata*. TCONS-14036, a tumor suppressive lncRNAs interferes with miR-1228-5p-mediated targeting of PRKCDBP. Importantly, PRKCDBP triggered the stimulation of NLRP3 inflammasomes and consequent activation of caspase-1-mediated cleavage of GSDMD (44). SNH suppressed NSCLC growth principally through activation of pyroptosis via TCONS-14036/miR-1228-5p/PRKCDBP pathway.

MALAT1 deletion led to reduction in the formation of tumor spheres and colony formation in cell culture studies. Moreover, MALAT1 deletion inhibited colonization and pulmonary metastatic spread in tumor-bearing mice. MALAT1-knockout tumors are characterized by substantial increment in the infiltration of T cells and concomitant decline in the accumulation of immunosuppressive neutrophils. MALAT1-wild-type tumors demonstrated high infiltration rates of maturing, immunosuppressive neutrophils. MALAT1- knockout tumor cells have the ability to undergo solitary dormancy after penetrating the stroma of the lungs and persist in this state for longer time period. There was a reactivation of tumors in $CD8^+$ T cells-depleted mice causing metastatic disease after injection of MALAT1-knockout 4T1 cells. MALAT1 loss causes downregulation of SERPINA3G, SERPINB6B, WNT3, WNT6 and WNT9B. Co-inhibition of SERPINA3G and SERPINB6B severely impaired the lung-colonizing ability of wild-type-MALAT1 4T1 cells. Reconstitution of SERPINB6B sufficiently rescued the metastatic abilities of MALAT1-knockout 4T1 cells. WNT3 markedly increased tumor-sphere forming properties of MALAT1-knockout 4T1 cells. MALAT1 promoted metastatic dissemination mainly through upregulation of SERPINB6B and inhibition of pyroptotic pathway. Treatment with MALAT1 Gapmer locked nucleic acid (LNA) antisense oligonucleotides (ASOs) not only reduced the levels of MALAT1 and SERPINB6B but also impaired lung colonization of cancer cells. ASOs enhanced the infiltration of $CD4^+$ and $CD8^+$ T cells and reduced the recruitment of Ly6G+ neutrophils within tumor microenvironment (45).

lncRNA RP1-85F18.6 acts as an oncogenic long non-coding RNA in colorectal cancer cells. lncRNA RP1-85F18.6 inhibition led to a robust increment in the generation of GSDMD-N domain and consequent induction of pyroptosis (Fig. 2) (46).

5. Regulation of Pyroptosis by Different proteins

EEBR is a chemically synthesized alkaloid and it contains a quaternary nitrogen basic skeleton. Earlier studies have shown that quaternary nitrogen is an important chemical group with notable pharmaceutical activities against cancers. EEBR potently increased the expression of N-GSDMD and potentiated its oligomerization in NSCLC cells. EEBR induced caspase-1-dependent cleavage of GSDMD. EEBR stimulates NFκB-mediated transcriptional upregulation of NLRP3. EEBR potently impairs the tumor development in BALB/c nude mice subcutaneously injected with A549 cells. EEBR efficiently blocks the progression of NSCLC in vivo by activation of NFκB-NLRP3-GSDMD pathway and consequent induction of pyroptosis (47).

Zinc Finger DHHC-Type Containing 1 (ZDHHC1/ZNF377) has recently been shown to trigger the activation of caspase-1/GSDMD and caspase-3/GSDME in cancer cells. ZDHHC1 not only suppressed epithelial-to-mesenchymal transition but also inhibited tumorigenesis in xenografted mice (48).

Sorcin (Soluble resistance-related calcium-binding protein) interacted with NLRP3 inflammasomes and inhibited pyroptosis in HCC cells. Knockdown of Sorcin caused significant shrinkage of the tumors in mice inoculated with HCC-LM3 cells (49).

CC-115 is a dual inhibitor of DNA-PK (DNA-dependent protein kinase) and mTOR (mechanistic Target of Rapamycin). CC-115 has been found to significantly increase the levels of both active caspase-3 and N-termi-

