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REVIEW

Novel diagnostic and therapeutic strategies based on PANoptosis for hepatocellular carcinoma

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ABSTRACT Hepatocellular carcinoma (HCC), a highly aggressive liver cancer, poses a large medical care burden worldwide. The prognosis of patients with HCC is poor, owing to recurrence and metastasis after common treatment methods. Therefore, identifying new targets to eliminate HCC cells is critical for treatment of HCC without recurrence. PANoptosis, a novel inflammatory cell death pathway, has become an intensively investigated area in recent years. The concept of PANoptosis has brought new hope for HCC therapy, given recent evidence implicating this form of programmed cell death in cancer progression, prognosis, and resistance to chemotherapy and immunotherapy. Despite increasing reviews describing the role of PANoptosis in various cancer types, to our knowledge, no systematic review has examined the implications of PANoptosis in HCC. Therefore, we sought to provide the first systematic review of the regulatory mechanisms and therapeutic potential of PANoptosis in HCC. We summarize recent progress in exploration of the role of PANoptosis in HCC, particularly regulation of the HCC tumor microenvironment by PANoptosis. Finally, we highlight the potential of PANoptosis-based diagnostic and therapeutic strategies for HCC.

KEYWORDS Hepatocellular carcinoma; PANoptosis; PANoptosome; cell death; tumor microenvironment

Introduction

Hepatocellular carcinoma (HCC) is a highly aggressive liver cancer that poses a substantial burden on medical care worldwide, particularly in China, where populations have high HCC risk because of the prevalence of hepatitis B virus infection[1,2]. Although the development of neonatal hepatitis B virus vaccination and effective anti-viral agents has decreased HCC incidence, other risk factors such as diabetes mellitus, obesity, and non-alcoholic fatty liver disease have recently contributed to an increase in HCC cases[1,3,4]. Moreover, HCC morbidity and mortality remain high, despite substantial prevention, early diagnosis, and treatment efforts[5]. The aggressive nature of HCC leads to poor patient prognosis, because of recurrence and metastasis after common treatment methods such as surgery, chemotherapy, or even recently proposed immunotherapy[6-9]. Therefore, identifying new targets to eliminate HCC cells is critical for treatment of HCC without recurrence.

In this context, the concept of PANoptosis has brought new hope for HCC therapy. PANoptosis, an inflammatory programmed cell death (PCD) pathway regulated by the PANoptosome complex, has key features of pyroptosis, apoptosis, and necroptosis that cannot be accounted for by any PCD pathway alone. Recent evidence has implicated PANoptosis in cancer progression, prognosis, and resistance to chemotherapy and immunotherapy[10,11]. To our knowledge, no published review has summarized the role of PANoptosis in HCC, although the implications of PANoptosis in other cancer types have recently been reviewed[12-22].

Therefore, we aimed to provide the first systematic review of the regulatory mechanisms and therapeutic potential of PANoptosis in HCC. We summarize recent progress in

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exploration of the role of PANoptosis in HCC, particularly the regulation of the tumor microenvironment (TME) of HCC by PANoptosis. Finally, we highlight the potential of PANoptosis-based diagnostic and therapeutic strategies for HCC.

PANoptosis is a novel inflammatory cell death pathway incorporating all features of pyroptosis, apoptosis, and necroptosis

PCD is an essential mechanism for removing unnecessary or potentially harmful cells and maintaining homeostasis in the body[23]. Apoptosis, pyroptosis, and necroptosis are 3 key PCD types identified to date[24]. Notably, growing evidence indicates extensive crossover and crosstalk among these 3 PCD types. Therefore, Malireddi et al.[25] proposed the concept of PANoptosis to integrate all these types of PCD. Moreover, the PANoptosome complex is defined as a molecular scaffold for contemporaneous engagement of key components involved in pyroptosis, apoptosis, and necroptosis[26]. The discovery of PANoptosis has provided novel insights into the crosstalk of various PCD pathways and aided in exploration of their roles in inflammatory cascades implicated in diverse diseases including cancer[27].

Apoptosis, pyroptosis, and necroptosis have different genetic characteristics. Specifically, apoptosis pathways include exogenous apoptotic signaling mediated by the binding of ligands to death receptors, endogenous apoptotic signaling mediated by B-cell lymphoma-2 (Bcl-2) family proteins, and caspase-independent apoptotic signaling triggered by endoplasmic reticulum stress. Caspase activation is a key step in regulating apoptosis[28]. Pyroptosis, an inflammatory cell death pathway induced by the pore-forming activity of the gasdermin (GSDM) protein family, includes the classical pathway, which is triggered by inflammasomes and activates caspase-1, and the non-classical pathway, which is triggered by lipopolysaccharide and activates caspase-4/5/11. The activation of inflammasomes and the release of pro-inflammatory molecules such as Interleukin-1β/18 (IL-1β/18) are hallmarks of pyroptosis[29]. Necroptosis, a cell death pathway with morphological characteristics of necrotic cells but signaling mechanisms of apoptotic cells, is mediated by receptor-interacting serine/threonine protein kinase 1 (RIPK1), Receptor-interacting serine/threonine protein kinase 3 (RIPK3), and mixed lineage kinase domain-like protein (MLKL)[30].

