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REVIEW

Nanomaterials evoke pyroptosis boosting cancer immunotherapy

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Immunosuppressive tumor microenvironment

Abstract Cancer immunotherapy is currently a very promising therapeutic strategy for treating tumors. However, its effectiveness is restricted by insufficient antigenicity and an immunosuppressive tumor microenvironment (ITME). Pyroptosis, a unique form of programmed cell death (PCD), causes cells to swell and rupture, releasing pro-inflammatory factors that can enhance immunogenicity and remodel the ITME. Nanomaterials, with their distinct advantages and different techniques, are increasingly popular, and nanomaterial-based delivery systems demonstrate significant potential to potentiate, enable, and augment pyroptosis. This review summarizes and discusses the emerging field of nanomaterials-induced pyroptosis, focusing on the mechanisms of nanomaterials-induced pyroptosis pathways and strategies to activate or enhance specific pyroptosis. Additionally, we provide perspectives on the development of this field, aiming to accelerate its further clinical transition.

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1. Introduction

Cancer immunotherapy is a breakthrough that mainly improves antitumor immune responses by enhancing the body's defense capability to eliminate tumor cells[1-3]. Recently, therapies such as immune checkpoint blockade (ICB) have achieved remarkable progress[4]. However, due to the low immunogenicity and the presence of the ITME, most patients either do not respond to ICB therapy or develop resistance following relapse, leading to unsatisfactory therapeutic effects[5-8]. Pyroptosis is a new type of programmed cell death (PCD) caused by the gasdermin (GSDM) protein family that targets the membrane and forms pores. First described in 2001, pyroptosis is recognized as a pro-inflammatory, immunogenic cell death predominantly mediated by GSDM family through the caspase family[9-13]. As a PCD mechanism, it features DNA fragmentation, chromatin condensation, and cell swelling with large bubbles, culminating in the release of inflammatory cytokines like IL-1β, IL-18, HMGB1, and ATP after membrane rupture[14-18]. These processes have been linked to various human diseases, including inflammatory disorders and malignant tumors. In contrast, apoptosis is an orderly death process leading to cellular structure degradation and morphological changes *via* caspase cascade activation[19], ferroptosis is characterized by iron dependence and increased lipid peroxidation[20], while autophagy involves the lysosomal breakdown and recycling of cellular components to meet metabolic demands and renew cellular structures[21]. Key features of pyroptosis include inflammasome formation, gasdermin (GSDM) protein family activation, and caspase involvement (Table 1[16,19-21]). When tumor cells undergo pyroptosis, they release numerous neoantigens that stimulate the systemic immune, thereby enhancing the antitumor immune response and addressing the issues of low immunogenicity and ITME challenges[22]. Therefore, pyroptosis offers a new way of immunotherapy and provides critical guidance for tumor treatment[23,24].

It has been reported that particular metal ions, molecules, and chemotherapy drugs can initiate GSDM family-induced pyroptosis across various cancers[25-27]. However, rapid clearance of these pyroptosis inducers from systemic circulation, unfavorable biodistribution, and inevitable side effects have limited their clinical use. Besides, increasing research has indicated that dysregulation of pyroptosis may weaken pathogen elimination and impair the adaptive immune response[28-31]. Therefore, given the dual role of pyroptosis in either promoting or inhibiting cancer, researchers are diligently exploring how to selectively use this double-edged sword for effective cancer treatment[32]. Thus, there is an urgent need to develop effective strategies that induce cell pyroptosis while minimizing non-specific tissue damage.

Nanotechnology can provide more effective and safer diagnostic and therapeutic methods, offering opportunities for cancer cure[33]. Particularly, nanomaterials have developed into a research hotspot in the scientific field. As the core of novel drug delivery systems, nanomaterials, typically ranging from 1 to 100 nm, exhibit unique advantages in cancer treatment, such as reducing drug toxicity, enhancing drug bioavailability, and improving drug penetration into tumors[34-38]. By delivering pyroptosis inducers, they can activate caspase and GSDM-related proteins, inducing tumor cells to undergo pyroptosis[39]. Nanomedicine-induced pyroptosis can complement the deficiencies of traditional therapeutic modality and further improve the effectiveness of tumor treatment, so it is necessary to provide an overview of nanomedicine that induces pyroptosis.

In this review, we provide a comprehensive summary and deep discussion of nanomaterial-mediated pyroptosis in tumor immunotherapy, focusing on the strategies for inducing pyroptosis with nanomaterials and the mechanisms by which pyroptosis enhances immunotherapy (Fig. 1). Firstly, we introduce the mechanism of pyroptosis and its impact on tumor immunotherapy. Subsequently, we focus on the strategies using various nanomaterials (including phospholipid and polymer-based nanomaterials, mesoporous nanomaterials, nanogels, metal-based nanomaterials, biomimetic nanomaterials, and carrier-free nanomaterials) to induce pyroptosis. Finally, we discuss the dual nature of pyroptosis and the future development and challenges of nanomaterials to potentiate their further clinical translation. We strongly believe that pyroptosis-induced nanomaterials signify a new strategic direction in the field of tumor immunotherapy, with broad prospects for application and clinical translation.

2. Pyroptosis strengthens cancer immunotherapy

2.1. *The function of pyroptosis in immunotherapy*

Pyroptosis, an inflammatory form of cell death, plays a dual role in regulating the tumor immune microenvironment. On one hand, prolonged chronic inflammation induced by pyroptosis promotes tumor growth by sustaining an inflammatory microenvironment around cancer cells. On the other hand, acute activation of pyroptosis triggers the infiltration of various immune cells,

Table 1 Differences between apoptosis, necrosis, autophagy, ferroptosis, and pyroptosis.

Type	Biochemical characteristic	Morphological characteristic	Critical molecule	Damage-associated molecule	Inflammation	Ref.
Pyroptosis	GSDM protein family, inflammatory caspase activation	Pore formation, cell swelling, membrane rupture, the release of intracellular contents	Caspases, GSDM protein family	HMGB1, ATP, IL-1β, IL-18	Yes	16
Apoptosis	Activation of the caspase cascade	Cell shrinkage, nuclear condensation, membrane blebbing	Caspases, p53, BCL-2, BAX	Ecto-CRT, HMGB1, ATP	No	19
Ferroptosis	Iron accumulation, lipid peroxidation	Membrane rupture, release of iron ions	GPX4, system X_c^-, ACSL4, ALOXs	HMGB1	Yes	20
Autophagy	Autophagy-related gene	The formation of double-membrane autophagosomes	Beclin1, VPS34, Atg family	HMGB-1	No	21

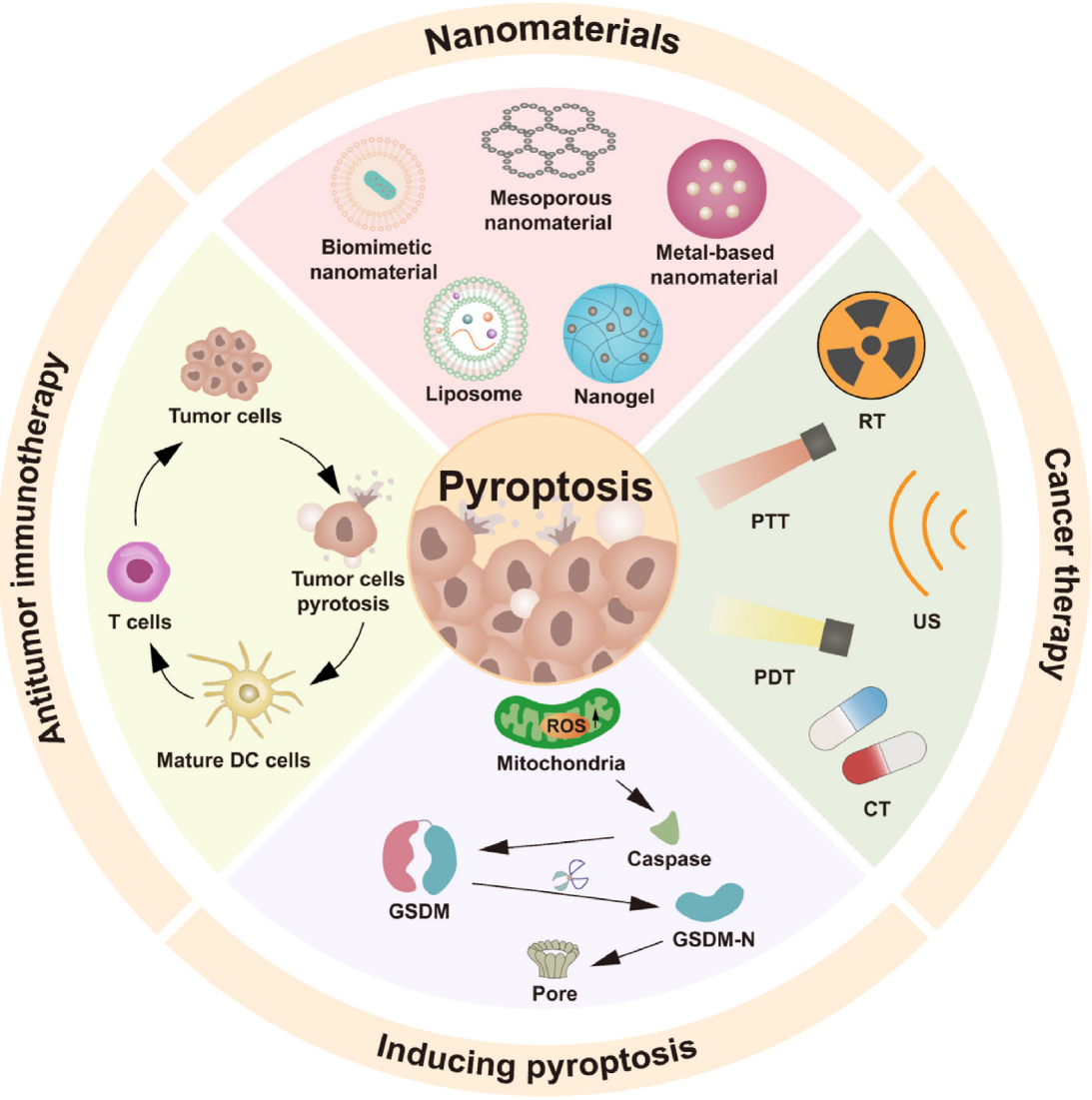

Figure 1 A schematic diagram of nanomaterials inducing pyroptosis to enhance antitumor immunotherapy.

inhibiting tumor growth tumor growth[40,41]. For instance, activation of Gasdermin E (GSDME) during pyroptosis can suppress tumor proliferation by facilitating the recruitment of T lymphocytes and natural killer (NK) cells[42].

Following pyroptosis, the release of inflammatory factors such as IL-1β, IL-18, and HMGB1 plays a significant part in the immune response[43-45]. Recent studies indicate that inflammasome activation in dendritic cells (DCs) induces an overactive state in certain subpopulations, which is dependent on IL-1β that can facilitate the eradication of tumors resistant to anti-programmed cell death1 therapy (aPD-1) therapy[46]. In addition, IL-18 can induce lymphocytes to produce interferon-γ (IFN-γ), enhancing NK and T cells activity in immunotherapy[47]. IL-18 is also involved in the differentiation of T-helper 1 (Th1) and T-helper 17 (Th17) cells, contributing to its antitumor effects[48]. In some cases, pyroptosis releases HMGB1 to promote tumor cell survival[49,50]. Furthermore, the composition of cytokine types may have tumor-promoting effects. IL-18 stimulates tumor growth in the absence of other cytokines, and IL-6 promotes tumor proliferation, metastatic dissemination, and survival by interacting with a variety of downstream mediators[51,52].

As a result, when integrating pyroptosis with immunotherapy, it is critical to guarantee that the immune-promoting effects of pyroptosis induction reduce side effects on normal cells and tissues, improve antitumor efficacy, and enhance therapeutic safety.

2.2. *Mechanisms of pyroptosis*

Pyroptosis is rapidly becoming a new target for inhibiting the occurrence and development of cancer. In recent years, numerous researchers are devoted to elucidating the mechanism of pyroptosis and its role in enhancing immunotherapy[53,54]. To date, pyroptosis signaling pathways are mainly divided into the canonical pathway, the non-canonical pathway, and other pathways. The canonical pathway, mediated by caspase-1, is triggered by pathogens[55], whereas intracellular lipopolysaccharide (LPS) from Gram-negative bacteria causes atypical pathways mediated by caspase-4/5/11[56,57]. Furthermore, caspase-3 and -8 primarily activated by chemotherapy, viruses, and cytotoxic stimuli, are also involved in pyroptosis[58,59]. Antigens released by pyroptosis can activate immune cells, thereby enhancing potent antitumor immune responses. Therefore, understanding the molecular

mechanism of pyroptosis provides valuable insights into developing tumor immunotherapy (Fig. 2)[60].

2.2.1. *The canonical pathway*

The canonical pyroptosis pathway is an inflammasome-mediated caspase-1-dependent pathway. Common pattern recognition receptors (PRRs) in the inflammasome, such as NLRP1, NLRP3, NLRC4, AIM2, and PYRIN, can be activated by various stimuli[42,54]. Among them, NLRP3 is the most extensively studied PRR, activated by damage signals including bacterial mycin and viral double-stranded RNA[61]. Activation of the NLRP3 inflammasome leads to the production of cytokines such as IL-1β and IL-18[62]. In addition, activated caspase-1 cleases gasdermin D (GSDMD) and releases its N-terminal domain, which is translocated to the cell membrane and forms pores that mediate the release of inflammatory cytokines IL-1β and IL-18, leading to inflammation and ultimately pyroptosis[63].

2.2.2. *The non-canonical pathway*

The non-canonical pyroptosis pathway is caused by caspase-4/5/11, which act as cytosolic sensor in response to LPS[64]. LPS directly binds to caspase-4/5/11 on entering the cytoplasm, activating them through autoproteolysis induced by dimerization[65]. Upon activation, caspase-4,5 and 11 cleave GSDMD, exposing the GSDMD-N terminus that forms nonselective pores in the plasma membrane, causing cell swelling, large bubble formation, rupture, and release of cellular contents, ultimately leading to cell death[66,67]. As research progressed, Chen et al.[68] used bacterial outer membrane vesicles to deliver LPS, triggering a caspase11-GSDMD non-canonical pyroptosis pathway for immunotherapy. In this research, AS1411, serving as a DNA aptamer, was coated on the surface of bacterial outer membrane vesicles (Apt-OMVs), which targeted tumor sites and helped to evade host immunity, thereby enhancing therapeutic outcomes of immunotherapy. In addition, folic acid-cholesterol-sodium alginate nanoparticles (FCA NPs) loaded with metformin (MET) and doxorubicin (DOX) induce melanoma pyroptosis *via* caspase-7/GSDMD, activating antitumor immunity[48].

2.2.3. *Other mediated pyroptosis pathways*

Subsequent studies have demonstrated that caspase-3 and -8 are also involved in pyroptosis, with GSDME acting as the substrate for caspase-3-mediated pyroptosis[69,70]. Chemotherapeutic agents and cytochrome c can cause cleavage of GSDME by caspase-3, producing GSDME-NT that penetrates the cell membrane to induce pyroptosis and pore formation[71]. Furthermore, studies of CAR T cell therapy show that granzyme B (Gzm B) derived from CAR T cells activates the caspase-3/GSDME pathway and induces pyroptosis by hydrolyzing caspase-3[72]. Gzm B also enhances antitumor immunity by directly cleaving GSDME at the same site as caspase-3[73]. Granzyme A (Gzm A) cleaves gasdermin B (GSDMB), releasing its pore-forming activity and causing pyroptosis in GSDMB-expressing cancer cells[74].