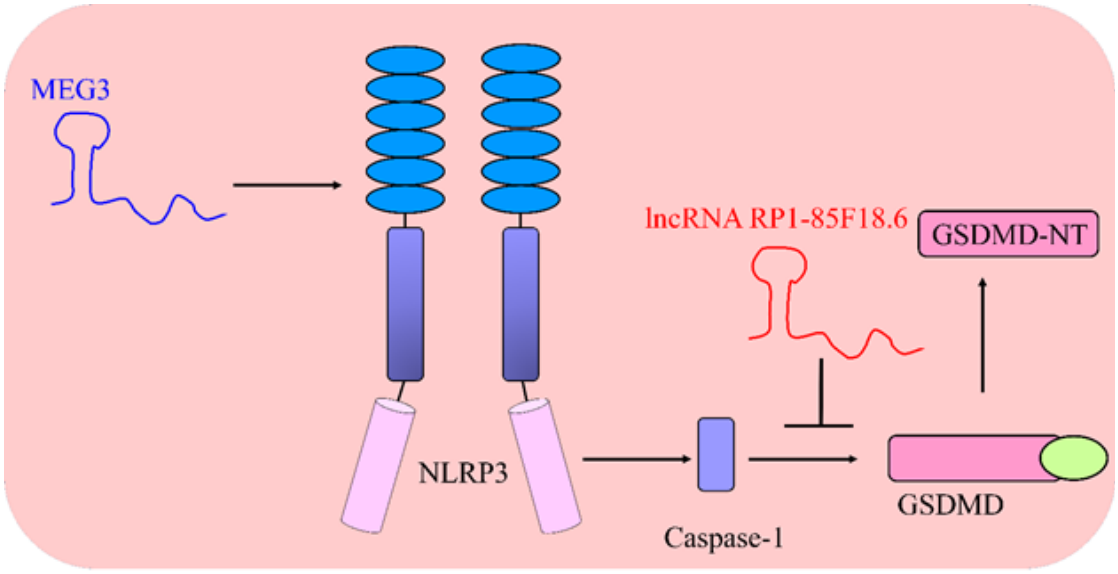

Fig. 2. Long non-coding RNAs regulate caspase-1/GSDMD pathway. Oncogenic lncRNA RP1-85F18.6 inactivates pyroptosis but MEG3 activates caspase-1/GSDMD pathway.

nal fragment of GSDME in H1650 and A549 cancer cells. It has been shown that mitochondrial intrinsic pathway efficiently induced pyroptotic death via Bax-caspase-3-GSDME pathway. CC-115 promoted the levels of Bax and cytochrome c release in lung cancer cells. CC-115 markedly reduced phosphorylation of AKT in A549 and H1650 cells. CC-115 failed to inhibit tumor growth in mice inoculated with GSDME-knockdown A549 cancer cells (50).

SF3B1 (Splicing factor 3b subunit-1) is the largest subunit of splicing factor 3b protein complex. Pladienolide B increased the levels of $CD8^+$T cells, $IFN\gamma^+CD8^+$T cells and $FOXP3^-CD4^+$ cells. However, Pladienolide B reduced the proportions of Treg cells (FOXP3+CD25+CD4+). Stable and higher expression of FOXP3 is required for suppressive functions and loss of FOXP3 decreases the ability of T_{reg} cells to exert immunosuppressive effects. Pladienolide B enhanced the proportions of M1 macrophages and reduced the levels of M2 macrophages. Essentially, SF3B1 proteins bind to BCL2L2 transcripts but pladienolide B causes the disassembly of these molecular interactions. Targeted inhibition of SF3B1 caused an increase in the levels of N-terminal GSDME and the concentration of interleukin-1β and interleukin-18. Pladienolide B induced the release of mtDNA from ovarian cancer cells. Macrophages recognize the damaged mtDNA from tumor cells as exogenous foreign bodies and engulf them leading to the activation of mtDNA-cGAS-STING cascade (51).

SH2 containing protein tyrosine phosphatase-2 (SHP2), an oncogenic phosphatase negatively regulates JNK/NFκB. However, inhibition of SHP2 not only relieves inhibitory effects on JNK/NFκB but also potentiates the activation of caspase-1/GSDMD-mediated pyroptotic pathway. There was an evident increase in the levels of p-JNK, p-NFκB, cleaved caspase-1 and N-GSDMD within the tumor tissues derived from the SHP2 knockdown cancer cells (52).

6. Natural products mediated regulation of Pyroptosis

Natural products and their derivatives have classically been viewed as a valuable source of therapeutic agents. Their rich structural diversity and complexity has revolutionized the field of molecular pharmacology (53-62). Wide-ranging natural products have been reported to inhibit the onset and progression of cancer (63-64).

Chaetoglobosins are primarily derived from fungal secondary metabolites. Chaetoglobosins belong to the cytochalasan alkaloid class of drugs. Chaetoglobosin E was found to be effective against esophageal squamous cell carcinoma (ESCC) cells. PLK1 (Polo-like kinase 1) inhibited the activation of GSDME. However, Chaetoglobosin E promoted the activation of GSDME mainly through inhibition of PLK1. Chaetoglobosin E and cisplatin/5-Fu synergistically inhibited the proliferation potential of KYSE-30 cells (65).

Mitochondrial hexokinase-II prevented mitochondrial translocation of BAD and BAX proteins and activation of caspase-3. Consequently, caspase-3 mediated activation of GSDME was also inactivated because of mitochondrial hexokinase-II. Triptolide, a natural diterpenoid epoxide has been found to be effective against head and neck cancer cells. Triptolide activated GSDME-mediated pyroptosis in HK1 and FaDu cells (66).