The differences among apoptosis, pyroptosis, necroptosis, and PANoptosis have recently been discussed and are listed in **Table 1**[31]. Recent evidence indicates crosstalk among apoptosis, pyroptosis, and necroptosis. Caspase-8 activation induces apoptosis. In contrast, caspase-8 cleaves and inactivates RIPK1 and RIPK3, 2 key proteins mediating the necroptotic pathway, as discussed above. Therefore, caspase-8 functions as a switch that promotes activation of apoptosis while preventing activation of necroptosis. When some pathogens or stimuli induce inactivation of caspase-8, RIPK1 and RIPK3 cleavage by caspase-8 is prevented, and these proteins subsequently bind MLKL, thus forming the necrosome and inducing necroptosis. In the crosstalk between pyroptosis and apoptosis, Caspase-1 functions as a switch. Caspase-1, a key mediator of pyroptosis, also activates apoptotic pathways in the absence of gasdermin D (GSDMD). GSDMD, a pore-forming protein, is crucial for pyroptosis. Caspase-1 cleaves GSDMD and subsequently induces pyroptosis. In the crosstalk between pyroptosis and necroptosis, necroptosis induces the efflux of potassium ions, which in turn activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome and induce pyroptosis[32-35] (**Figure 1**).

The PANoptosome is the core component regulating PANoptosis

The PANoptosome concept was proposed to describe the complex machine driving PANoptosis. The PANoptosome incorporates the inflammasome in pyroptosis, the apoptotic body and related signaling complex in apoptosis, and the dead body in necroptosis[36]. The composition of the PANoptosome is divided into 3 categories: sensors such as Z-DNA binding protein 1 (ZBP1), absent in melanoma 2 (AIM2), and NLRP3; adapters such as apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and Fas-associated death domain (FADD); and effectors such as RIPK1, RIPK3, Caspase-1, and Caspase-8 (**Figure 2**). PANoptosome assembly facilitates the integration of various molecules from different cell death pathways, which act as a molecular scaffold that induces signal transduction and crosstalk among these PCDs in response to different stimuli[37].

A variety of PANoptosomes have been identified, including the ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, and NLRP12-PANoptosome, which are assembled in response to microbial infections or changes in cell

Table 1 Differences among apoptosis, pyroptosis, necroptosis, and PANoptosis

Cell death pathway	Apoptosis	Pyroptosis	Necroptosis	PANoptosis
Cell morphology	Cell shrinkage	Cell swelling	Cell swelling	Cell swelling/contraction
Cell membrane	Cell membrane blebbing maintain structural integrity	Cell membrane rupture and loss of integrity	Cell membrane rupture and loss of integrity	Cell membrane rupture and loss of integrity
Nucleus	Chromatin condensation and fragmentation	Nuclear condensation, chromatin DNA breakage and degradation	No nuclear chromatin agglomeration	Nuclear chromatin condensation
Organelle	Organelle condensation	Damage and dissolution of mitochondria and lysosomes	Swelling and disintegration of mitochondria and endoplasmic reticulum	Organelle swelling
Cytoplasm	Cytoplasmic shrinkage, formation of apoptotic bodies	Osmotic swelling, release of contents from the cell	Osmotic swelling, release of contents from the cell	
Biochemical hallmark	Activation of caspases, activation of DNA fragments	Activation of Caspase-1, cleavage of GSDMD	RIPK1, RIPK3, and MLKL activation, necrotic body formation, and reactive oxygen species production	PANoptosome assembly
Immunological hallmark	No release of inflammatory mediators	Release of inflammatory mediators	Release of inflammatory mediators	Release of inflammatory mediators
Microstructure	Apoptotic body	Pyrogenic corpuscle	Necrosome	PANoptotic body
Regulators	RIPK1, FADD, APAF	NLRP1, NLRP3, NLRC4, AIM2, Pyrin	RIPK1, RIPK3, MLKL	ZBP1, AIM2, NLRC4, RIPK1, NLRP112
Effectors	Caspase-3/6/7	GSDMD family	MLKL	Caspase-3/6/7, Caspase-1/4/5/11, MLKL

AIM2, absent in melanoma 2; APAF, Apoptotic Protease Activating Factor; FADD, Fas-associated death domain; GSDMD, gasdermin D; MLKL, mixed lineage kinase domain-like protein; NLRP1, NLR family pyrin domain containing 1; NLRP3, NLRP1, NLR family pyrin domain containing 3; NLRP112, NLR family pyrin domain containing 112; NLRC4, NOD-like receptor family CARD domain-containing protein 4; RIPK1, receptor-interacting serine/threonine protein kinase 1; RIPK3, receptor-interacting serine/threonine protein kinase 3; ZBP1, Z-DNA binding protein 1.

homeostasis (**Figure 2**). The details of the structure and function of these PANoptosomes have been reviewed recently[38-40].