Another caspase involved in pyroptosis is caspase-8, which cleaves gasdermin C (GSDMC). Specifically, GSDMC is cleaved by caspase-8 under the action of TNF-α, inducing cell pyroptosis[75]. Additionally, the non-immune checkpoint function of programmed cell death-ligand 1 (PD-L1) significantly induces GSDMC/caspase 8-mediated pyroptosis[76]. Upon activation by

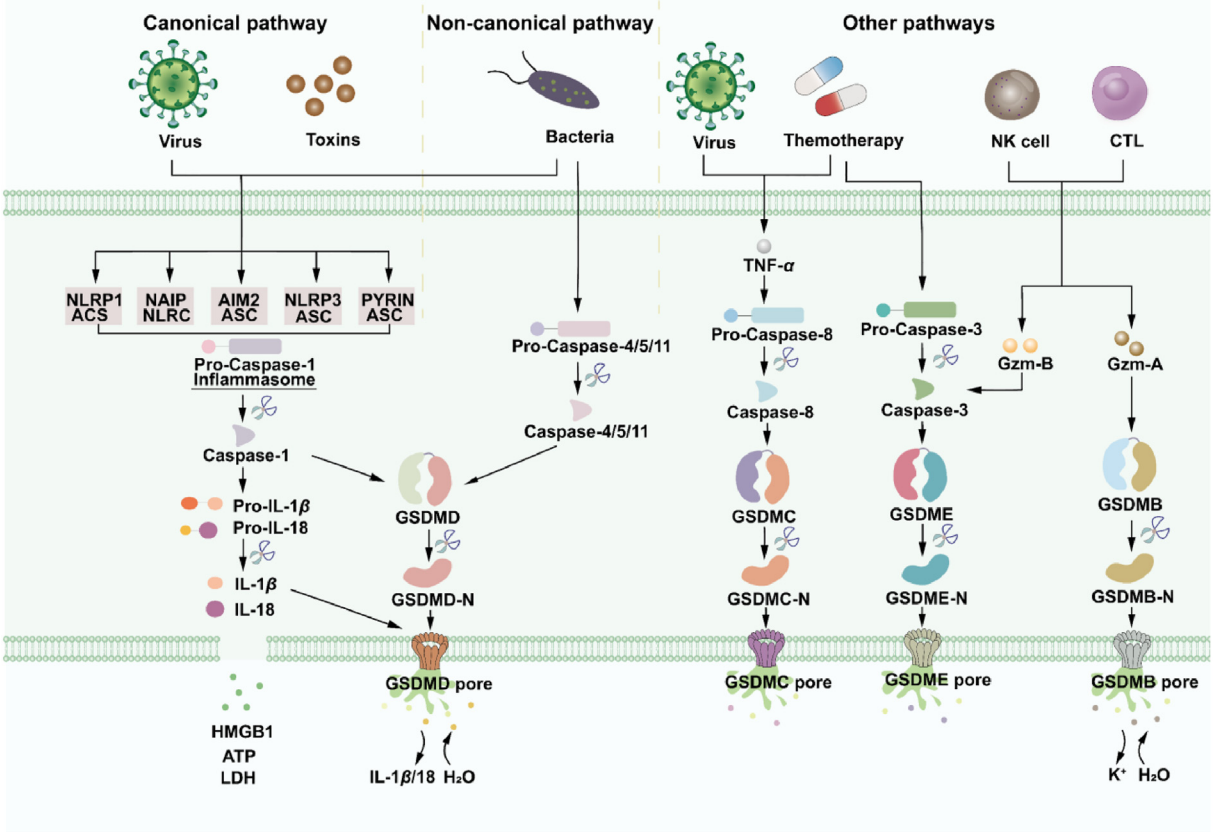

Figure 2 Proposed mechanism of pyroptosis.

TNF-α, caspase-8 cleaves GSDMC, releasing its amino-terminus and forming a pore in tumor cells. This process prevents caspase-8 from recruiting caspase-3 for apoptosis process, transforming TNF-α induced apoptosis into pyroptosis[77].

3. Application of nanomaterial-induced pyroptosis in tumor immunotherapy

With the emergence of nanotechnology, drug delivery systems based on nanomaterials have made great progress in tumor treatment by the induction of pyroptosis. Researchers apply nanomaterials to drug delivery systems and adopt strategies to induce pyroptosis to improve tumor treatment. Therefore, we summarize pyroptosis-induced nanomaterials, including phospholipid and polymer-based nanomaterials, mesoporous nanomaterials, nanogels, metal-based nanomaterials, biomimetic nanomaterials, and carrier-free nanomaterials (Table 2[82-91,97-105,110,111,113-115,121,125-127,131-135,140-153,155-171,175-179,181-188,191-198,201]). In this section, we mainly review the applications of nanodrug delivery systems (NDDS) to induce pyroptosis and enhance immunotherapy in conjunction with chemotherapy (CT), radiotherapy (RT), photothermal therapy (PTT), photodynamic therapy (PDT), sonodynamic therapy (SDT), and ultrasound (US).

3.1. *Phospholipid and polymer-based nanomaterials*

Polymer nanovesicles, with a particle size of only a few hundred nanometers, can carry both hydrophilic and hydrophobic substances and characteristically circulate long in the body (Fig. 3A)[78-81].

Lipid nanoparticles (LNPs) encapsulate mRNA containing the N-terminal of GSDMD, effectively delivering GSDM-NT to induce pyroptosis, thereby recruiting immune cells and transforming cold tumors into hot tumors. In addition, LNPs synergize with aPD-1 to enhance the therapeutic effects and achieve long-term overall survival (Fig. 3B)[82]. LipoDDP, loaded with decitabine (DAC), elevates the expression of methylated genes in tandem with CT, leading to pronounced pyroptosis in tumor cells through the caspase-3 pathway, and releasing IL-1β, HMGB1, and tumor antigens to amplify the immune response (Fig. 3C)[83]. Long et al.[84] synthesized a biomimetic pH-responsive liposomal drug with tumor-targeting capability and immune escape inhibition, composed of a hybrid membrane from red blood cells and cancer cells membranes, encapsulating AP and CS-1. Compared to single drug treatments, this dual drug delivery system demonstrated stronger antitumor activity in a gastric cancer mouse model by inducing pyroptosis, autophagy, and apoptosis (Fig. 3D). In addition, researchers constructed cationic liposomes based on 1,2-dioleoyl-3-trimethylammonium-propane, chloride (DOTAP) and 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), which effectively accumulated at tumor sites and upregulated GSDME in tumor cells (Fig. 3E)[85]. By studying the feasibility and molecular mechanism of magnetic fluid hyperthermia (MFH) with temozolomide (TMZ) chemotherapy to treat Glioblastoma, Yao et al.[86] found that tumor cell death induced by TMZ/Fe-TSL+AMF occurred through pyroptosis, not apoptosis.

BTN@LND exhibits thermal responsiveness and can deliver lonidamine to the tumor site under PTT conditions[87]. Its combination with CT maximally prevents tumor growth, representing a viable cancer treatment approach. Xiao et al.[88] formulated a physical targeting nanodrug called PCL@GSK-diABZI/aPD-1, capable of delivering the STING agonist diABZI-C2-NH_2, aPD-1, and the DNA methyltransferase inhibitor GSK-3484862. This formulation induced a powerful immunogenic cell death (ICD) phenotype, increased DCs maturation, and initiated a cascade of anticancer immune responses. The NCSNP, comprising β-cyclodextrin conjugated with nitric oxide (NO) donors and immune checkpoint inhibitors (NLG), is designed to block indoleamine 2,3-dioxygenase (IDO)-mediated immune suppression and achieves a self-amplifying effect of inflammation-associated cell pyroptosis[89]. Meanwhile, Zhou's research team used an improved β-cyclodextrin (TMCD) to prepare homomultivalent polymeric nanotraps, which showed significant cytotoxicity to tumor cells by disrupting lipid metabolic homeostasis and inducing pyroptosis, thereby exerting antitumor effects *in vivo*[90]. SW8@NPs simultaneously induce necroptosis and apoptosis in cells *via* PTT, leading to the ablation of osteosarcoma, thereby enhancing its potential for future clinical applications[91].

In summary, these materials can induce pyroptosis and elicit a robust immune response independently when used as pyroptosis inducers. Liposomes, notable for their simple preparation methods, are representative of such materials, enhancing their potential for clinical application.

3.2. *Mesoporous nanomaterials*

Mesoporous nanomaterials, characterized by pore diameters between 2−50 nm, exhibit an extremely high specific surface area, regular pore structure, and adjustable pore diameter. These properties have led to their widespread use in the medical field[92], particularly in drug delivery systems where they improve drug dissolution, bioavailability, controlled release, and targeted delivery[93,94]. In this section, the application of mesoporous materials in inducing pyroptosis is mainly introduced from metal-organic frameworks (MOFs), zeolitic imidazolate frameworks (ZIFs), covalent organic frameworks (COFs), and mesoporous silica-based nanoparticles (MSNs).

MOFs, organic-inorganic hybrid materials bonded by metallic bonds and covalent bonds[95], have been designed through various synthetic strategies and received widespread attention in cancer therapy (Fig. 4A)[96].

Researchers have reported that MOFs modified with mannose and Fe_3O_4 effectively remodel the immune microenvironment and promote the infiltration of T lymphocytes. M-FNM significantly increases reactive oxygen species (ROS), activating the PERK-eIF2α-ATF4-CHOP signaling pathway and showing outstanding targeting and antitumor effectiveness[97]. Feng et al.[104] developed FeMn@R@H that concurrently delivered therapeutic metal ions and immune adjuvant R848 to enhance immunotherapy and overcome both innate immune evasion and immunological compensatory regulation of the tumors (Fig. 4B). In addition, cholesterol oxidase (COD) can increase cell membrane tension, reassemble the cytoskeleton, and improve intracellular osmotic pressure *in vitro*. The photosensitive Hf-TBP and COD synergistically induce pyroptosis and enhance the antitumor effects of PDT, meanwhile, cholesterol depletion downregulates immunosuppressive checkpoints, thereby revitalizing T cells[98]. Wang et al.[99] designed TPL@TFBF to induce both ferroptosis and pyroptosis, enhancing antitumor immunity by generating large amounts of damage-associated molecular patterns (DAMPs) and integrating with ICB to inhibit tumor growth. Xu et al.[100] synthesized Tf-LipoMof@PL, a pH-sensitive nanomedicine, which exhibited desirable anticancer effects. Lipid-coated iron-based MOF

Table 2 Overview of pyroptosis induction in NDDS.

Nanomaterial	NDDS	Therapy	Pathway	Cancer type	Ref.
Phospholipid and polymer-based materials	$GSDMB^{NT}$mRNA @LNP	GT	GSDMB	Breast cancer/melanoma	82
	LipoDDP	CT	Caspase-3/GSDME	Breast cancer/colon carcinoma	83
	LP-R/C@AC	CT	Caspase-3/GSDME	Gastric cancer	84
	GM@LR	–	Caspase-3/GSDME	Breast cancer	85
	TMZ/Fe-TSL	CT	Caspase-1/GSDMD	Glioblastoma	86
	BTN@LND	PTT/CT	Caspase-1/GSDMD	Breast cancer	87
	PCL@GSK-diABZI/aPD-1	CT	GSDME	Breast cancer	88
	NCSNP	–	Caspase-3/GSDME	Melanoma	89
	PTMCD4	–	Caspase-1/GSDMD	Breast cancer	90
	SW8@NPs	PTT	Caspase-1/GSDMD	Osteosarcoma	91
Mesoporous nanomaterials	M-FNM	CDT	Caspase-1/GSDMD	OSCC	97
	Hf-TBP/COD	PDT	Caspase-1/GSDMD	TNBC	98
	TPL@TFBF	–	Caspase-3/GSDME	Malignant melanoma	99
	Tf-LipoMof@PL	–	Caspase-1/GSDMD	Breast cancer	100
	Lip-MOF	–	Caspase-3/GSDME	Breast cancer	101
	MP@PI	CDT/PTT	Caspase-1/GSDMD	Breast cancer	102
	GOx@Cu MOF	–	Caspase-1/GSDMD	Cervical cancer	103
	FeMn@R@H	CDT	Caspase-1/GSDMD	Breast cancer	104
	Cu-THBQ/AX	PDT	Caspase-3/GSDME	Breast cancer	105
	DOX@ZIF-8 @PCBMA-DAC	CT	Caspase-3/GSDME	Breast cancer	110
	AE@ZIF-8/Tf-PEG-PLGA	–	Caspase-3/GSDME	Glioblastoma	111
	(M + H) @ZIF/HA	CT	Caspase-3/GSDME	Breast cancer	113
	^{F127}ZIF-8_{CCCP}	–	Caspase-1/GSDMD	Breast cancer	114
	IDN@MC	NIR	Caspase-3/GSDME	Breast cancer	115
	COF-909-Cu	CDT/PTT	Caspase-3/GSDME	Breast cancer	121
	COF-919	PDT/PTT	Caspase-3/GSDME	Breast cancer	125
	TPy-vinyl COF	PDT/PTT	Caspase-3/GSDME	Breast cancer	126
	TD@COFs	PDT/CT	Caspase-3/GSDME	Breast cancer	127
	MMSN-cRGD@Ce6	PDT	Caspase-1/3/GSDME	Breast cancer	131
	NaCl@ssss-VHMS	–	Caspase-1/GSDMD	Liver cancer	132
	Na-^{IV}Al-DMSN	–	Caspase-1/GSDMD	Colon cancer	133
	VTPA	–	Caspase-1/GSDMD	Breast cancer	134
	MF@SOR	–	Caspase-1/GSDMD/Caspase-3/GSDME	Hepatocellular carcinoma	135
Nanogels	PDONPs	–	Caspase-3/GSDME	HNSCC	140
	VB12-sericin-PBLG-IR780	PDT/PTT	Caspase-1/GSDMD	Gastric cancer	141
	CANPs	PDT	Caspase-3/GSDME	Breast cancer	142
	LDNPs	CT	Caspase-3/GSDME	Breast cancer	143
	AOZN	–	Caspase-1/GSDMD	Malignant melanoma	144
	CDNPs	–	Caspase-3/GSDME	Malignant melanoma	145
	OA@IR820	NIR	Caspase-1/GSDMD	Malignant melanoma	146
	IMs	PDT/PTT	Caspase-3/GSDME	Breast cancer	147
	GelTAMNPs	AMF	NLRP3/GSDMD	Melanoma	148
	RSL3/BP@PLEL	PTT	Caspase-1/GSDMD and caspase-3/GSDME	Liver cancer	149
	IRA/αPD-L1 gel	PTT	Caspase-3/GSDME	Breast cancer	150
	H-CNP@pGMD	–	Caspase-1/GSDMD	Colon cancer	151
	IR780-ZnS@HSA	PDT/PTT	Caspase-3/GSDME	Breast cancer	152
	OPDEA-PDCA	–	GSDMD	Osteosarcoma	153
Metal-based nanomaterials	PWE NPs	RT	Caspase-3/GSDME	Breast cancer	155
	biGC@PNA+DCT	RF irradiation	Caspase-3/GSDME	Breast cancer	156
	VNP-GD/EI-NP@Gel	–	Caspase 1/GSDMD	Metastatic breast/melanoma and inoperable ovarian cancer	157

(*continued on next page*)

Table 2 (*continued*)