NLRP3 inflammasome is formed by NLRP3, ASC (Apoptosis speck protein with caspase recruitment) and caspase-1. Excessive ROS levels trigger the formation of NLRP3 inflammasomes and activation of caspase-1-mediated-GSDMD. Intraperitoneally administered luteolin induced shrinkage of the tumors in mice xenografted with HT-29 cells (67).

Nigericin, an antibiotic derived from *Streptomyces hydrophobicus* has been shown to be effective against breast cancer. Nigericin induced pyroptosis via caspase-1/GSDMD pathway in MDA-MB-231 and 4T1 cancer cells. Pyroptosis boosted inflammatory responses and potentiated anti-tumor immunological functions. Nigericin and anti-PD-1 effectively increased the release of TNFα from CD8+ T cells. Combinatorial treatment not only induced tumor shrinkage but also enhanced tumor infiltration of CD4+ or CD8+ T cells in BALB/c mice orthotopically transplanted with 4T1 cells (68).

Diosbulbin-B, a natural product has been shown to be effective against cancers. PD-L1 exerted inhibitory effects on NLRP3 inflammasomes and impaired pyroptotic cell

death. Diosbulbin-B triggered NLRP3-mediated pyroptotic death in cisplatin-treated gastric cancer cells by inhibition of PD-L1 (69).

7. TRAIL-based therapeutics mediated Pyroptosis

Death receptor mediated apoptotic death has gathered significant attention because of its unique ability to target cancer cells (70-79). TRAIL-resistant cancer cells have hyperactive survival signaling. Different natural and synthetic molecules have been tested to increase the sensitivity of cancer cells to TRAIL-based therapeutics (80-84).

Mapatumumab (HGS-ETR1) and lexatumumab (HGS-ETR2) are humanized monoclonal antibodies. These agonistic antibodies have been reported to be effective against different cancers (85-88).

HGS-ETR1/2 induced cleavage of GSDME in HepG2 and Huh7 hepatoma cells. Carboxypeptidase A4 (CPA4) severely impaired HGS-ETR1/2-mediated pyroptosis. HGS-ETR1/2 effectively impeded the tumor growth in mice xenografted with CPA4-silenced-HLZ01 cells (89).

Andrographolide and TRAIL induced "pyroptosis-like phenotypes" such as GSDME cleavage and pyroptotic-body-like bubbles generation in MCF-7 cells (90).

8. Darker Side of Pyroptosis in Context of CAR T-cell Therapy

CAR T cells triggered GSDME for the activation of pyroptosis in target cells. It was noted that introduction of GSDME-expressing vectors into GSDME-deficient tumor cells restored CAR T cell-directed pyroptotic death. Cells have unique capability to promptly repair the formed membrane pores to prevent the pyroptotic death induced by low levels of GSDME. Therefore, high levels of active GSDME have the ability to counteract the pore-repairing properties of the cells and induce pyroptotic death. GSDME-mediated pyroptosis triggered cytokine release syndrome during CAR T cell therapy (91). Pyroptotic supernatants from GSDME-expressing cells activated caspase-1 in macrophages whereas supernatants from GSDME knockout cells failed to trigger the activity of caspase-1 in macrophages. Intraperitoneal injections of $GSDME^{-/-}$ NALM-6 or Raji cells in SCID-beige mice severely impaired CRS symptoms upon treatment with CAR T cells (**91**). Collectively, these findings indicated that GSDME knockout in target tumor cells, depletion of macrophages or blockade of caspase-1/GSDMD resulted in efficient inhibition of CRS.

CD19 occupancy with CD19 monoclonal antibody leads to lesser activation of CART19, which reduces CAR T-cell apoptosis and tumor cell pyroptosis. Overall, CD19 masking with tafasitamab before CART19 cell therapy further reduced the levels of CRS (92).

9. Concluding Remarks

The discussions offered above were summarized to provide an overview related to the mechanistic insights and consequences of GSDMD and GSDME activity in cancer inhibition. Recent technological advancements have stimulated a wave of research into the functional aspects of pyroptosis in the inhibition of cancer. Interdisciplinary researchers have collected and re-interpreted the immunostimulatory role of pyroptosis in tumor microenvironment. Non-coding RNAs have further added complications to the regulatory role of pyroptosis in molecular oncology. Accumulating preclinical studies related to fundamental role of pyroptosis in different cancers provide novel insights into molecular and translational oncology and pave the way for the clinical development of pyroptosis-based therapeutic strategies. Overall, in this mini-review, we have outlined open questions and exciting future research avenues. Therefore, combinatorial approaches that target different cell death pathways while improving therapeutic efficiency will truly be advantageous.

Conflict of Interests

The authors have no conflicts with any step of the article preparation.

Consent for publications

The authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present review article.

Informed Consent

The authors declare that no patients were used in this study.

Authors' contributions

Rukset Attar: Research design and supervision; Muhammad. Z. Qureshi: Sorted most relevant articles for preparation of the review article and edited the article; Uteuliyev Y Sabitaliyevich, Ishmuratova Margarita Yulaevna and Mirna Azalea Romero: Help with writing

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