PANoptosis, the TME, and HCC therapy

The TME plays an important role in the progression and metastasis of HCC, because interactions among immune cells, tumor-associated fibroblasts, and hepatic stellate cells in the TME promote inflammation and the progression of HCC[41-44]. Indeed, the inflammasome, a multiprotein complex that initiates the innate immune response, has been recognized as an important player in HCC progression and a promising therapeutic target[45-50]. The finding that the inflammasome is a key part of the PANoptosome enables better understanding of the roles of PANoptosis in the regulation of the HCC TME and its potential in HCC immunotherapy.

Necroptosis is an inflammatory programmed cell death that facilitates immune cell infiltration in the TME by inducing the release of inflammatory cytokines and contributes to antitumor immunity[51]. Necroptosis also facilitates dendritic cell maturation and increases the antitumor potential of CD8 + T cells[52]. PANoptosis exhibits characteristics of immunogenic cell death and release of proinflammatory cytokines such as IL-1B and IL-18, thereby facilitating immune cell infiltration into the TME[53]. Natural killer (NK) cells, as part of the innate immune system, recognize and selectively kill tumor cells through surface receptors. NK cells promote a favorable microenvironment for the antigen-specific T-cell immune

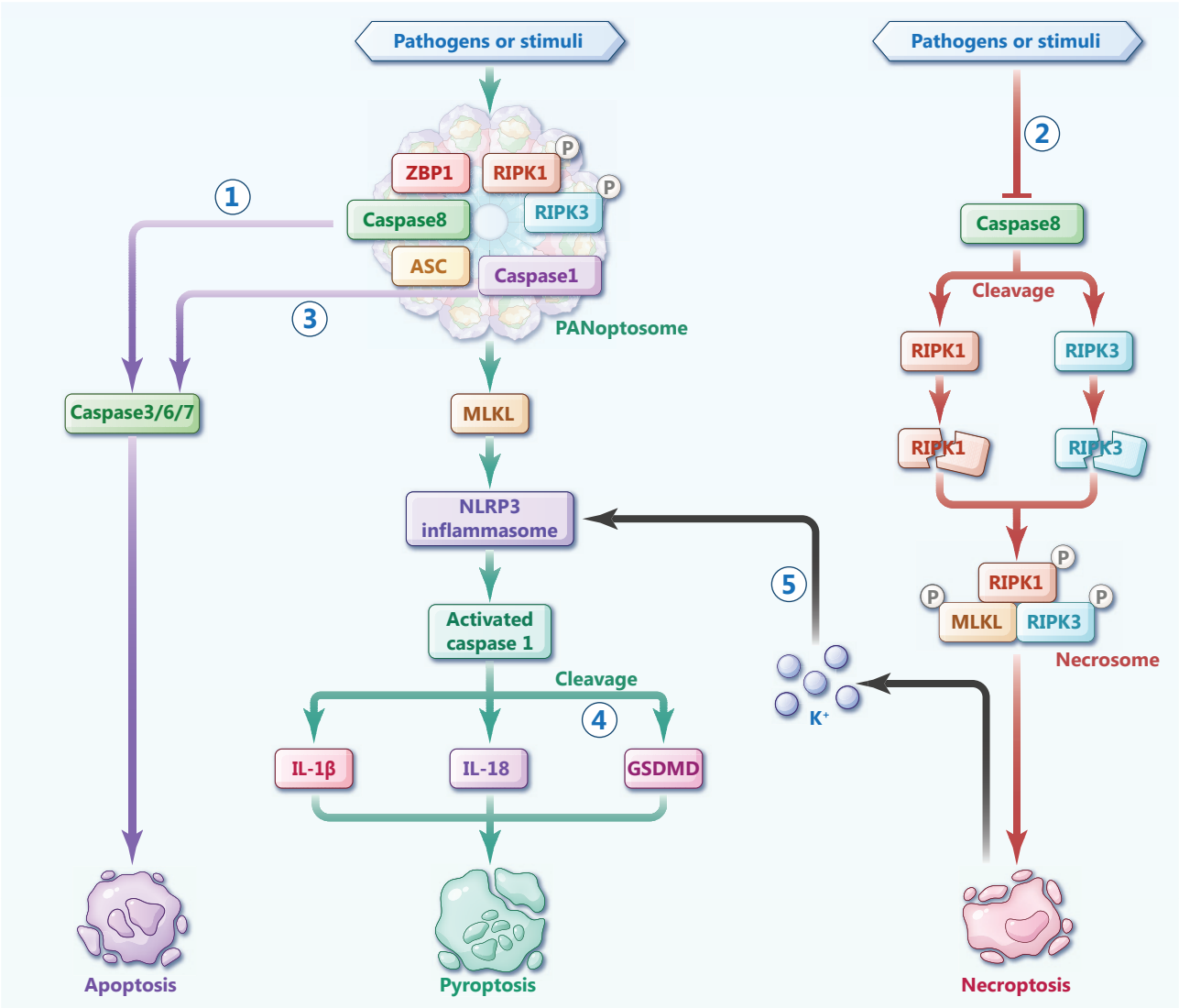


Figure 1 Crosstalk among apoptosis, pyroptosis, and necroptosis. The PANoptosome components, such as Caspase-8 and Caspase-1, engage in crosstalk with other components and consequently modulate the execution of various branches of PANoptosis. ① Some pathogens or stimuli induce Caspase-8 