

Pyroptosis in Hepatocellular Carcinoma: A Retrospective Analysis

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Abstract

Hepatocellular carcinoma (HCC) is characterized by dysregulated cell death pathways, with pyroptosis emerging as a critical modulator of tumor inflammation and immune surveillance. Pyroptosis, a pro-inflammatory programmed cell death mediated by gasdermin D (GSDMD) pores, is governed by NLRP3 inflammasome activation and caspase-1/4/5 signaling. This retrospective analysis synthesizes evidence from 38 recent studies (PubMed, 2020–2025) to dissect the role of pyroptosis in HCC pathogenesis, diagnosis, and therapy. Key findings include dysregulation of pyroptosis-related genes (NLRP3, GSDMD, CASP1) associated with tumor progression, immune microenvironment remodeling, and treatment response. Clinically, pyroptosis signatures predict prognosis and inform precision therapies, with inflammasome inhibitors and pyroptosis inducers showing promise in preclinical models. This review highlights the translational potential of pyroptosis research for enhancing HCC management through inflammatory pathway targeting.

Keywords

Hepatocellular carcinoma; Iron metabolism genes; Antioxidant System Genes; Molecular mechanisms; Oncogenic signaling crosstalk; T Cell.

Introduction

HCC, the most common primary liver cancer, has a dismal prognosis due to aggressive progression and immune evasion. Pyroptosis, identified as a distinct cell death modality in 2015, is characterized by plasma membrane pore formation, cytokine release (IL-1 β , IL-18), and sterile inflammation. Key components include nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3

(NLRP3) inflammasome, caspase-1/4/5, and gasdermin D (GSDMD). Dysregulation of pyroptosis in HCC has been linked to hepatitis virus infection, metabolic stress, and tumor-associated macrophage polarization, making it a pivotal target for immune-oncological interventions.

Methods

Literature search

A systematic PubMed search was performed using keywords: ("hepatocellular carcinoma" OR "HCC") AND ("pyroptosis" OR "inflammasome" OR "gasdermin D" OR "caspase-1"). Inclusion criteria: English studies (2020–2025) reporting pyroptosis-related mechanisms, gene expression, or clinical outcomes in HCC. Exclusion criteria: reviews, non-clinical studies, or non-HCC cancer types.

Data synthesis

Studies were categorized by molecular pathways (inflammasome activation, GSDMD processing, cytokine secretion), clinical relevance (diagnosis, prognosis), and therapeutic interventions. Quantitative data (gene expression levels, survival statistics, treatment efficacy) were extracted and tabulated.

Results

Pyroptosis-related gene dysregulation in HCC

I. Inflammasome components

- **NLRP3:** Overexpressed in 68% of HCC tissues (mRNA: 2.15 ± 0.78 vs. normal liver 1.00 ± 0.19 , $p < 0.001$, Table 1), correlated with IL-1 β secretion and macrophage recruitment.
- **CASP1:** Activated caspase-1 protein levels increased 1.8-fold in HCC, promoting GSDMD cleavage and pore formation [1].

II. Gasdermin family

- **GSDMD:** Full-length GSDMD (55 kDa) reduced in advanced HCC, while cleaved GSDMD-NT (30 kDa) increased in tumor margins, indicating active pyroptosis (Western blot intensity: 0.65 ± 0.21 vs. 1.23 ± 0.35 in normal, $p = 0.008$, [2]).
- **GSDME:** Downregulated in 55% of HCC, correlating with reduced pyroptosis and increased chemoresistance (OR=2.5, 95% CI: 1.3–4.8, $p = 0.012$, [3]).

Gene	HCC (n=200)	Normal Liver (n=50)	Fold Change	p-value
NLRP3	2.15 ± 0.78	1.00 ± 0.19	2.15x	<0.001
CASP1	1.72 ± 0.65	1.00 ± 0.22	1.72x	0.003
GSDMD	0.89 ± 0.31	1.00 ± 0.15	0.89x	0.045
GSDME	0.68 ± 0.25	1.00 ± 0.20	0.68x	0.008
Note: Data shown as mean $\pm$ SD (qRT-PCR/Western blot); fold change relative to normal liver.				

Table 1: Key Pyroptosis Gene Expression in HCC Tissues.

Molecular mechanisms of pyroptosis in HCC

I. Inflammasome activation pathways

- **Oxidative Stress:** Hepatitis B virus (HBV) X protein induces NLRP3 inflammasome activation via reactive oxygen species (ROS) generation, promoting IL-18 secretion and tumor angiogenesis (Figure 1), [4]).
- **Metabolic Dysfunction:** Steatotic HCC cells activate NLRP3 through mitochondrial damage-associated molecular patterns (mtDAMPs), enhancing pyroptosis in tumor stroma (GSEA NES=2.3, $p<0.01$, [5]).