Nanomaterial	NDDS	Therapy	Pathway	Cancer type	Ref.
	Cu-TBB	PDT	Caspase 1/GSDMD	Breast cancer	158
	$Cu_2(PO_4)$ (OH)NPs	−	Caspase 1/GSDMD	Colon cancer	159
	(Nig DAC)@ HMA NPs	CT	NLRP3/GSDMD	Bladder tumor/Breast cancer	160
	CA-Re	PDT	Caspase-1/GSDMD	TNBC/colon cancer	161
	TiO_2@Ru@siRNA	PDT	Caspase 1/GSDMD	OSCC	162
	As_2O_3-NP	−	Caspase-3/GSDME	Hepatocellular carcinoma	163
	MnGA	NIR	Caspase-3/GSDME	Osteosarcoma	164
	DSe@POC	CT/PDT	Caspase-3/GSDME	Breast cancer	165
	^{177}Lu-YNP@FA	PTT/RT	Caspase-1/GSDMD	Cervical cancer	166
	Re(I)-g-C_3N_4	PDT	Caspase-1/GSDMD	TNBC	167
	MCSP	−	Caspase-3/GSDME	Cervical cancer	168
	^{PVP}CuO	−	Caspase-1/GSDMD	Pancreatic cancer	169
	Mn-HSP	−	GSDME	Breast cancer	170
	FZOH	−	Caspase-1/GSDMD	Breast cancer	171
Biomimetic nanomaterials	MPNP	−	Caspase-3/GSDME	Breast cancer	175
	Lmo@RBC	−	Caspase-8/GSDMC	Breast cancer	176
	DNF@LIPO	−	Caspase-1/GSDMD	Breast cancer	177
	GOx-Mn/HA	−	GSDMD	Osteosarcoma	178
	LFO@GOx	US	Caspase-1/GSDMD	Breast cancer	179
	NiCoOx	US	Caspase-1/GSDMD	Breast cancer	181
	Pt-NS/HCS	−	Caspase-1/GSDMD/ Caspase-3/GSDME	Colon cancer	182
	DNFs@ZnMn	PTT	Caspase-1/GSDMD	Cervical cancer	183
	LPZ	−	Caspase-1/GSDMD	Breast cancer	184
	BNP	NIR/CT	Caspase-3/GSDME	Solid tumors	185
	CS-1@PB[HM] NPs	PTT/CT	Caspase-3/GSDME	TNBC	186
	M-Cu-T	PDT	Caspase-3/GSDME	Colon cancer/lung cancer	187
	ZTC@M	SDT/US/ CT	Caspase-1/GSDMD	Gastric cancer	188
	ZPHM	PDT	Caspase 1/GSDMD	Breast cancer	191
	ROZM	CT	Caspase-3/GSDME	Melanoma	192
	Ir-HEcN	PDT	GSDMD	Solid tumors	193
	Ca@Gox	−	Caspase-3/GSDME	Breast cancer	194
	DOX/Ce6-OMVs@M	PDT/CT	Caspase-1/GSDMD	TNBC	195
	EMM@DJHAD	−	Caspase-3/GSDME	Breast cancer	196
	C-PMet	−	Caspase-1/GSDMD	Colon cancer	197
	MFG@TCM	PTT	Caspase-3/GSDME	Osteosarcoma	198
Carrier-free nanomaterials	A-C/NPs	PDT/CT	Caspase-3/GSDME	Breast cancer	201

−, not applicable. CT, chemotherapy; PDT, photodynamic therapy; PTT, photothermal therapy; CDT, chemodynamical therapy; SDT, sonodynamic therapy; RF irradiation, radiofrequency irradiation; US, ultrasound; RT, radiation therapy; GT, gene therapy; NIR, near-infrared ray; AMF, alternating magnetic fields; TNBC, triple negative breast cancer; OSCC, oral squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma.

nanoparticles can directly affect primary tumors and induce pyroptosis in acidic environment (Fig. 4C)[101]. A polydopamine (PDA) coated MOF nanoparticle, which delivers chemotherapy drug piperlongumine (PL) and photosensitizer IR820 to induce pyroptosis, kills tumor cells, and evokes immune response to antitumor (Fig. 4D)[102]. To deliver glucose oxidase (GOx) intracellularly, Shao et al.[103] designed a biodegradable MOF, GOx@Cu, selectively inducing pyroptosis in cancer cells and promoting intracellular cascade biocatalysis. Cu-THBQ/AX simultaneously triggers pyroptosis, cuproptosis and secondary necrosis, successfully converting the "cold" tumors into a "hot" state, inducing a continuous immune effect, and providing a potent antitumor effect[105].

ZIF-8, a MOF constructed with a zinc base, exhibits high porosity and a large specific surface area[106,107]. In particular, it is prone to degradation in acidic environments[108], allowing drug-loaded ZIF-8 to release the therapeutic agent in the acidic tumor microenvironment (TME), thereby enhancing the antitumor effect (Fig. 5A)[109].

Zhu et al.[110] prepared DOX@ZIF-8@PCBMA-DAC, which potently activated caspase-3 to induce GSDME-dependent pyroptosis through sustained release of decitabine (DAC) and doxorubicin (DOX), achieving excellent tumor suppression. AE@ZIF-8 NPs significantly increase intracranial distribution and tumor tissue accumulation, providing the possibility for glioblastoma (Fig. 5B)[111]. With the development of antitumor immune mechanisms, tumors actively adopt various immune evasion mechanisms to weaken immunotherapy[112]. Therefore, the primary challenge is designing a delivery platform that can trigger immune responses and inhibit immune evasion. A MOF-based nanoplatform encapsulating mitoxantrone (MIT)

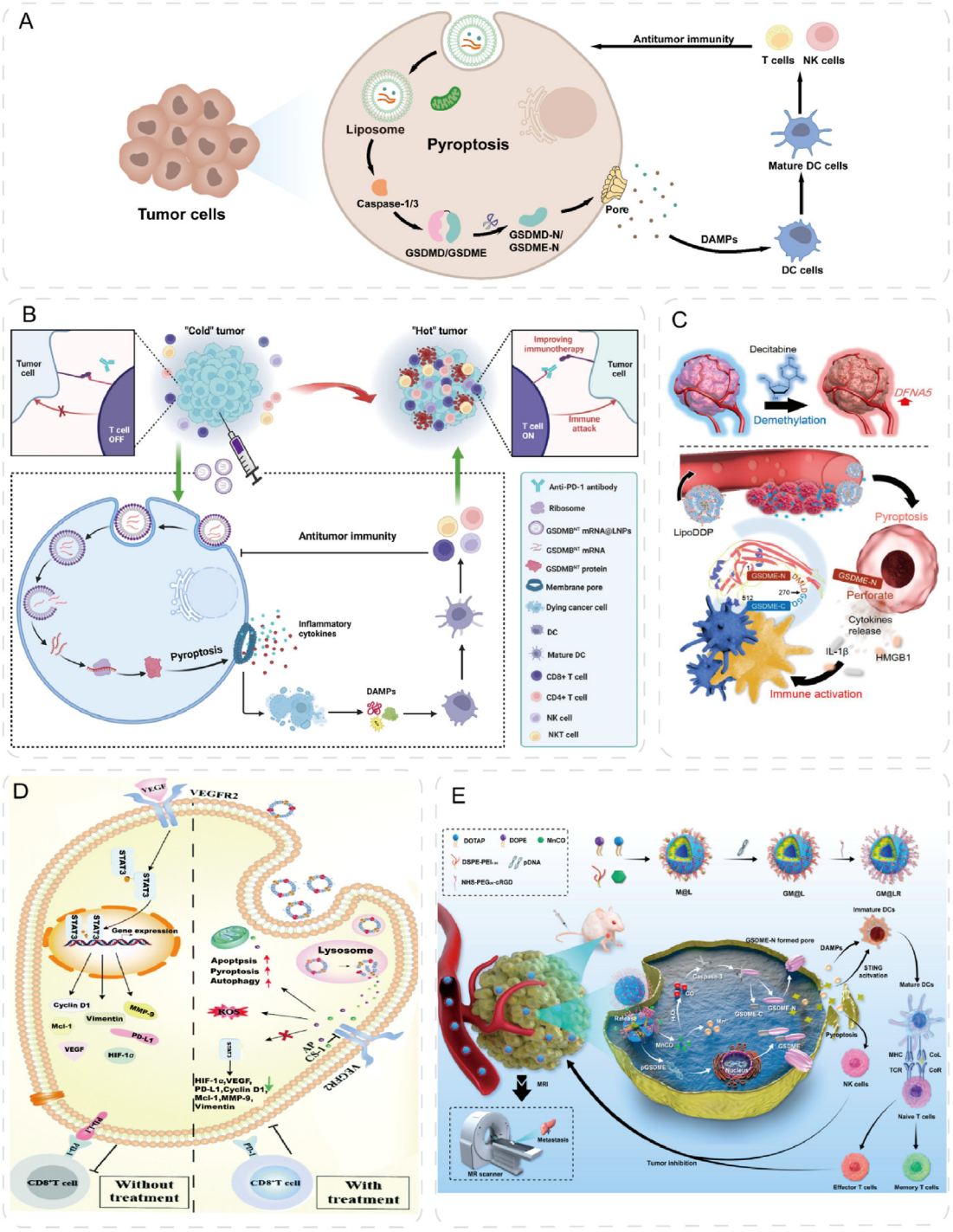

Figure 3 Schematic diagram of pyroptosis-inducing phospholipid and polymer-based nanomaterials. (A) A brief mechanism diagram based on phospholipids and polymers. (B) Mechanistic map of pyroptosis induced in tumor cells targeted by GSDMB^{NT} mRNA@LNP. Reprinted with the permission from Ref. 82. Copyright © 2023, The Authors. (C) Schematic representation of cell pyroptosis induction by LipoDDP. Reprinted with the permission from Ref. 83. Copyright © 2019 American Chemical Society. (D) Schematic illustration of LP-R/C@AC. Reprinted with the permission from Ref. 84. Copyright © 2021 Royal Society of Chemistry. (E) Schematic process of cell pyroptosis induced by GM@LR. Reprinted with the permission from Ref. 85. Copyright © 2023 American Chemical Society.

and hydralazine (HYD) demonstrates robust apoptosis-to-pyroptosis conversion that disrupts myeloid-derived suppressor cells (MDSCs)-mediated T cell paralysis. This two-pronged nanoplatform stimulates immune responses, inhibits immune evasion, and supports long-term immune memory (Fig. 5D)[113]. As one of the most commonly used MOFs, ZIF-8 is suitable for the treatment of various tumors. ^{F127}ZIF-8_{CCCP}NPs can induce pyroptosis through the caspase-1/GSDMD pathway to activate antitumor immunity and reprogram the ITME for efficient tumor growth inhibition

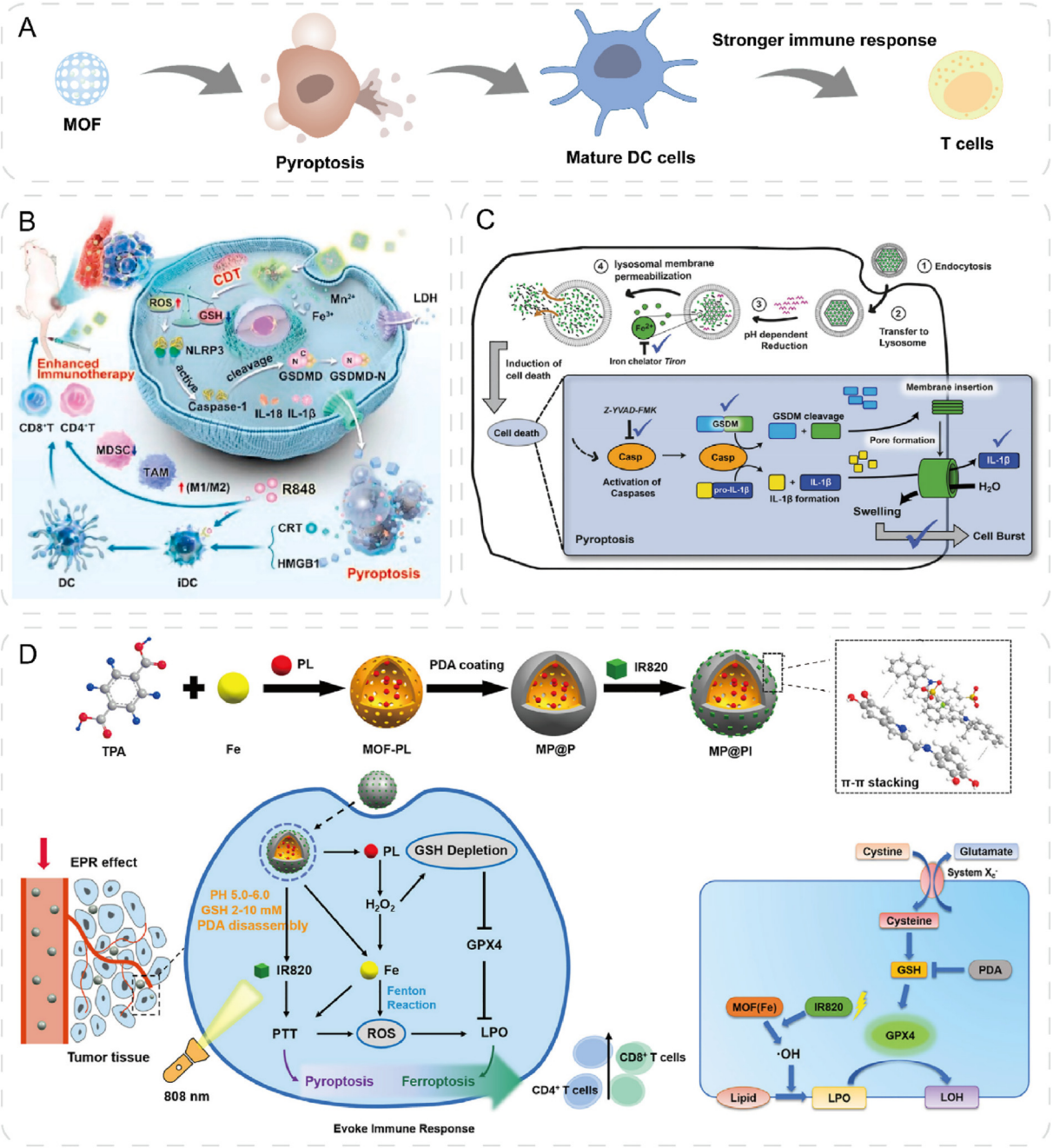

Figure 4 Induction of pyroptosis by MOFs. (A) A brief mechanism diagram based on MOFs. (B) Schematic diagram of FeMn@R@H. Reprinted with the permission from Ref. 104. Copyright © 2023 Elsevier Ltd. (C) Diagram of the pyroptosis mechanism of Lip-MOF. Reprinted with the permission from Ref. 101. Copyright © 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weingeim. (D) Induction ferroptosis and pyroptosis of MP@PI under CDT and PTT. Reprinted with the permission from Ref. 102. Copyright © 2022 American Chemical Society.

(Fig. 5C)[114]. IDN@MC, a macrophage-based biohybrid microrobot constructed through the fusing macrophages with MOF, induces pyroptosis under PTT conditions[115].

COFs, as porous polymers formed by connecting active building blocks *via* dynamic covalent bonds, exhibit outstanding light absorption, photostability, and biocompatibility in cancer photodynamic therapy (Fig. 6A)[116-120].