activation and induce apoptosis (pathway marked in purple). In contrast, caspase-8 cleaves and inactivates RIPK1 and RIPK3, 2 key proteins mediating the necroptotic pathway. ② When some pathogens or stimuli induce caspase-8 inactivation, RIPK1 and RIPK3 cleavage by caspase-8 is prevented, and these proteins subsequently bind MLKL, form the necrosome and induce necroptosis (pathway marked in red). ③ In the crosstalk between pyroptosis and apoptosis, Caspase-1 functions as a switch. Caspase-1, a key mediator of pyroptosis, also activates apoptotic pathways in the absence of GSDMD (pathway marked in purple). ④ GSDMD, a pore-forming protein, is crucial in pyroptosis. Caspase-1 cleaves GSDMD, thereby inducing pyroptosis and activating the release of the pro-inflammatory molecules interleukin-1β and interleukin-18, 2 hallmarks of pyroptosis (pathway marked in green). ⑤ In the crosstalk between pyroptosis and necroptosis, necroptosis induces the efflux of potassium ions, which then activate the NLRP3 inflammasome and induce pyroptosis (pathway marked in black). ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; K^+, potassium ions; MLKL, mixed lineage kinase domain like pseudokinase; NLRP3, NLR family pyrin domain containing 3; RIPK1, receptor-interacting serine/threonine kinase 1; RIPK3, receptor-interacting serine/threonine kinase 3; ZBP1, Z-DNA binding protein 1.

response, and directly kill cancer cells through a variety of mechanisms including PANoptosis[54]. Notably, Shi et al.[55] have constructed a PANoptosis related gene model of HCC, and analyzed tumor-infiltrating immune cells. The abundance of NK cells in TME in the high-PAN score group highlighted the role of NK cells in PANoptosis in the HCC TME.