II. Immune microenvironment interaction

- **Macrophage Polarization:** Pyroptotic HCC cells release HMGB1 and ATP, recruiting M1-like macrophages (CD86⁺, iNOS⁺) and activating dendritic cells (DCs), enhancing anti-tumor immunity (Table 2, [6]).
- **T Cell Regulation:** IL-1 β /IL-18 secretion promotes Th17 cell differentiation, while excessive pyroptosis induces T cell exhaustion via PD-L1 upregulation (PD-L1+ T cells: 30% vs. 10% in non-pyroptotic tumors, $p<0.01$, [7]).

Cell Type	Stimulus	Functional Impact
M1 Macrophages	GSDMD-NT pores, IL-1 β	Tumor cell phagocytosis, IFN- γ secretion
Dendritic Cells	ATP/P2X7R signaling	MHC class I upregulation, T cell priming
Tregs	Excessive IL-1 β	FoxP3+ T cell expansion, immune suppression

Figure 2: Immune microenvironment interaction.

Clinical Relevance of Pyroptosis Signatures

I. Diagnostic and prognostic biomarkers

- **Pyroptosis Score (PS):** A 4-gene panel (NLRP3, CASP1, GSDMD, GSDME) achieves AUC-ROC=0.89 for distinguishing HCC from cirrhosis (n=300, $p<0.001$,) (Table 3).
- **Prognosis:** High PS predicts better overall survival (median OS: 28 vs. 16 months, HR=0.6, 95% CI: 0.4–0.9, $p=0.015$, [2]), while NLRP3 overexpression correlates with vascular invasion (OR=3.2, 95% CI: 1.8–5.6, $p<0.001$).

II. Therapeutic interventions

Inflammasome inhibitors

- **MCC950:** Blocks NLRP3 inflammasome, reducing IL-1 β secretion and tumor growth (tumor volume: $0.6 \pm 0.1 \text{ cm}^3$ vs. control $1.2 \pm 0.2 \text{ cm}^3$, $p=0.005$, Table 4, [8]).
- **CRID3:** Inhibits caspase-1, decreasing GSDMD cleavage and promoting HCC cell survival (IC50 increase: 2-fold in CRID3-treated cells, $p<0.01$, [9]).

III. Pyroptosis inducers

- **RSL3:** Sensitizes sorafenib-resistant HCC cells to pyroptosis via GSDME upregulation, inducing 40% cell death in vitro (Table 4), [10]).

- **5-FU:** Enhances pyroptosis in HCC by activating caspase-4, increasing IL-18 release and immune cell infiltration (IL-18 levels: 250 ± 35 pg/mL vs. control 100 ± 20 pg/mL, *p*<0.001, [11]).

Biomarker	Diagnostic AUC-ROC	Median (Months) (High vs. Low PS)	OS (High vs. Low PS)	HR (95% CI)	<i>p</i> -value
4-gene PS	0.89	28 vs. 16		0.6 (0.4–0.9)	0.015
NLRP3 expression	–	20 vs. 26		1.9 (1.2–3.1)	0.028

Table 3: Diagnostic and Prognostic Performance of Pyroptosis Signatures.

Agent	Model	In Vitro Cell Death (%)	In Vivo Tumor Growth Reduction (%)	Cytokine Change (pg/mL)
MCC950	Xenograft	25 ± 4 (72 h)	50 ± 8	IL-1β ↓60%
RSL3	HCC cell lines	40 ± 5 (48 h)	45 ± 7 (orthotopic)	GSDMD-NT ↑30%
5-FU	Huh7 xenograft	35 ± 6 (96 h)	35 ± 6	IL-18 ↑150%

Table 4: Therapeutic Efficacy of Pyroptosis-targeted Agents.

Discussion

This retrospective analysis underscores the dual role of pyroptosis in HCC: pro-inflammatory effects enhancing immune surveillance versus pro-tumorigenic impacts via excessive inflammation. Dysregulated NLRP3 inflammasome and GSDMD processing are key drivers of tumor-stroma crosstalk, with clinical signatures offering diagnostic and prognostic value. Therapeutic strategies targeting inflammasome activation or promoting pyroptosis in cancer cells show promise, particularly in sensitizing drug-resistant subsets.

Challenges include the context-dependent effects of pyroptosis (tumor-suppressive vs. tumor-promoting), off-target inflammation induced by pyroptosis inducers, and inter-patient variability in inflammasome component expression. Future research should prioritize clinical validation of pyroptosis biomarkers, develop combinatorial therapies (e.g., pyroptosis inducers + PD-1 inhibitors), and explore the crosstalk between pyroptosis and other cell death pathways (ferroptosis, apoptosis).

Conclusion

Pyroptosis represents a critical interface between cell death and inflammation in HCC, with dysregulated pathways offering actionable targets for immune modulation and precision therapy. Translating mechanistic insights into clinical applications could improve patient stratification and treatment efficacy, particularly in leveraging inflammatory cues to enhance anti-tumor immunity.

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