COF-909-Cu is the first COF pyroptosis inducer, which can simulate various enzyme activities, destroy H_2O_2 homeostasis, and synergize with CDT/PTT to enhance the immunotherapeutic effect of aPD-1 (Fig. 6B)[121]. However, aggregation-caused quenching (ACQ) effect reduces the fluorescence intensity and ROS generation capacity of COF-based photosensitizers[122-124]. COF-919 acts as a dual-inducer of pyroptosis and ferroptosis, improving these processes through PTT[125]. Zhang et al.[126] designed TPy-vinyl COF, which leveraged an aggregation-induced emission effect (AIEgens) to overcome undesirable ACQ effect, eliciting pyroptosis and boosting cancer immunotherapy (Fig. 6C and D). In addition, Liu's team used a combination of PDT and CT to provide valuable insights into cancer

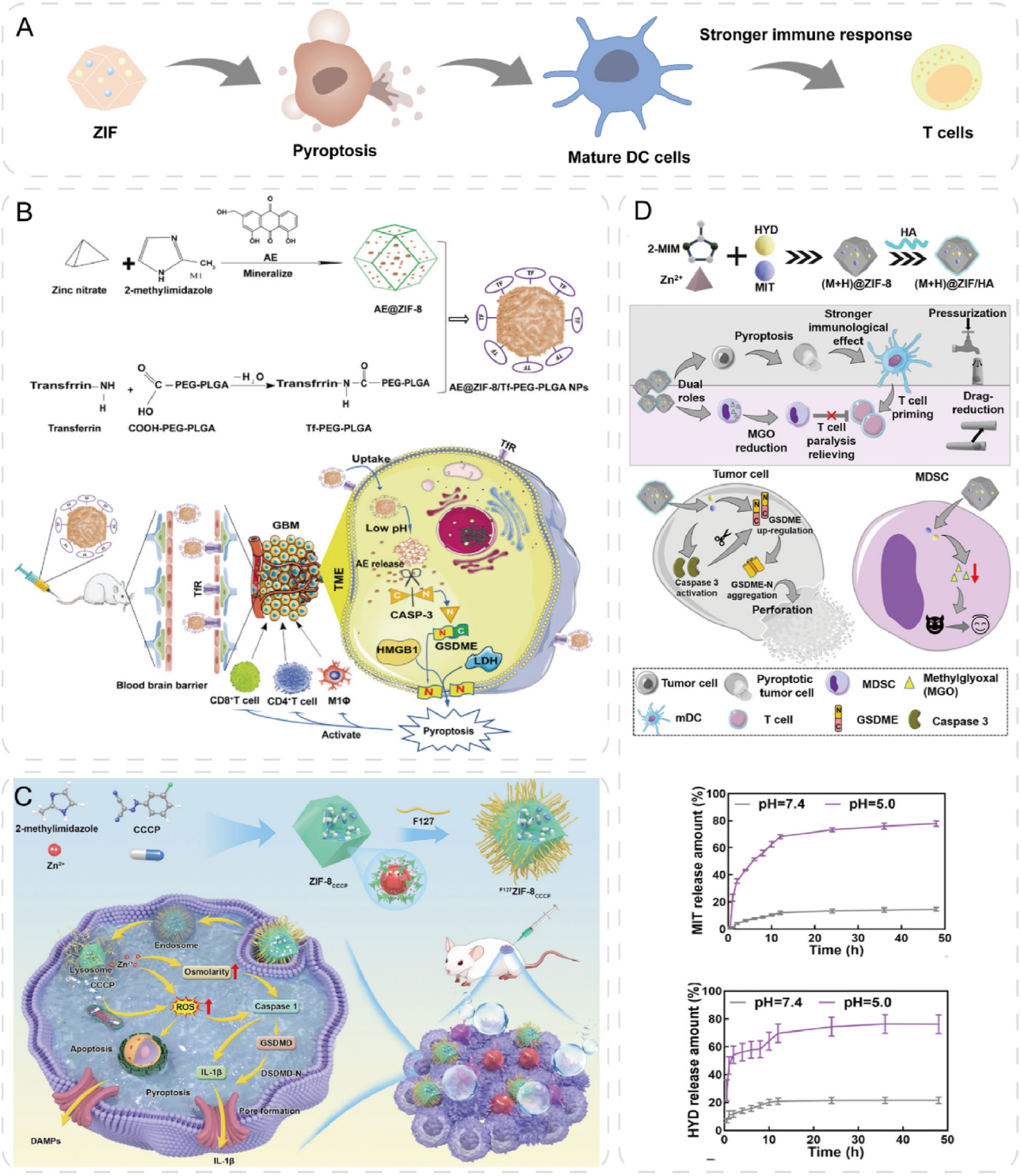

Figure 5 Mechanism diagram of immune response enhanced by pyroptosis-inducing ZIF-8. (A) A brief mechanism diagram based on ZIFs. (B) AE@ZIF-8 NPs induce mechanism of pyroptosis. Reprinted with the permission from Ref. 111. Copyright © 2023 The Authors. Small published by Wiley-VCH GmbH. (C) Schematic diagram of breast cancer treated with ^{F127}ZIF-8_{CCCP}NPs induced pyroptosis. Reprinted with the permission from Ref. 114. Copyright © 2023 Wiley-VCH GmbH. (D) Scheme of fabrication process and therapeutic mechanism of (M+H) @ZIF/HA. Reprinted with the permission from Ref. 113. Copyright © 2021 American Chemical Society.

immunotherapy. TD@COFs, loaded with AIEgen and DAC, synergistically enhance PDT efficacy and control drug release, effectively inducing pyroptosis and eliciting a strong immune response[127].

Another material featuring a porous structure is mesoporous silica-based nanoparticles, which, due to their high loading capacity and adjustable pore size, are also used to induce pyroptosis (Fig. 7A)[128-130].

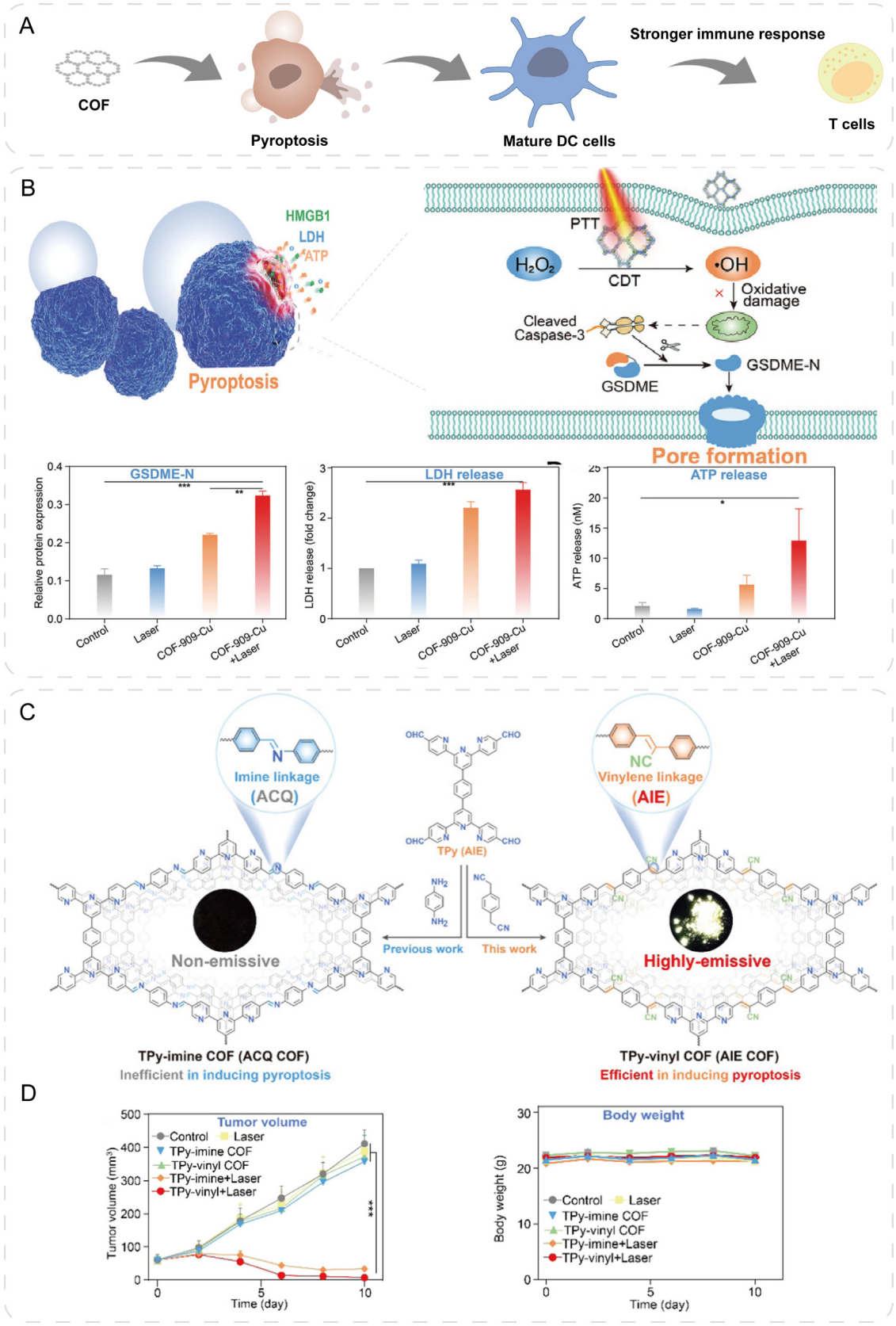

Figure 6 Induction of pyroptosis by COFs. (A) A brief mechanism diagram based on COFs. (B) Proposed mechanism of COF-909-Cu triggered pyroptosis. Reprinted with the permission from Ref. 121. Copyright © 2022 Wiley-VCH GmbH. (C) Schematic diagram of the construction of TPy-imine COF and TPy-vinyl COF. (D) Tumor volumes and body weights. Reprinted with the permission from Ref. 126. Copyright © 2023 American Chemical Society.

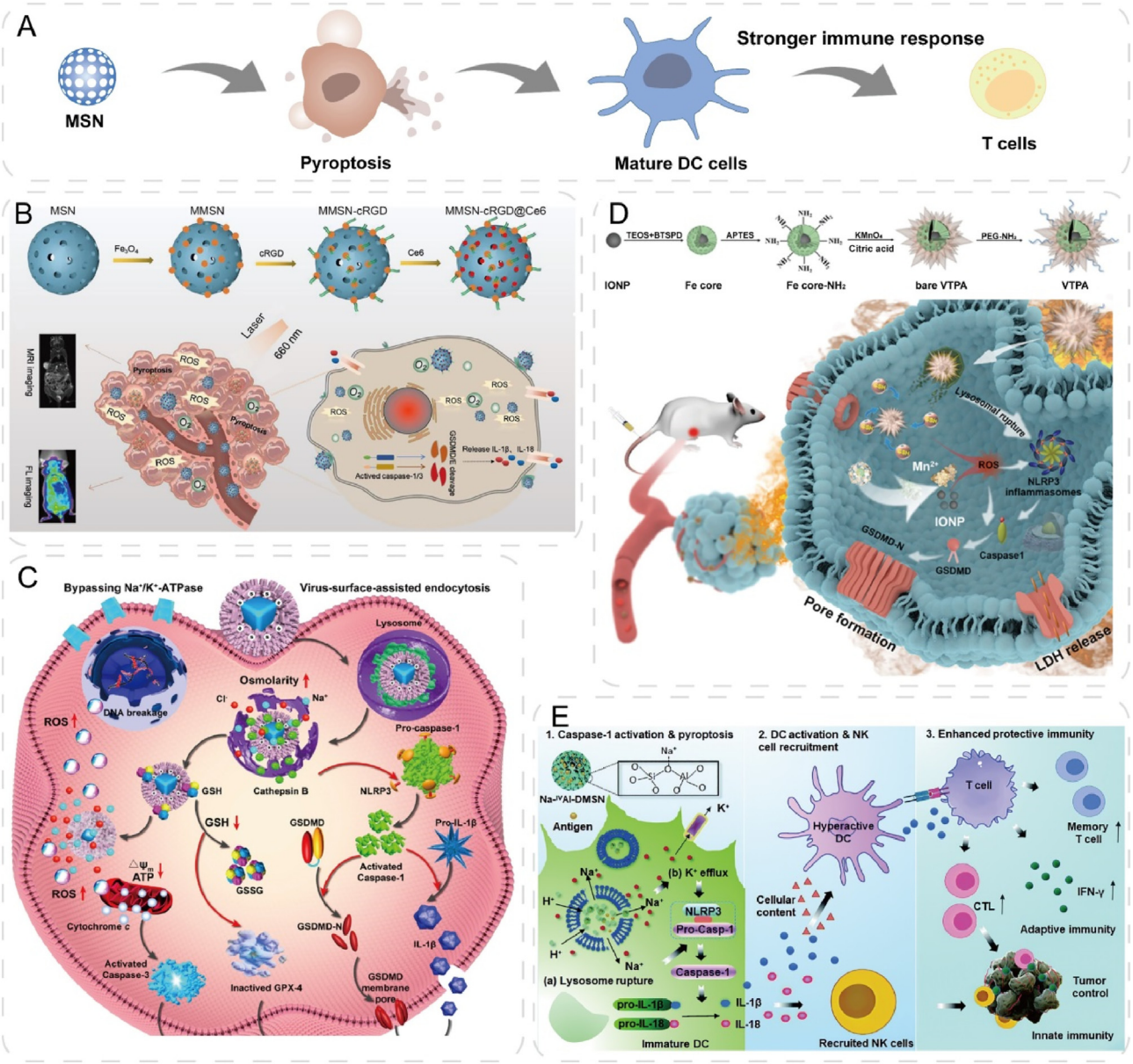

Figure 7 Induction of pyroptosis by mesoporous silica-based nanoparticles. (A) A brief mechanism diagram based on MSNs. (B) Schematic diagram of MMSN-cRGD@Ce6. Reprinted with the permission from Ref. 131. Copyright © 2022 Elsevier Ltd. (C) Diagram of the pyroptosis mechanism of NaCl@ssss-VHMS. Reprinted with the permission from Ref. 132. Copyright © 2022 American Chemical Society. (D) Induction pyroptosis of Na-^{IV}Al-DMSN. Reprinted with the permission from Ref. 134. Copyright © 2021 Wiley-VCH. (E) Schematic diagram of VTPA. Reprinted with the permission from Ref. 133. Copyright © 2022 Royal Society of Chemistry.

Chen et al.[131] developed MMSN-cRGD@Ce6, a cRGD-modified and pyroptosis-engineered theranostic agent (PETA) that used Fe_3O_4 embedded magnetic mesoporous silica nanoparticles (MMSN) as a carrier to transport chlorin e6 (Ce6). In combination with PDT, Ce6 photosensitizer increased intratumoral ROS accumulation, ultimately boosting the antioxidant impact of pyroptosis activation (Fig. 7B). NaCl@ssss-VHMS can circumvent the cell membrane's ion transporter *via* endocytosis, transporting a significant amount of Na^+/Cl^- into tumor cells, disrupting ion homeostasis, and efficiently producing ROS, which can effectively kill tumor cells (Fig. 7C)[132]. Furthermore, DMSN nanomedicine activates DCs through caspase-1-dependent pyroptosis, inducing enhanced immune responses mediated by NK cells and T cells (Fig. 7E)[133]. Nadeem et al.[134] discovered VTPA therapy that induced the activation of the NLRP3 inflammasome and the release of lactate dehydrogenase in tumor cells to evoke pyroptosis (Fig. 7D). Due to the unsatisfactory prognosis of hepatocellular carcinoma (HCC), Du et al.[135] induced pyroptosis through the dual pathway of caspase-1/GSDMD and caspase-3/GSDME. The nanovaccine (MF@SOR) responds intelligently to specific chemical signals in TME, such as low pH and high GSH, boosting DCs maturation.

After putting the aforementioned instances together, it can be shown that the pyroptosis pathway's activation is highly compatible with the characteristics and applications of mesoporous materials. These materials are related to PTT, PDT, or CDT to activate

pyroptosis by the generation of ROS, and they possess adequate internal space to accommodate various pyroptosis inducers.

3.3. Nanogels

Nanogels are three-dimensional (3D) network polymers, formed by physical or chemical cross-linking of hydrophilic polymers[136]. They possess characteristics such as high drug loading capacity, good biocompatibility, long blood circulation time, stimulus responsiveness, and targeted release[137,138]. As innovative biomaterials, nanogels have received considerable attention, exhibiting great potential and broad application prospects (Fig. 8A)[139].