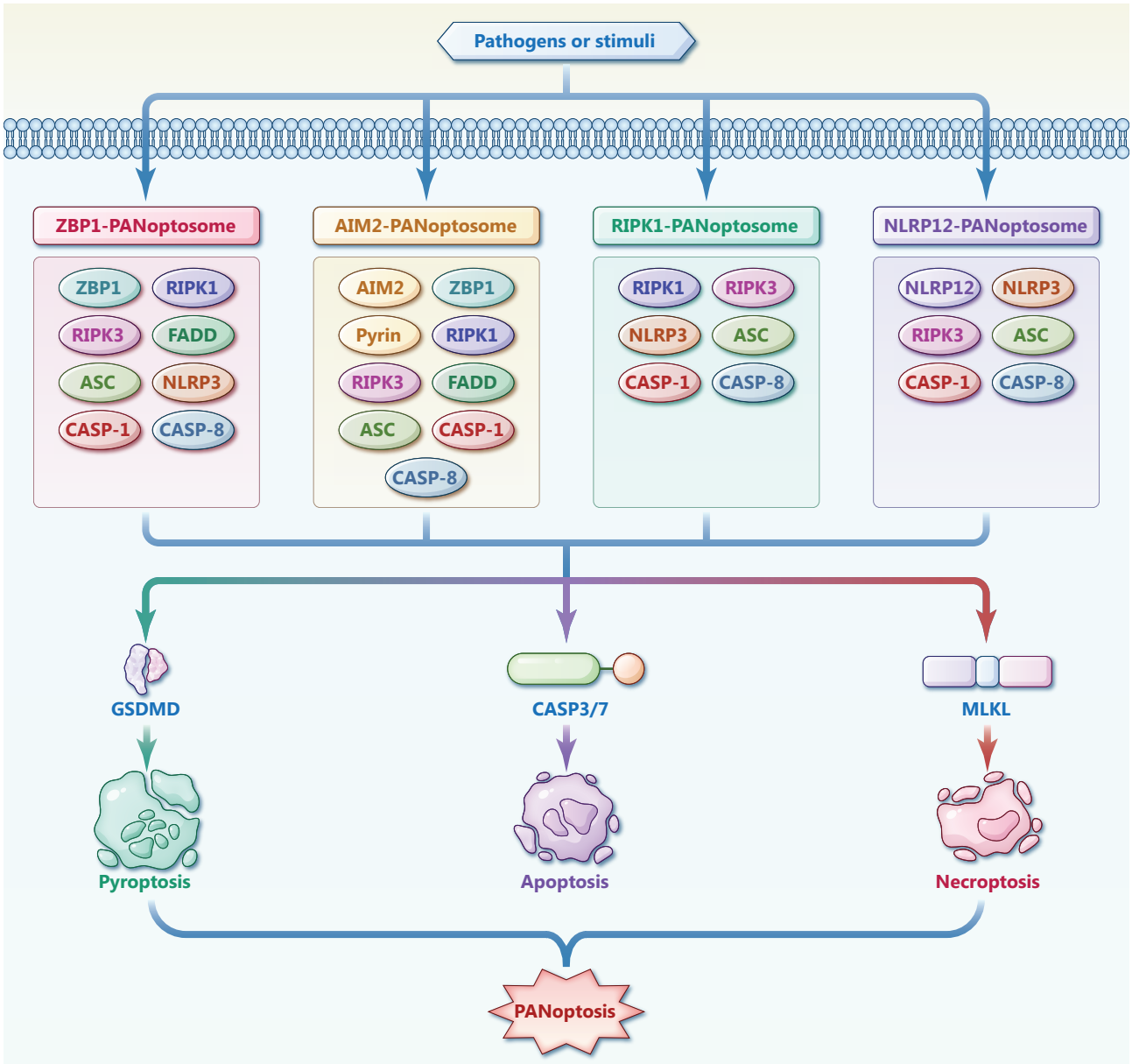


Figure 2 Composition of the PANoptosome. After pathogen infection or other cell homeostasis stimuli, sensors such as ZBP1, AIM2, RIPK1, and NLRP12 are activated and subsequently recruit a variety of partners (such as ASC, CASP-1, and CASP-8, which are indicated by the same color), thus forming PANoptosomes referred to as the ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, and NLRP12-PANoptosome. The different PANoptosomes activate downstream effectors such as GSDMD, caspase-3/7, and MLKL, thus inducing pyroptosis, apoptosis, and necroptosis, which together constitute PANoptosis. AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CASP-1, caspase 1; CASP-3, caspase 3; CASP-7, caspase 7; CASP-8, caspase 8; FADD, Fas associated *via* death domain; GSDMD, gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; K+, potassium ions; MLKL, mixed lineage kinase domain like pseudokinase; NLRP3, NLR family pyrin domain containing 3; NLRP12, NLR family pyrin domain containing 12; RIPK1, receptor-interacting serine/threonine kinase 1; RIPK3, receptor-interacting serine/threonine kinase 3; ZBP1, Z-DNA binding protein 1.

HCC therapy is notoriously difficult, because the TME of HCC actively suppresses the immune system and allows HCC cells to evade immune destruction[56,57]. Therefore, PANoptosis may be used to overcome the immunosuppressive TME of HCC. PANoptosis reprograms the immunosuppressive TME and enhances innate immune responses. PANoptosis

promotes dendritic cell maturation and macrophage polarization *via* the release of damage-associated molecular patterns. Consequently, the release of cytokines triggers inflammatory cell death[58]. Targeting the PANoptotic cell death pathway not only helps counteract immune evasion but also facilitates a positive feedback loop of immune activation. Therefore, resistance in refractory tumors such as HCC can be overcome.

PANoptosis markedly boosts tumor-specific immunity and is positively associated with the infiltration of a range of immune cells including CD4 + T cells, CD8 + T cells, and NK cells within the TME[59,60]. Furthermore, immune checkpoint molecules such as CCL2, CD274, CD4, CXCR4, and LAG3 positively correlate with the PANoptotic signature[53]. Therefore, PANoptosis exerts positive effects in antitumor immunity by promoting immune cell infiltration, upregulating immune checkpoint molecules, and boosting tumor immunogenicity. Unfortunately, few studies have explored the role of PANoptosis in HCC immunotherapy to date. Further investigation of the association between TME of HCC and PANoptosis would aid in the development of novel strategies for HCC immunotherapy. Interestingly, a very recent study using a consensus clustering approach based on TCGA-LIHC data has identified PANoptosis genes associated with the TME of HCC[61]. Therefore, we believe that detailed dissection of the interplay between PANoptosis and various components in the TME of HCC would reveal therapeutic and prognostic potential for patients with HCC. On the basis of the regulatory role of PANoptosis in the TME, further exploration of its application in predicting treatment response and prognosis in HCC will be highly important.

Application of the PANoptosis signature in predicting HCC therapy response and prognosis

Given the emerging role of PANoptosis in HCC progression, researchers have used bioinformatics tools and online databases to explore the PANoptosis signature of HCC to predict HCC therapy response and prognosis. Liu et al.[62] have used single-cell sequencing (scRNA-seq) to categorize patients with HCC into low- and high-PANoptosis groups with diverse biogenic and pharmacotherapy heterogeneity. The PANoptosis index derived from machine learning provides a succinct framework for predicting outcomes and deciphering the immunological ecology hallmarks of patients with HCC. Other groups have identified PANoptosis-associated differentially expressed genes in HCC (named HPAN_DEGs) or PANoptosis-associated genes in HCC (named PANRGs or PRGs by various groups), and constructed a PANoptosis signature to profile the TME landscape of HCC, predict responses to chemotherapy and immunotherapy, and evaluate HCC prognosis[55,63-70]. Most recently, Wang et al.[71] have explored the role of PANoptosis-associated long non-coding RNAs (lncRNAs) in HCC and developed the first PANoptosis-associated lncRNA based risk index in HCC to assess prognosis, the TME, and response to immunotherapy. Another study has explored HCC related PANoptosis-associated lncRNAs (PRLs) and established HCC-associated PRL scores through WGCNA, LASSO analysis, and multivariate Cox assessment. The relationships of the PRL score with immune infiltration and drug sensitivity were further analyzed to evaluate the clinical value of the PRL score-based prognosis model[72]. Together, these studies have provided new evidence of the roles of PANoptosis-associated lncRNAs in HCC. In summary, PANoptosis signatures consisting of differential genes, RNAs, and proteins might provide novel biomarkers for HCC prognosis.

Use of PANoptosis in HCC therapy

Because PANoptosis is an inflammatory PCD pathway, it has promise in achieving killing of HCC cells. The activation of several PCD pathways such as apoptosis, pyroptosis, and necroptosis has been proposed as a therapeutic strategy for HCC[73-75]. Recently, Wang et al.[76] have reported that deoxyribonuclease 1 like 3 (DNASE1L3) facilitates the generation of double-strand deoxyribonucleic acid breaks and activates the AIM2 PANoptosome during sorafenib-induced HCC cell death. Moreover, DNASE1L3 induced PANoptosis boosts antitumor immunity in the TME and enhances the efficacy of combined sorafenib chemotherapy and PD-1 targeted immunotherapy. Therefore, DNASE1L3 is a promising predictive biomarker and target for HCC therapy. Wei et al.[77] have designed a $Bi2Sn_2O_7$ nanozyme with ultrasound-magnified multienzyme-mimicking properties as a PANoptosis inducer and shown that triggering PANoptosis activation inhibits lung metastasis in HCC, thus opening a novel avenue for HCC therapy. In detail, $Bi2Sn_2O_7$ destroys the mitochondrial function of HCC cells and enhances intracellular accumulation of reactive oxygen species, thus leading to PANoptosis activation. Moreover, the inclusion of external ultrasonic irradiation significantly augments the enzyodynamic therapeutic efficiency of $Bi2Sn_2O_7$[77]. In summary, PANoptosis signatures can be used

to personalize HCC treatment by predicting patient response and tailoring therapies accordingly, and the development of targeted therapies that modulate PANoptosis pathways is a promising strategy for HCC therapy.

Conclusions and perspectives

PANoptosis is a newly discovered cell death pathway characterized by the incorporation of pyroptosis, apoptosis, and necrosis. PANoptosis is a complex process that is not completely understood but has been implicated in a wide range of diseases including HCC. Current studies on PANoptosis and HCC remain very limited, but are expected to expand, given the important roles of PANoptosis in HCC progression, TME regulation, and the therapy response.

Current studies on PANoptosis and HCC have focused primarily on the definition of the PANoptosis signature[55,62-72]. The selection of databases in these studies was not uniform and might present challenges for future studies. The development of PANoptosis inducer drugs, particularly nanomedicine, might bring hope in increasing the efficacy of traditional chemotherapy and new immunotherapies[77-79].

Several areas for future investigations should be highlighted. First, the poor prognosis of HCC is due partially to the niche of cancer stem cells, which promote HCC recurrence and metastasis[80,81]. Inducing PANoptosis of stem cells of HCC is a promising approach to HCC eradication. Second, the prediction of an HCC prognosis based on the PANoptosis signature alone might not be accurate, and combination with other parameters such as HCC angiogenesis should be considered in future studies to construct better prognostic models[82-84]. Third, with better understanding of holistic tumor ecosystems through the lens of genomics[85], PANoptosis related proteins, genes, and RNAs should easily be identifiable in the context of HCC and the HCC related TME, thus achieving breakthroughs in HCC diagnosis, prognostication, and therapy[86] (**Figure 3**).