Pyroptosis, an inflammatory process, activates and proliferates immune cells, and has great potential for tumor treatment. PDONPs regulate drug release in response to the acidity of tumors, boosting tumor accumulation and therapeutic efficacy, producing tumor cell pyroptosis, and eliciting T cell-mediated immunity in mouse models of head and neck squamous cell carcinomas (HNSCC) models[140]. In PTT/PDT, VB12-sericin-PBLG-IR780 stimulates NLRP3/caspase-1/GSDMD-dependent pyroptosis and provokes DCs maturation *via* pyroptosis[141]. Researchers constructed CANP nanogels that generated ROS by releasing Ce6 and 17-AAG (heat shock protein 90 inhibitor tanespimycin) under PDT conditions, thereby inducing GSDME-mediated pyroptosis and inhibiting the growth of primary tumors and distant tumors (Fig. 8B)[142]. LDNPS combines histone deacetylase inhibitors (HDACI) LAQ824 and DOX to reshape tumor immunity through pyroptosis, significantly improving the response rate and survival of aPD-1 treatment (Fig. 8C and D)[143]. Moreover, AOZN and CDNP, which are glutathione (GSH)-responsive, effectively trigger pyroptosis and enhance antitumor immunity[144,145]. Upon exposure to near-infrared light, OA@IR820 may prevent the synthesis of mitochondrial ATP, which increases the release of ROS and triggers cell pyroptosis[146]. Xu et al.[147] covered IMs, a GSH/ROS dual-responsive nanogel system, as a pyroptosis inducer to improve tumor immunogenicity. IMs are characterized by their small volume, ultra-stable photothermal performance, and active targeting of cancer cells, providing an excellent platform for light-triggered apoptosis and offering insights for future immunotherapy strategies (Fig. 8E). Furthermore, Wang et al.[148] developed a magnetic thermoresponsive hydrogel (GelTAMNPs) that induced sustained immune activation when used postoperatively to address post-surgical tumor recurrence and metastasis.

Additionally, researchers suggested cascading oxidative stress may be an effective approach to treat cancer[25]. RSL3/BP@PLEL is a biocompatible and biodegradable hydrogel formulation that can induce pyroptosis, repolarize macrophages from M2 to M1, and enhance antitumor efficacy[149]. IRA/aPD-L1 gel effectively induces apoptosis and pyroptosis[150]. Studies have shown that it can persist at the tumor site for 15 days and significantly prolong the survival time of 4T1 tumor-bearing mice (Fig. 8F and G). The survival rate remains above 75% within 100 days (Fig. 8H), which has a good curative effect. H-CNP@pGMD can be degraded in an acidic environment to release plasmid pGMD into the cytoplasm of tumor cells, which activates SRY-box transcription factor 4 (Sox4), expresses GSDMD and is cleaved by MMP2 to induce tumor cell-specific pyroptosis[151]. Yang et al.[152] synthesized IR780-ZnS@HSA, which synergistically enhanced the immune response by activating the caspase-3-GSDME signaling pathway and the Cyclic GMP-AMP synthase cGAS-STING signaling pathway, providing new ideas for tumor treatment. Jin et al.[153] developed OPDEA-PDCA, triggering pyroptosis by mitochondrial oxidative stress. When combined with aPD-L1, it can significantly reduce osteosarcoma proliferation and extend T cells activation.

In short, nanogels exhibit excellent responsive characteristics, such as pH, ROS, and GSH responsiveness, facilitating the development of diverse drug delivery systems tailored to the TME. This establishes the foundation for the creation of new and more effective prodrugs.

3.4. Metal-based nanomaterials

With their excellent biocompatibility and easy modification, metal nanomaterials are a type of nanomaterials containing metal elements, widely used in tumor drug delivery[154]. By integrating these metal-based nanomaterials into various therapeutic modalities, we can overcome the current limitations of single therapies that struggle to completely eliminate tumors (Fig. 9A).

PWE can activate the epigenetic inheritance of cell pyroptosis during RT, converting apoptosis into pyroptosis and amplifying the immune effect of traditional RT[155]. Zhang et al.[156] designed an RF-responsive bivalent gold nanocluster (biGC@PNA) and decitabine (DCA) co-delivery strategy, which activated caspase-3 under radiofrequency irradiation, while DCA can upregulate GSDME, thereby inducing pyroptosis. Due to the multiple improvements of radiofrequency-activated pyroptosis on the tumor immune microenvironment, biGC@PNA effectively enhances the antitumor efficacy of aPD-1 immunotherapy (Fig. 9D). Li et al.[157] synthesized EI-NP and VNP-GD which ensured the intracellular delivery of GSDM, prevented endosomal sorting complexes required for transport (ESCRT)III-mediated cell membrane repair, and achieved pyroptosis-mediated cancer immunotherapy.

Researchers designed a nanosheet containing copper ions (Cu-TBB) that generated ROS under light conditions and activated GSDMD-mediated pyroptosis, thereby enhancing DC maturation and the initiation of cytotoxic T lymphocytes (CTLs), and triggering systemic immune response (Fig. 9B)[158]. Zhao et al.[159] injected $Cu_2(PO_4)$ (OH) NPs into colon cancer sites, inducing copper apoptosis and pyroptosis. Niu et al.[160] used hexahistidine (His6)-metal assemble (HmA) to load nigericin (Nig) and DAC, which avoided lysosomes and distributed the drugs at the tumor site, inducing pyroptosis that polarized M2 macrophages into M1 macrophages (Fig. 9C). Moreover, Su et al.[161] synthesized CA-Re, which promoted the generation of ROS and lipid peroxidation, exhibited extremely high PDT efficiency under hypoxic conditions, effectively induced GSDMD-mediated pyroptosis, and also demonstrated strong antitumor immune activity. Furthermore, TiO_2@Ru@siRNA, a photothermal and immunotherapeutic nanosystem, is adapted to hypoxic conditions, capable of inducing lysosomal damage under PDT, effectively enhancing siRNA escape, and triggering pyroptosis in oral squamous cell carcinoma (OSCC) cells, thereby activating the cancer immune response[162]. In addition, Hu et al.[163] covered As_2O_3 therapy could induce pyroptosis in hepatocellular carcinoma (HCC) cells expressing GSDME, likely due to the upregulation of GSDME-N and the downregulation of PCNA and DNMT-related proteins. MnGA can avoid heat shock protein (HSP) restriction, enhance the effect of PTT, and induce pyroptosis[164]. DSe@POC is used as a pyroptosis inducer because the diselenium bond can be broken by elevated glutathione levels in the TME and ROS produced by PDT. When combined with aPD-1 treatment, it efficiently inhibits distal tumor growth and improves long-term immunological memory[165].

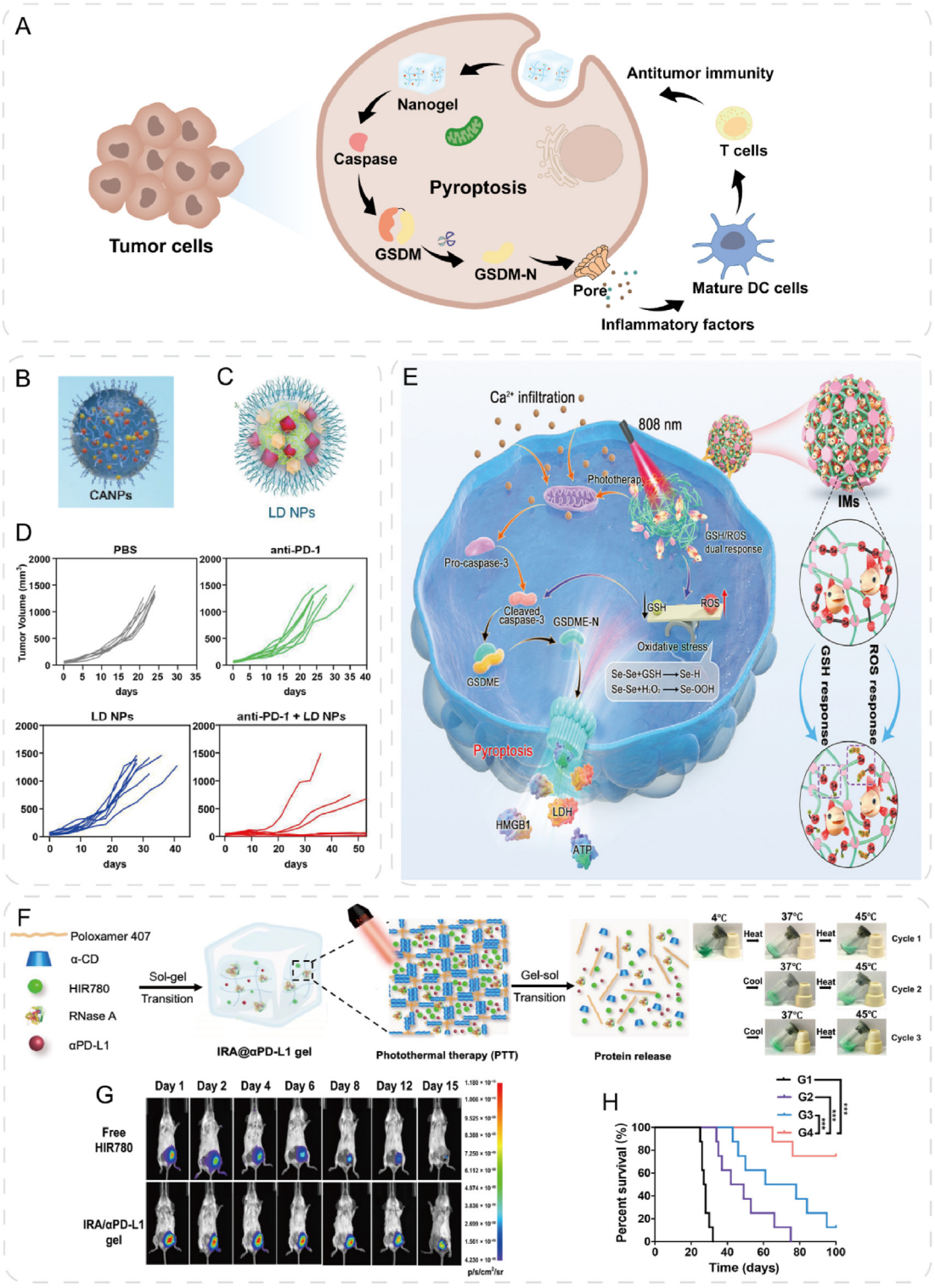

Figure 8 Schematic illustration of synthesis and characterization of nanogel-induced pyroptosis. (A) A brief mechanism diagram based on nanogels. (B) Schematic diagram of CANPs. Reprinted with the permission from Ref. 142. Copyright © 2021 Tsinghua University Press and Springer-Verlag GmbH Germany, part of Springer Nature. (C) Schematic diagram of LDNPs. (D) Tumor growth curve. Reprinted with the permission from Ref. 143. Copyright © 2022 Elsevier Ltd. (E) Schematic illustration of IMs. Reprinted with the permission from Ref. 147. Copyright © 2023 Elsevier B.V. (F) Conversion of sol and gel. Survival curve after therapy (G) and Fluorescence imaging of *in vivo* retention of the gel (H). Reprinted with the permission from Ref. 150. Copyright © 2022 The American Association for the Advancement of Science.

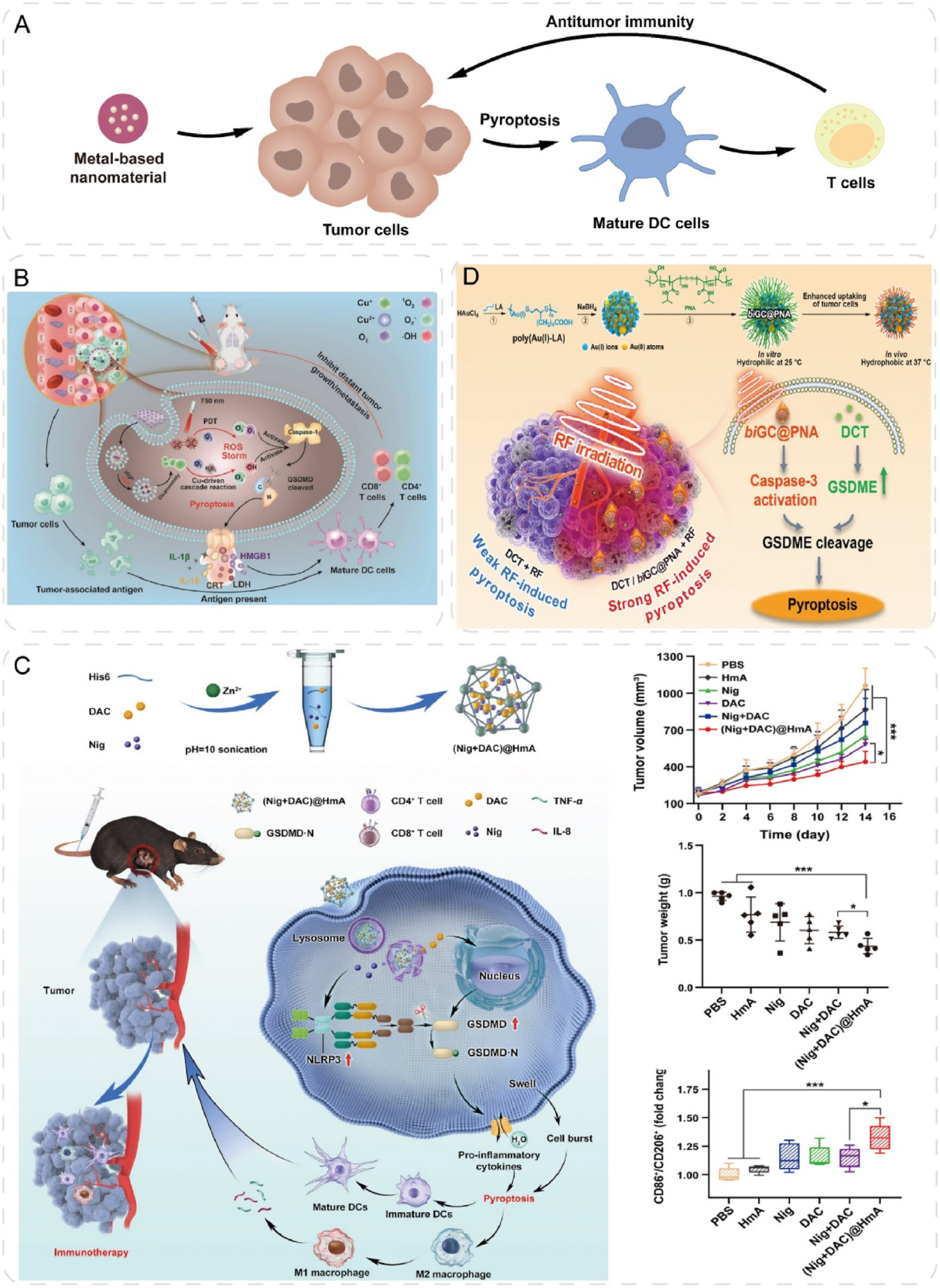

Figure 9 Induction of pyroptosis by metal nanomaterials. (A) A brief mechanism diagram based on metal nanomaterials. (B) Mechanistic map of pyroptosis induction by Cu-TBB in combination with PDT. Reprinted with the permission from Ref. 158. Copyright © 2023 Wiley-VCH GmbH. (C) Scheme of fabrication process and therapeutic mechanism of (Nig DAC)@HMA NPs. Reprinted with the permission from Ref. 160. Copyright © 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V. (D) Schematic representation of cell pyroptosis induction by biGC@PNA. Reprinted with the permission from Ref. 156. Copyright © 2023 American Chemical Society.

To achieve efficient tumor fluorescence localization and RT, Wu et al.[166] developed ^{177}Lu-YNP@FA nano-prodrug (NPD), which precisely targeted cervical cancer cells in the abdominal cavity of BALB/c nude mice under NIR-II lights, exhibiting excellent antitumor effects. Re(I)-g-C_3N_4 can deliver type II ICD inducers, overcoming TNBC's resistance to DOX and enhancing immune response[167]. MCSP activates both pyroptosis and the STING pathway *via* metal immunotherapy and H_2S gas therapy, significantly boosting antitumor immune responses in cervical cancer[168]. Chen et al.[169] first proposed the redox imbalance triggered by cysteine (Cys) depletion. PVPCuO nanoparticles can activate ferroptosis mediated by lipid peroxidation and also induce caspase-1/GSDMD-dependent pyroptosis, with synergistic effects that enhance antitumor therapeutic efficacy and achieve efficient targeting of pancreatic cancer with Cys. A novel nanoplatform (Mn-HSP) enables closed-loop circulating immunotherapy (Pyroptosis-CTLs-GZMB-Pyroptosis) to effectively inhibit primary, distant, and metastatic tumors *in vivo*[170]. Lu et al.[171] prepared dual-metal nanoparticles (FZOH), which simultaneously induced ferroptosis and pyroptosis, bridging the constraints of cancer immunotherapy, and significantly enhancing the antitumor immune response.