Furthermore, several unresolved questions should be addressed in future studies. For example, how to ensure

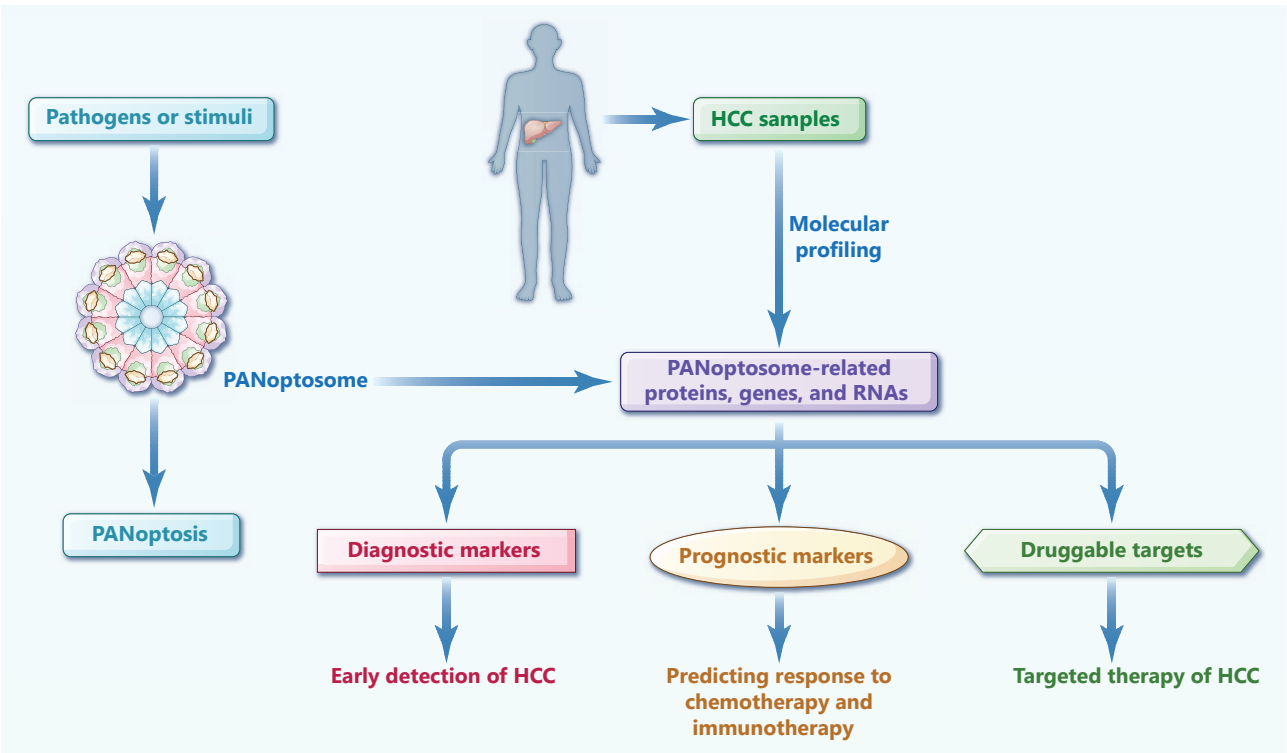


Figure 3 Implications of the PANoptosis concept in HCC. The development of the PANoptosis concept and the exploration of PANoptosome related proteins, genes, and RNAs in HCC samples are expected to provide powerful strategies for HCC diagnosis, prognostication, and therapy. PANoptosis-associated molecular markers may provide a basis for early diagnosis, prognosis prediction, and personalized treatment of HCC. HCC, hepatocellular carcinoma.