In summary, researchers have prepared various types of nanoparticles using metal-based nanomaterials, with copper-based, manganese-based, and iron-based applications being the most widespread. These nanomaterials are widely utilized not only in tumor treatment but also in diagnostics.

3.5. *Biomimetic nanomaterials*

Biomimetic nanomaterials, inspired by natural sources and biological materials, exhibit excellent biocompatibility, non-toxicity, and low immunogenicity[172-174]. At present, biomimetic nanomaterials mainly include bionic nanozymes, bionic microorganisms, and bionic biofilm drug delivery systems (Fig. 10A).

The initial focus is on the application of bionic microorganisms as pyroptosis inducers. Bionic microorganisms function as nanoparticles composed of oncolytic viruses. Su et al.[175] proposed a strategy combining activators of transcription 3 inhibitor nanoprodrugs (MPNP) with oncolytic viruses (Ovs), which demonstrated enhanced tumor penetration ability and significantly mediated GSDME pyroptosis, thereby reshaping the TME and transforming "cold" tumors into "hot" tumor. Listeria monocytogenes (Lmo) encapsulated by red blood cells can induce caspase-8 activation and upregulate the expression of GSDMD by NADPH oxidase-mediated ROS, triggering tumor cell pyroptosis, reversing immune suppression, and promoting a strong and sustained systemic antitumor immune response (Fig. 10B)[176]. DNF@LIPO, a virus-like particle, causes pyroptosis mediated by the AIM2 (absent in melanoma 2) inflammasome and cGAS-STING activation, offering a reliable and effective method for cancer immunotherapy[177].

The second area involves the application of bionic enzymes. By hybridizing nanozymes with GOx, it is possible to create nanoparticles that possess dual enzyme activity, effectively inhibiting tumor metastasis and recurrence while also regulating tumor glucose metabolism and immunotherapy[178]. LFO@GOx combines US and enzyme kinetics to produce ROS that induce specific pyroptosis, expected to regulate the pyroptosis-dominated therapeutic process[179]. Moreover, nanozymes in cancer cells initiate a self-accelerating cascade that consumes glucose and suppresses the production of HSPs, thereby intensifying thermotherapy in response to near-infrared light, activating pyroptosis and inducing a powerful immune response[180]. NiCoOx nanosheets serve as multi-enzyme simulated pyroptosis inducers, with their catalytic activity enhanced under acidic conditions and US, promoting cancer treatment[181]. Chen et al.[182] created Pt-NS/HCS, which showed selectively improved peroxidase (POD)-like activity. It significantly induced GSDMD and GSDME-mediated pyroptosis, with *in vivo* data further confirming the therapeutic effect of Pt-NS/HCS when combined with PD-L1 immunotherapy. DNA nanocomposites (DNFs@ZnMn) promote pyroptosis by utilizing dynamic cascades to impair autophagy and ameliorate tumor hypoxia[183]. LPZ possesses POD and superoxide dismutase (SOD)-like properties that produce significant quantities of ROS on cancer cell membranes and intracellularly, resulting in pyroptosis and powerful antitumor immunity[184].

Finally, the application of bionic biofilms in inducing pyroptosis is discussed. Biomimetic nanoparticles (BNP) are a nanodrug delivery system that uses cancer cell membranes to coat indocyanine green (ICG) and decitabine (DCT), inducing pyroptosis by caspase-3/GSDME and promoting systemic antitumor immunity[185]. In addition, Prussian blue nanoparticles (PB NPs) were loaded with Cinobufagin (CS-1) and then coated with a mixed membrane of erythrocyte, and triple-negative breast cancer (TNBC) cell membrane form CS-1@PB[HM] NPs[186]. Upon accumulation, laser irradiation of the tumor area rapidly induces GSDME-dependent tumor cell pyroptosis, promotes the release of tumor antigens and DAMPs, and ultimately induces DCs maturation and enhances T cell immune responses (Fig. 10C). Targeted and concentrated on tumor cells, the M-Cu-T initiates pyroptosis upon laser activation, further triggering immunogenic cell death and initiating antitumor immunity[187]. ZTC@M contains the chemotherapy drug tirapazamine (TPZ), which can be combined with SDT/US to enhance pyroptosis[188].

Although the above methods effectively induce pyroptosis, cancer cells exhibit higher autophagy activity than normal cells, resulting in reduced pyroptosis effect[189,190]. Zhang's group developed ZPHM coated with cancer cell membranes that induce pyroptosis and disrupt checkpoints[191]. Under light conditions, the nanoparticles release hexyl 5-aminolevulinate hydrochloride (HAL), which induces the photosensitizer protoporphyrin IX (PpIX) to produce ROS, activating the NLRP3 inflammasome and the caspase 1/GSDMD pathway. Additionally, nanoparticles can produce the autophagy inhibitor 3-methyladenine (3-MA) *in situ*, which can prevent the degradation of NLRP3, caspase 1, and IL-1β, thus enhancing the efficiency of pyroptosis (Fig. 10E). ROZM nanoparticles effectively counteract the drawbacks of small molecule chemotherapeutic drugs through receptor-mediated endocytosis, such as poor water solubility and non-targeting, producing significant *in vitro* and *in vivo* impacts on tumor control and immune response[192].

Ir-HecN is a metal photosensitizer and bacterial heterozygote, which is self-actuated and hypoxic, and targets tumor tissues to cause solid tumor regression under the combined application of PDT and immunotherapy[193]. Deng et al.[194] discovered a delivery strategy using Ca@GOx, consisting of calcium phosphate and glucose oxidase coated by erythrocyte and cancer cell membranes. This system induces mitochondria to produce a large amount of ROS and activate caspase-3/GSDME to cause pyroptosis. Chloroquine, loaded into the nanosystem, inhibits mitophagy and enhances pyroptosis, improving antitumor immune responses (Fig. 10D). In addition, Li et al.[195] proposed a strategy to load Ce6 and DOX into bacterial outer membrane vesicles (denoted as

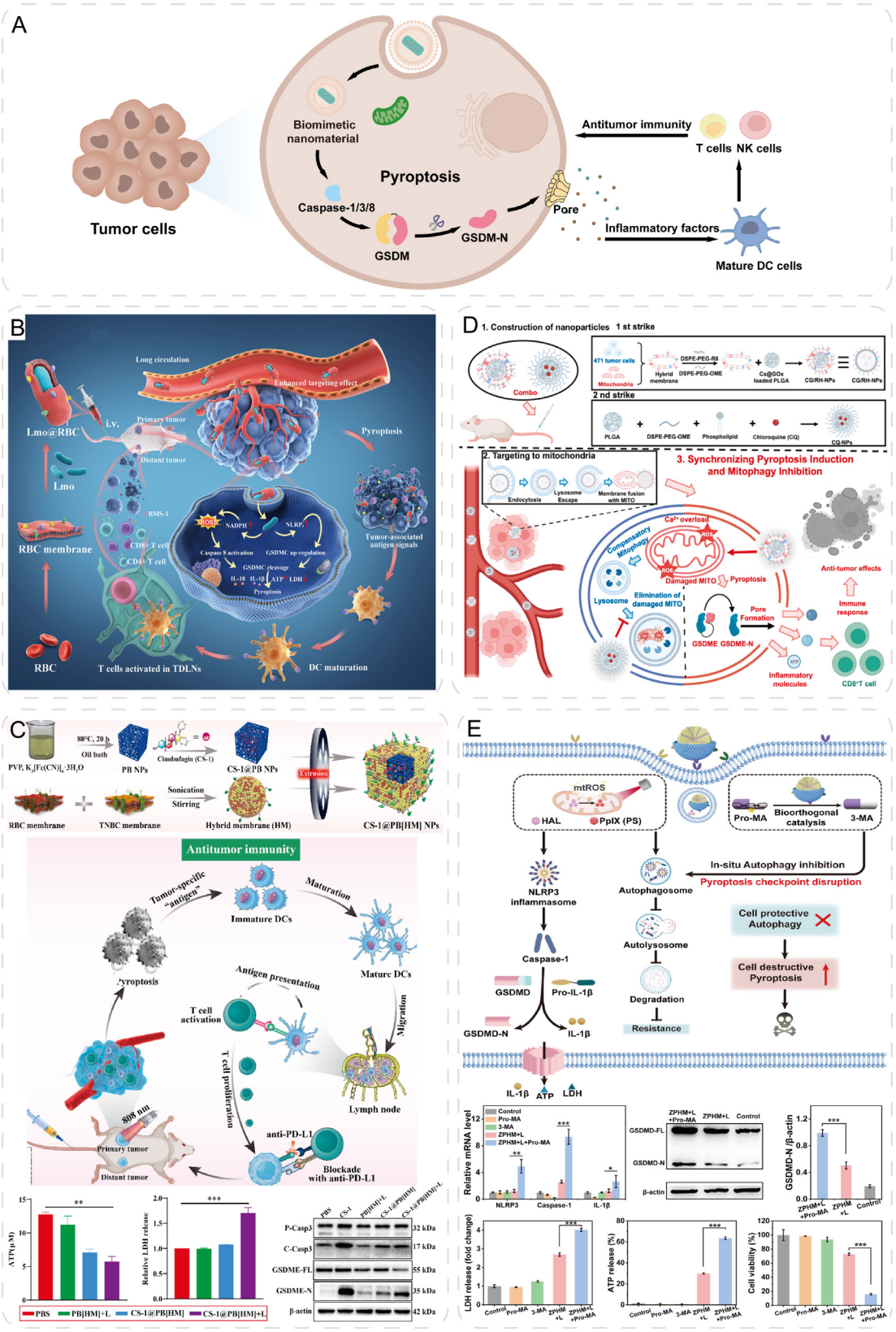

Figure 10 Schematic illustration of antitumor immunity activated by biomimetic nanomaterials. (A) A brief mechanism diagram based on biomimetic nanomaterials. (B) Illustration of the role of Lmo@RBC induces pyroptosis, immunogenic cell death, and immune responses. Reprinted with the permission from Ref. 176. Copyright © 2022 American Chemical Society. (C) Schematic diagram of CS-1@PB[HM] NPs induces pyroptosis and enhances antitumor immunotherapy. Reprinted with the permission from Ref. 186. Copyright © 2023 Elsevier Ltd. (D) The overview of pyroptosis induced by targeting the mitochondria combined with CG/RH-NPs+CQ-NPs to enhance antitumor immunotherapy. Reprinted with the permission from Ref. 194. Copyright © 2023 Elsevier Ltd. (E) Schematic of pyroptosis uses the laser to induce cancer cell death. Reprinted with the permission from Ref. 191. Copyright © 2023 American Chemical Society.

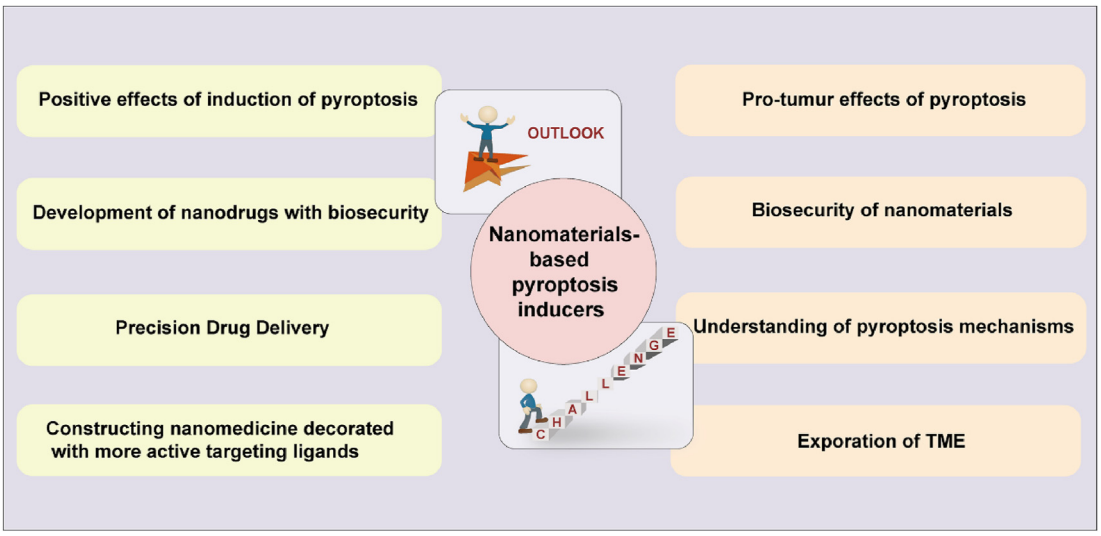

Figure 11 Outlook and challenges in nanomaterials for inducing pyroptosis in tumor therapy.

DOX/Ce6-OMVs@M), which, combined with PDT, CT, and immunotherapy, could eradicate TNBC in mice and prevent tumor metastasis. Furthermore, Zheng et al.[196] designed an M1 macrophage membrane (EMM) biomimetic nanoplatform (EMM@DJHAD) for treating breast cancer with bone metastases, showing excellent inhibitory effects on tumor development, metastasis, and analgesic activities. Among these, JTC801 stimulated caspase-3 to cleave GSDME and trigger tumor pyroptosis, whereas DAC enhanced the level of GSDME *via* demethylating the DFNA5 gene. Finally, exosomes, with minimal immunogenicity, can deliver drugs to tumor sites, such as C-PMet, loaded with ectoenzyme (CD39) inhibitor POM-1 (sodium polyoxotungstate) and AMP-activated protein kinase (AMPK) agonist metformin, stimulating macrophage pyroptosis and improving DC maturation to trigger antitumor immunity[197]. Another study team developed the MFG@TCM nanoplatform to combat the ITME in osteosarcoma (OS) *via* stimulating cGAS-STING pathway in conjunction with mild PTT[198].

This section elaborates on three types of biomimetic drug delivery systems that primarily activate the downstream GSDMD signaling pathway through caspase-1/3/8 to induce pyroptosis. Due to their high biocompatibility and the ability to mimic natural drug and release processes, they have attracted extensive attention from researchers.

3.6. *Carrier-free nanomaterials*

Carrier-free nanomaterials enable drug delivery directly to tumor sites without the need for additional carrier[199]. The nanodrug delivery system formed by the self-assembly of small molecule prodrugs acts as both carrier and cargo, significantly enhancing drug delivery efficiency[200]. Li et al.[201] developed a stable and controllable carrier-free nanoplatform (A-C/NPs) which was a co-assembly method of cytarabine (Ara-C) and Ce6, showing excellent suppressive effects on cancer and enhancing anticancer immune response by GSDME-mediated pyroptosis in a breast cancer mouse model.

Taken together, nanomaterial-induced pyroptosis represents a novel therapeutic method for tumors and an interdisciplinary field of study. Researchers have developed several novel nanodrug delivery systems that target tumor cells and adapt to the TME, such as pH and ROS responsiveness. These adaptations help improve therapeutic effects and minimize damage to normal cells. Furthermore, nanomaterials can trigger pyroptosis and synergize with PDT, CT, and RT to enhance the immune system's response to tumor cells, thereby improving the overall efficacy of immunotherapy. Recently, various nanomaterials have demonstrated promising therapeutic effects in animal models, providing a solid foundation for their potential clinical application. Despite the progress made in developing nanomaterials that induce pyroptosis through antitumor immunotherapy, there are still some challenges, such as the development of new nanomaterials, the potential toxicity of nanomaterials, and the efficiency of inducing pyroptosis.

4. Conclusions and outlooks

In recent years, pyroptosis has garnered widespread attention as a promising approach for treating cancer, rapidly becoming a hot research area. When cells undergo pyroptosis, they release pro-inflammatory factors that enhance the immune response, thereby improving the efficacy of cancer immunotherapy. Nanomaterials are also favored by researchers in the field of drug delivery due to their unique physical and chemical properties, emerging as a promising avenue in cancer therapy, particularly for their ability to induce pyroptosis, which can reduce side effects and improve immunotherapeutic outcomes. In summary, with the advancement of nanomaterials and cancer immunotherapy, as well as our further understanding of the pyroptosis mechanism, a variety of nanodrug delivery systems have been developed for cancer treatment, offering potential therapeutic solutions. This article aims to provide an overview of the three main mechanisms of action related to pyroptosis, as well as the latest progress in employing nanomaterials to coordinate pyroptosis in treating various tumors. In addition, this article focuses on the recent advancements in tumor therapy and nanomaterials in enhancing cancer immunotherapy through the induction of pyroptosis.

The combined use of delivery systems and pyroptosis is a breakthrough in cancer treatment, but clinical applications remain

limited. Therefore, future research should focus on addressing the following challenging questions and exploring other possibilities (Fig. 11):

First, the antitumor immune response induced by pyroptosis requires precise modulation. With further research, the tumor-promoting effect of pyroptosis has also been revealed. Therefore, controlling the induction of pyroptosis requires a nuanced approach to stimulate its positive effects on tumor diseases while minimizing the potential for tumor promotion. In addressing this issue, diagnostic tools are crucial as they can effectively mitigate the pro-tumor effects of pyroptosis. After pyroptosis occurs, specific biomarkers are released, such as members of the GSDM protein family, pro-inflammatory factors, and caspase proteases[202]. Diagnostic probes targeting these biomarkers can be developed to detect cellular pyroptosis and enable real-time monitoring. For example, dual-locking and tandem activatable probes can perform non-invasive real-time detection of cancer chemo-immunotherapy based on near-infrared signals[203]. Multicolor fluorescent nanoprobes (Cas-NP) can detect the activation sequence of caspase-1/3/4, providing new support for the detection of multiple pathways[204].

Second, the biosafety of drug delivery systems based on nanomaterials has not been fully confirmed. Although preliminary data indicates that some drug delivery systems possess excellent biological safety, their long-term toxicity and biological effects have not been fully proven. For example, nanoparticles composed of metal nanomaterials act on cancer cells, but retained metal ions may also induce pyroptosis in normal cells, posing potential risks. In addition, certain nanomaterials are complex to synthesize, which can result in residues of organic solvents, thereby causing biosafety concerns and increasing the difficulty of scaling up production on an industrial scale for clinical applications. Thus, nanomaterials that are biodegradable, easy to synthesize, and require low doses are of great significance for translating pyroptosis-mediated antitumor immune responses into clinical applications.

Third, the mechanism that triggers cell pyroptosis is incomplete. When combined with nanomaterials for cancer treatment, the complexity of the TME *in vivo* may alter pyroptosis processes and mechanisms. In addition, the relevant mechanisms of pyroptosis treatment based on nanomedicines remain largely unexplored, hindering further optimization of pyroptosis efficiency. Therefore, it is important to develop strategies that combine nanodrug delivery systems with diagnostic tools that can assess treatment response in real-time, allowing oncologists to dynamically adjust treatments and significantly improve patient outcomes.

Fourth, racial differences affect treatment efficacy. Human and rodent tumors differ in complexity, human tumors are smarter, and each tumor may have a different TME, thus significantly reducing the efficiency of nanomaterial-based drug delivery. It is necessary to construct nanomedicines decorated with more active targeting ligands to improve this situation in the future.

The use of nanomaterials to regulate pyroptosis is an increasingly focused topic in the field of cancer treatment. With researchers delving deeper into the connection between pyroptosis and cancer, there's a growing anticipation for the clinical application of nanomaterials that regulate this process. In conclusion, the development of innovative nanomaterials that focus on modulation of pyroptosis presents a promising avenue for the treatment of different types of cancer. Consequently, we expect that in the coming years, highly effective nanoparticles will show great capacity in cancer treatments that rely on the regulation of pyroptosis.

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Author contributions

Zhenhua Li: Writing − review & editing, Writing − original draft. Ziyue Xi: Supervision. Chuanyong Fan: Visualization. Xinran Xi: Visualization. Yao Zhou: Visualization. Ming Zhao: Writing − review & editing, Supervision, Conceptualization. Lu Xu: Supervision, Investigation, Conceptualization.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Xie YQ, Wei L, Tang L. Immunoengineering with biomaterials for enhanced cancer immunotherapy. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2018;**10**:e1506.
2. Szeto GL, Finley SD. Integrative approaches to cancer immunotherapy. *Trends Cancer* 2019;**5**:400−10.
3. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol* 2020;**17**:807−21.
4. Liu X, Hogg GD, DeNardo DG. Rethinking immune checkpoint blockade: 'beyond the T cell'. *J Immunother Cancer* 2021;**9**:e001460.
5. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. *Nat Rev Drug Discov* 2019;**18**:175−96.
6. Kennedy LB, Salama AK. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* 2020;**70**:86−104.
7. Rosenbaum SR, Wilski NA, Aplin AE. Fueling the fire: inflammatory forms of cell death and implications for cancer immunotherapy. *Cancer Discov* 2021;**11**:266−81.
8. Duan Q, Zhang H, Zheng J, Zhang L. Turning cold into hot: firing up the tumor microenvironment. *Trends Cancer* 2020;**6**:605−18.
9. D'Souza CA, Heitman J. Dismantling the cryptococcus coat. *Trends Microbiol* 2001;**9**:112−3.
10. Ding J, Wang K, Liu W, She Y, Sun Q, Shi J, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature* 2016;**535**:111−6.
11. Evavold CL, Hafner-Bratkovič I, Devant P, D'Andrea JM, Ngwa EM, Boršić E, et al. Control of gasdermin D oligomerization and pyroptosis by the Ragulator-Rag-mTORC1 pathway. *Cell* 2021;**184**:4495−511.e19.
12. Mulvihill E, Sborgi L, Mari SA, Pfreundschuh M, Hiller S, Müller DJ. Mechanism of membrane pore formation by human gasdermin-D. *Embo J* 2018;**37**:e98321.
13. Broz P, Pelegrín P, Shao F. The gasdermins, a protein family executing cell death and inflammation. *Nat Rev Immunol* 2020;**20**:143−57.
14. Cookson BT, Brennan MA. Pro-inflammatory programmed cell death. *Trends Microbiol* 2001;**9**:113−4.
15. Chen B, Yan Y, Yang Y, Cao G, Wang X, Wang Y, et al. A pyroptosis nanotuner for cancer therapy. *Nat Nanotechnol* 2022;**17**:788−98.
16. Liu X, Xia S, Zhang Z, Wu H, Lieberman J. Channelling inflammation: gasdermins in physiology and disease. *Nat Rev Drug Discov* 2021;**20**:384−405.
17. Zhang Y, Chen X, Gueydan C, Han J. Plasma membrane changes during programmed cell deaths. *Cell Res* 2018;**28**:9−21.

18. Karmakar M, Minns M, Greenberg EN, Diaz-Aponte J, Pestonjamasp K, Johnson JL, et al. N-GSDMD trafficking to neutrophil organelles facilitates IL-1β release independently of plasma membrane pores and pyroptosis. *Nat Commun* 2020;**11**:2212.
19. Medina CB, Mehrotra P, Arandjelovic S, Perry JSA, Guo Y, Morioka S, et al. Metabolites released from apoptotic cells act as tissue messengers. *Nature* 2020;**580**:130−5.
20. Lei G, Zhuang L, Gan B. Targeting ferroptosis as a vulnerability in cancer. *Nat Rev Cancer* 2022;**22**:381−96.
21. Dikic I, Elazar Z. Mechanism and medical implications of mammalian autophagy. *Nat Rev Mol Cell Biol* 2018;**19**:349−64.
22. Tan Y, Chen Q, Li X, Zeng Z, Xiong W, Li G, et al. Pyroptosis: a new paradigm of cell death for fighting against cancer. *J Exp Clin Cancer Res* 2021;**40**:153.
23. Hsu SK, Li CY, Lin IL, Syue WJ, Chen YF, Cheng KC, et al. Inflammation-related pyroptosis, a novel programmed cell death pathway, and its crosstalk with immune therapy in cancer treatment. *Theranostics* 2021;**11**:8813−35.
24. Wang X, Hua P, He C, Chen M. Non-apoptotic cell death-based cancer therapy: molecular mechanism, pharmacological modulators, and nanomedicine. *Acta Pharm Sin B* 2022;**12**:3567−93.
25. Zhou B, Zhang JY, Liu XS, Chen HZ, Ai YL, Cheng K, et al. Tom20 senses iron-activated ROS signaling to promote melanoma cell pyroptosis. *Cell Res* 2018;**28**:1171−85.
26. Yu P, Wang HY, Tian M, Li AX, Chen XS, Wang XL, et al. Eukaryotic elongation factor-2 kinase regulates the cross-talk between autophagy and pyroptosis in doxorubicin-treated human melanoma cells *in vitro*. *Acta Pharmacol Sin* 2019;**40**:1237−44.
27. Wang L, Li K, Lin X, Yao Z, Wang S, Xiong X, et al. Metformin induces human esophageal carcinoma cell pyroptosis by targeting the miR-497/PELP1 axis. *Cancer Lett* 2019;**450**:22−31.
28. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. *Nat Rev Microbiol* 2009;**7**:99−109.
29. Wang YY, Liu XL, Zhao R. Induction of pyroptosis and its implications in cancer management. *Front Oncol* 2019;**9**:971.
30. Lamkanfi M, Dixit VM. Inflammasomes and their roles in health and disease. *Annu Rev Cell Dev Biol* 2012;**28**:137−61.
31. Zheng Z, Li G. Mechanisms and therapeutic regulation of pyroptosis in inflammatory diseases and cancer. *Int J Mol Sci* 2020;**21**:1456.
32. Xia X, Wang X, Cheng Z, Qin W, Lei L, Jiang J, et al. The role of pyroptosis in cancer: pro-cancer or pro-"host". *Cell Death Dis* 2019;**10**:650.
33. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer* 2008;**8**:473−80.
34. Ali ES, Sharker SM, Islam MT, Khan IN, Shaw S, Rahman MA, et al. Targeting cancer cells with nanotherapeutics and nanodiagnostics: current status and future perspectives. *Semin Cancer Biol* 2021;**69**:52−68.
35. Wang L, Li LL, Fan YS, Wang H. Host-guest supramolecular nanosystems for cancer diagnostics and therapeutics. *Adv Mater* 2013;**25**:3888−98.
36. Shen Z, Wu H, Yang S, Ma X, Li Z, Tan M, et al. A novel trojan-horse targeting strategy to reduce the non-specific uptake of nanocarriers by non-cancerous cells. *Biomaterials* 2015;**70**:1−11.
37. Bazak R, Houri M, Achy SE, Hussein W, Refaat T. Passive targeting of nanoparticles to cancer: a comprehensive review of the literature. *Mol Clin Oncol* 2014;**2**:904−8.
38. Wu D, Wang S, Yu G, Chen X. Cell death mediated by the pyroptosis pathway with the aid of nanotechnology: prospects for cancer therapy. *Angew Chem Int Ed Engl* 2021;**60**:8018−34.
39. Zhang Y, Fang C, Zhang W, Zhang K. Emerging pyroptosis-engineered nanobiotechnologies regulate cancers and inflammatory diseases: a double-edged sword. *Matter* 2022;**5**:3740−74.
40. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol* 2007;**19**:209−16.
41. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. *Nat Rev Immunol* 2004;**4**:641−8.
42. Aachoui Y, Sagulenko V, Miao EA, Stacey KJ. Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection. *Curr Opin Microbiol* 2013;**16**:319−26.
43. Schneider KS, Groß CJ, Dreier RF, Saller BS, Mishra R, Gorka O, et al. The inflammasome drives GSDMD-independent secondary pyroptosis and IL-1 release in the absence of caspase-1 protease activity. *Cell Rep* 2017;**21**:3846−59.
44. Tan G, Huang C, Chen J, Zhi F. HMGB1 released from GSDME-mediated pyroptotic epithelial cells participates in the tumorigenesis of colitis-associated colorectal cancer through the ERK1/2 pathway. *J Hematol Oncol* 2020;**13**:149.
45. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev* 2018;**281**:8−27.
46. Zhivaki D, Borriello F, Chow OA, Doran B, Fleming I, Theisen DJ, et al. Inflammasomes within hyperactive murine dendritic cells stimulate long-lived T cell-mediated anti-tumor immunity. *Cell Rep* 2020;**33**:108381.
47. Poznanski SM, Lee AJ, Nham T, Lusty E, Larché MJ, Lee DA, et al. Combined stimulation with interleukin-18 and interleukin-12 potently induces interleukin-8 production by natural killer cells. *J Innate Immun* 2017;**9**:511−25.
48. Song M, Xia W, Tao Z, Zhu B, Zhang W, Liu C, et al. Self-assembled polymeric nanocarrier-mediated co-delivery of metformin and doxorubicin for melanoma therapy. *Drug Deliv* 2021;**28**:594−606.
49. Erkes DA, Cai W, Sanchez IM, Purwin TJ, Rogers C, Field CO, et al. Mutant BRAF and MEK inhibitors regulate the tumor immune microenvironment *via* pyroptosis. *Cancer Discov* 2020;**10**:254−69.
50. Klune JR, Dhupar R, Cardinal J, Billiar TR, Tsung A. HMGB1: endogenous danger signaling. *Mol Med* 2008;**14**:476−84.
51. Faria SS, Fernando AJ, de Lima VCC, Rossi AG, de Carvalho JMA, Magalhães KG. Induction of pyroptotic cell death as a potential tool for cancer treatment. *J Inflamm* 2022;**19**:19.
52. Tu S, Bhagat G, Cui G, Takaishi S, Kurt-Jones EA, Rickman B, et al. Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell* 2008;**14**:408−19.
53. Hou J, Hsu JM, Hung MC. Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity. *Mol Cell* 2021;**81**:4579−90.
54. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. *Signal Transduct Target Ther* 2021;**6**:128.
55. Sharma BR, Kanneganti T-D. NLRP3 inflammasome in cancer and metabolic diseases. *Nat Immunol* 2021;**22**:550−9.
56. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature* 2015;**526**:666−71.
57. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* 2015;**526**:660−5.
58. Zhang Z, Zhang Y, Xia S, Kong Q, Li S, Liu X, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature* 2020;**579**:415−20.
59. Wang Y, Gao W, Shi X, Ding J, Liu W, He H, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature* 2017;**547**:99−103.
60. Kesavardhana S, Malireddi RS, Kanneganti TD. Caspases in cell death, inflammation, and pyroptosis. *Annu Rev Immunol* 2020;**38**:567−95.
61. Wang L, Qin X, Liang J, Ge P. Induction of pyroptosis: a promising strategy for cancer treatment. *Front Oncol* 2021;**11**:635774.
62. Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature* 2012;**481**:278−86.
63. Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. *Cell Mol Immunol* 2021;**18**:2114−27.
64. Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature* 2014;**514**:187−92.