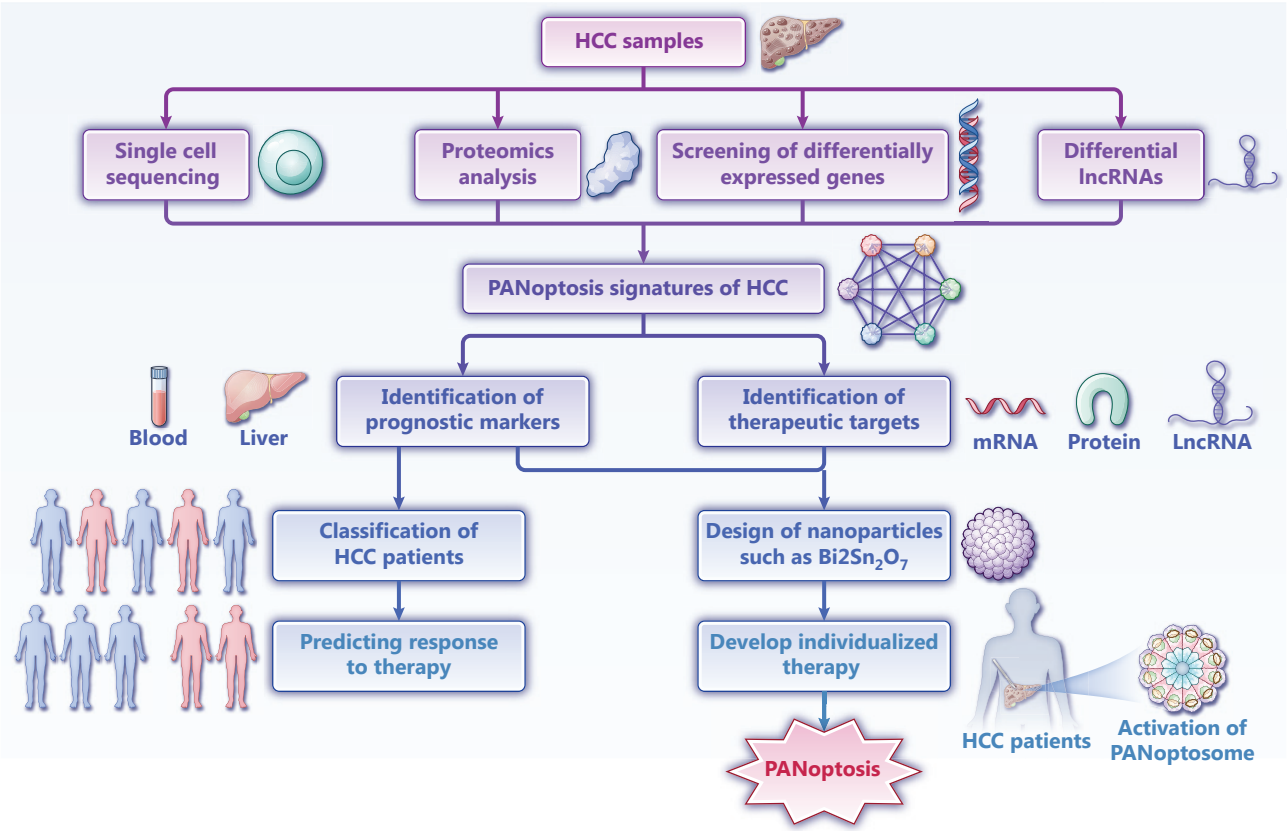


Figure 4 PANoptosis signatures of HCC and the design of PANoptosis inducing drugs for individualized HCC therapy. Various approaches such as single cell sequencing, proteomics analysis, screening of differentially expressed genes and differential lncRNAs have been used to analyze HCC samples and construct PANoptosis signatures of HCC. From HCC PANoptosis signatures, prognostic markers can be identified to classify patients with HCC into groups and predict their responses to chemotherapy and immunotherapy. Furthermore, therapeutic targets including mRNAs, proteins, and lncRNAs can be identified to design nanoparticles such as $Bi2Sn_2O_7$. These specially designed drugs could activate the PANoptosome and induce PANoptosis, thus achieving individualized HCC therapy. HCC, hepatocellular carcinoma.

tissue-specific regulation of PANoptosis in HCC will be important in increasing therapy efficacy and minimizing adverse effects. The use of an HCC specific promoter to drive tissue-specific expression of PANoptosis related genes and proteins should help overcome off-target effects in therapy.

In conclusion, PANoptosis has emerged as a hotspot in cancer research, and the prospects of harnessing PANoptosis for HCC treatment are substantial. Taking advantage of the PANoptosis concept is expected to provide powerful strategies for HCC diagnosis and treatment (**Figure 4**). Moreover, the integration of novel trends such as machine learning based on artificial intelligence should aid in the development of PANoptosis related diagnosis and prognosis models for HCC, and optimization of the design of PANoptosis targeting drugs[87,88]. The next major challenges will be to translate diagnostic, prognostic, and therapeutic models into clinical trials, on the basis of understanding of the roles and mechanisms of PANoptosis in HCC. Patients with HCC may be recruited to validate the diagnostic and prognostic models based on PANoptosis related biomarkers. Moreover, PANoptosis targeting drugs may be administered to patients with late-stage HCC for individualized therapy (**Figure 4**). We are optimistic that these endeavors will greatly benefit patients with HCC in the coming years.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yang Ke, Zhiwei Li.
Collected the data: Jie Xiang, Yukai Li, Shengmin Mei, Zhiyan Ou, Li Wang.
Contributed data or analysis tools: Yang Ke, Zhiwei Li.
Performed the analysis: Jie Xiang, Yukai Li, Shengmin Mei, Zhiyan Ou, Li Wang.
Wrote the paper: Jie Xiang, Yukai Li, Shengmin Mei, Zhiyan Ou, Li Wang.
Reviewed and revised the paper: Yang Ke, Zhiwei Li.

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