65. Kayagaki N, Wong MT, Stowe IB, Ramani SR, Gonzalez LC, Akashi-Takamura S, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science* 2013;**341**:1246−9.
66. Matikainen S, Nyman TA, Cypryk W. Function and regulation of noncanonical caspase-4/5/11 inflammasome. *J Immunol* 2020;**204**:3063−9.
67. Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death Dis* 2019;**10**:128.
68. Chen L, Ma X, Liu W, Hu Q, Yang H. Targeting pyroptosis through lipopolysaccharide-triggered noncanonical pathway for safe and efficient cancer immunotherapy. *Nano Lett* 2023;**23**:8725−33.
69. Orning P, Lien E, Fitzgerald KA, Orning P, Lien E, Fitzgerald KA. Gasdermins and their role in immunity and inflammation. *J Exp Med* 2019;**216**:2453−65.
70. Wang S, Wu ZZ, Zhu SW, Wan SC, Zhang MJ, Zhang BX, et al. CTLA-4 blockade induces tumor pyroptosis *via* $CD8^+$ T cells in head and neck squamous cell carcinoma. *Mol Ther* 2023;**31**:2154−68.
71. Orzalli MH, Prochera A, Payne L, Smith A, Garlick JA, Kagan JC. Virus-mediated inactivation of anti-apoptotic Bcl-2 family members promotes Gasdermin-E-dependent pyroptosis in barrier epithelial cells. *Immunity* 2021;**54**:1447−62.e5.
72. Wang W, Zhang L, Sun Z. Eliciting pyroptosis to fuel cancer immunotherapy: mechanisms and strategies. *Cancer Biol Med* 2022;**19**:948−64.
73. Rao Z, Zhu Y, Yang P, Chen Z, Xia Y, Qiao C, et al. Pyroptosis in inflammatory diseases and cancer. *Theranostics* 2022;**12**:4310−29.
74. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science* 2020;**368**:eaaz7548.
75. Zhang JY, Zhou B, Sun RY, Ai YL, Cheng K, Li FN, et al. The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. *Cell Res* 2021;**31**:980−97.
76. Zhang MJ, Wang YY, Han LL, Liu XY, Xie YY, Xu Z, et al. Biomaterials elicit pyroptosis enhancing cancer immunotherapy. *Adv Funct Mater* 2024;**34**:2311362.
77. Hou J, Zhao R, Xia W, Chang C-W, You Y, Hsu J-M, et al. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. *Nat Cell Biol* 2020;**22**:1264−75.
78. Photos PJ, Bacakova L, Discher B, Bates FS, Discher DE. Polymer vesicles *in vivo*: correlations with PEG molecular weight. *J Control Release* 2003;**90**:323−34.
79. Li D, Zhang X, Chen X, Li W. Research progress and prospects for polymeric nanovesicles in anticancer drug delivery. *Front Bioeng Biotechnol* 2022;**10**:850366.
80. Antimisiaris SG, Marazioti A, Kannavou M, Natsaridis E, Gkartziou F, Kogkos G, et al. Overcoming barriers by local drug delivery with liposomes. *Adv Drug Deliv Rev* 2021;**174**:53−86.
81. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics* 2017;**9**:12.
82. Li F, Zhang XQ, Ho W, Tang M, Li Z, Bu L, et al. mRNA lipid nanoparticle-mediated pyroptosis sensitizes immunologically cold tumors to checkpoint immunotherapy. *Nat Commun* 2023;**14**:4223.
83. Fan JX, Deng RH, Wang H, Liu XH, Wang XN, Qin R, et al. Epigenetics-based tumor cells pyroptosis for enhancing the immunological effect of chemotherapeutic nanocarriers. *Nano Lett* 2019;**19**:8049−58.
84. Long Y, Wang Z, Fan J, Yuan L, Tong C, Zhao Y, et al. A hybrid membrane coating nanodrug system against gastric cancer *via* the VEGFR2/STAT3 signaling pathway. *J Mater Chem B* 2021;**9**:3838−55.
85. Zhong H, Chen G, Li T, Huang J, Lin M, Li B, et al. Nanodrug augmenting antitumor immunity for enhanced TNBC therapy *via* pyroptosis and cGAS-STING activation. *Nano Lett* 2023;**23**:5083−91.
86. Yao J, Feng X, Dai X, Peng G, Guo Z, Liu Z, et al. TMZ magnetic temperature-sensitive liposomes-mediated magnetothermal chemotherapy induces pyroptosis in glioblastoma. *Nanomedicine* 2022;**43**:102554.
87. Chen P, Zhang C, He L, Li M, Rong J, Sun P, et al. A thermoresponsive nanocomposite integrates NIR-II-absorbing small molecule with lonidamine for pyroptosis-promoted synergistic immunotherapy. *J Nanobiotechnology* 2024;**22**:163.
88. Xiao H, Li X, Liang S, Yang S, Han S, Huang J, et al. Dual-responsive nanomedicine activates programmed antitumor immunity through targeting lymphatic system. *ACS Nano* 2024;**18**:11070−83.
89. Hu W, Ye B, Yu G, Yang H, Wu H, Ding Y, et al. Dual-responsive supramolecular polymeric nanomedicine for self-cascade amplified cancer immunotherapy. *Adv Sci* 2024:e2305382.
90. Zhou J, Ji J, Li X, Zhang Y, Gu L, Zheng X, et al. Homomultivalent polymeric nanotraps disturb lipid metabolism homeostasis and tune pyroptosis in cancer. *Adv Mater* 2024;**36**:e2312528.
91. Shi Z, Bai H, Wu J, Miao X, Gao J, Xu X, et al. Acceptor engineering produces ultrafast nonradiative decay in NIR-II AZA-BODIPY nanoparticles for efficient osteosarcoma photothermal therapy via concurrent apoptosis and pyroptosis. *Research (Wash D C)* 2023;**6**:0169.
92. Zou Y, Huang B, Cao L, Deng Y, Su J. Tailored mesoporous inorganic biomaterials: assembly, functionalization, and drug delivery engineering. *Adv Mater* 2021;**33**:e2005215.
93. Vallet-Regí M, Balas F, Arcos D. Mesoporous materials for drug delivery. *Angew Chem Int Ed Engl* 2007;**46**:7548−58.
94. Hang Y, Liu Y, Teng Z, Cao X, Zhu H. Mesoporous nanodrug delivery system: a powerful tool for a new paradigm of remodeling of the tumor microenvironment. *J Nanobiotechnology* 2023;**21**:101.
95. Daliran S, Oveisi AR, Peng Y, López-Magano A, Khajeh M, Mas-Ballesté R, et al. Metal-organic framework (MOF)-, covalent-organic framework (COF)-, and porous-organic polymers (POP)-catalyzed selective C−H bond activation and functionalization reactions. *Chem Soc Rev* 2022;**51**:7810−82.
96. Wu MX, Yang YW. Metal-organic framework (MOF)-based drug/cargo delivery and cancer therapy. *Adv Mater* 2017;**29**:1606134.
97. Jin N, Wang B, Liu X, Yin C, Li X, Wang Z, et al. Mannose-doped metal-organic frameworks induce tumor cell pyroptosis *via* the PERK pathway. *J Nanobiotechnology* 2023;**21**:426.
98. Zhen W, Luo T, Wang Z, Jiang X, Yuan E, Weichselbaum RR, et al. Mechanoregulatory cholesterol oxidase-functionalized nanoscale metal-organic framework stimulates pyroptosis and reinvigorates T Cells. *Small* 2023;**19**:e2305440.
99. Wang S, Guo Q, Xu R, Lin P, Deng G, Xia X. Combination of ferroptosis and pyroptosis dual induction by triptolide nano-MOFs for immunotherapy of Melanoma. *J Nanobiotechnology* 2023;**21**:383.
100. Xu R, Yang J, Qian Y, Deng H, Wang Z, Ma S, et al. Ferroptosis/pyroptosis dual-inductive combinational anti-cancer therapy achieved by transferrin decorated nanoMOF. *Nanoscale Horiz* 2021;**6**:348−56.
101. Ploetz E, Zimpel A, Cauda V, Bauer D, Lamb DC, Haisch C, et al. Metal-organic framework nanoparticles induce pyroptosis in cells controlled by the extracellular pH. *Adv Mater* 2020;**32**:e1907267.
102. Deng H, Zhang J, Yang Y, Yang J, Wei Y, Ma S, et al. Chemodynamic and photothermal combination therapy based on dual-modified metal-organic framework for inducing tumor ferroptosis/pyroptosis. *ACS Appl Mater Inter* 2022;**14**:24089−101.
103. Shao L, Gao X, Liu J, Zheng Q, Li Y, Yu P, et al. Biodegradable metal-organic-frameworks-mediated protein delivery enables intracellular cascade biocatalysis and pyroptosis *in vivo*. *ACS Appl Mater Inter* 2022;**14**:47472−81.
104. Feng Z, Chen G, Zhong M, Lin L, Mai Z, Tang Y, et al. An acid-responsive MOF nanomedicine for augmented anti-tumor immunotherapy *via* a metal ion interference-mediated pyroptotic pathway. *Biomaterials* 2023;**302**:122333.
105. Liu Y, Niu R, Zhang X, Zhang B, Chen X, Guo J, et al. Metal-organic framework-based nanovaccine for relieving immunosuppressive tumors *via* hindering efferocytosis of macrophages and promoting

pyroptosis and cuproptosis of cancer cells. *ACS Nano* 2024;**18**:12386−400.
106. Kim M, Xin R, Earnshaw J, Tang J, Hill JP, Ashok A, et al. MOF-derived nanoporous carbons with diverse tunable nanoarchitectures. *Nat Protoc* 2022;**17**:2990−3027.
107. Xie H, Liu X, Huang Z, Xu L, Bai R, He F, et al. Nanoscale zeolitic imidazolate framework (ZIF)-8 in cancer theranostics: current challenges and prospects. *Cancers (Basel)* 2022;**14**:3935.
108. An J, Hu YG, Li C, Hou XL, Cheng K, Zhang B, et al. A pH/ultrasound dual-response biomimetic nanoplatform for nitric oxide gas-sonodynamic combined therapy and repeated ultrasound for relieving hypoxia. *Biomaterials* 2020;**230**:119636.
109. Cai W, Wang J, Chu C, Chen W, Wu C, Liu G. Metal-organic framework-based stimuli-responsive systems for drug delivery. *Adv Sci* 2019;**6**:1801526.
110. Zhu W, Xu J, Yao X, Mai S, Shu D, Yang W. Metal-organic-framework-based pyroptosis nanotuner with long blood circulation for augmented chemotherapy. *Biomater Sci* 2023;**11**:5918−30.
111. Fang X, Chen Z, Zhou W, Li T, Wang M, Gao Y, et al. Boosting glioblastoma therapy with targeted pyroptosis induction. *Small* 2023;**19**:e2207604.
112. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;**3**:991−8.
113. Zhou S, Shang Q, Ji J, Luan Y. A nanoplatform to amplify apoptosis-to-pyroptosis immunotherapy *via* immunomodulation of myeloid-derived suppressor cells. *ACS Appl Mater Inter* 2021;**13**:47407−17.
114. Ding B, Chen H, Tan J, Meng Q, Zheng P, Ma P, et al. ZIF-8 nanoparticles evoke pyroptosis for high-efficiency cancer immunotherapy. *Angew Chem Int Ed Engl* 2023;**62**:e202215307.
115. Xing G, Yu X, Zhang Y, Sheng S, Jin L, Zhu D, et al. Macrophages-based biohybrid microrobots for breast cancer photothermal immunotherapy by inducing pyroptosis. *Small* 2024;**20**:e2305526.
116. Liang S, Li MH, Qi M, Wang L, Yang YW. Nanoplatforms based on covalent organic frameworks (COFs) for biomedical applications. *Chem Mater* 2023;**35**:8353−70.
117. Rodríguez-San-Miguel D, Montoro C, Zamora F. Covalent organic framework nanosheets: preparation, properties and applications. *Chem Soc Rev* 2020;**49**:2291−302.
118. Mi Z, Yang P, Wang R, Unruangsri J, Yang W, Wang C, et al. Stable radical cation-containing covalent organic frameworks exhibiting remarkable structure-enhanced photothermal conversion. *J Am Chem Soc* 2019;**141**:14433−42.
119. Zhang L, Wang S, Zhou Y, Wang C, Zhang XZ, Deng H. Covalent organic frameworks as favorable constructs for photodynamic therapy. *Angew Chem Int Ed Engl* 2019;**58**:14213−8.
120. Shi Y, Yang J, Gao F, Zhang Q. Covalent organic frameworks: recent progress in biomedical applications. *ACS Nano* 2023;**17**:1879−905.
121. Zhang L, Yang QC, Wang S, Xiao Y, Wan SC, Deng H, et al. Engineering multienzyme-mimicking covalent organic frameworks as pyroptosis inducers for boosting antitumor immunity. *Adv Mater* 2022;**34**:e2108174.
122. Zhang Z, Kang M, Tan H, Song N, Li M, Xiao P, et al. The fast-growing field of photo-driven theranostics based on aggregation-induced emission. *Chem Soc Rev* 2022;**51**:1983−2030.
123. Ascherl L, Sick T, Margraf JT, Lapidus SH, Calik M, Hettstedt C, et al. Molecular docking sites designed for the generation of highly crystalline covalent organic frameworks. *Nat Chem* 2016;**8**:310−6.
124. Tu Y, Zhao Z, Lam JW, Tang BZ. Aggregate science: much to explore in the meso world. *Matter* 2021;**4**:338−49.
125. Zhang L, Song A, Yang QC, Li SJ, Wang S, Wan SC, et al. Integration of AIEgens into covalent organic frameworks for pyroptosis and ferroptosis primed cancer immunotherapy. *Nat Commun* 2023;**14**:5355.
126. Zhang L, Wan SC, Zhang J, Zhang MJ, Yang QC, Zhang B, et al. Activation of pyroptosis using AIEgen-based sp^2 carbon-linked covalent organic frameworks. *J Am Chem Soc* 2023;**145**:17689−99.
127. Liu D, Liang M, Tao Y, Liu H, Liu Q, Bing W, et al. Hypoxia-accelerating pyroptosis nanoinducers for promoting image-guided cancer immunotherapy. *Biomaterials* 2024;**309**:122610.
128. Barkat A, Beg S, Panda SK, Alharbi KS, Rahman M, Ahmed FJ. Functionalized mesoporous silica nanoparticles in anticancer therapeutics. *Semin Cancer Biol* 2021;**69**:365−75.
129. Nguyen TL, Cha BG, Choi Y, Im J, Kim J. Injectable dual-scale mesoporous silica cancer vaccine enabling efficient delivery of antigen/adjuvant-loaded nanoparticles to dendritic cells recruited in local macroporous scaffold. *Biomaterials* 2020;**239**:119859.
130. Feng Y, Liao Z, Li M, Zhang H, Li T, Qin X, et al. Mesoporous silica nanoparticles-based nanoplatforms: basic construction, current state, and emerging applications in anticancer therapeutics. *Adv Healthc Mater* 2023;**12**:e2201884.
131. Chen M, Liao H, Bu Z, Wang D, Fang C, Liang X, et al. Pyroptosis activation by photodynamic-boosted nanocatalytic medicine favors malignancy recession. *Chem Eng J* 2022;**441**:136030.
132. Li Y, Lin J, Wang P, Zhu F, Wu M, Luo Q, et al. Tumor microenvironment-responsive yolk-shell NaCl@virus-inspired tetrasulfide-organosilica for ion-interference therapy *via* osmolarity surge and oxidative stress amplification. *ACS Nano* 2022;**16**:7380−97.
133. Tang J, Yang Y, Qu J, Ban W, Song H, Gu Z, et al. Mesoporous sodium four-coordinate aluminosilicate nanoparticles modulate dendritic cell pyroptosis and activate innate and adaptive immunity. *Chem Sci* 2022;**13**:8507−17.
134. Nadeem S, Yang C, Du Y, Li F, Chen Z, Zhou Y, et al. A virus-spike tumor-activatable pyroptotic agent. *Small* 2021;**17**:e2006599.
135. Du Q, Luo Y, Xu L, Du C, Zhang W, Xu J, et al. Smart responsive Fe/Mn nanovaccine triggers liver cancer immunotherapy *via* pyroptosis and pyroptosis-boosted cGAS-STING activation. *J Nanobiotechnology* 2024;**22**:95.
136. Wang H, Gao L, Fan T, Zhang C, Zhang B, Al-Hartomy OA, et al. Strategic design of intelligent-responsive nanogel carriers for cancer therapy. *ACS Appl Mater Inter* 2021;**13**:54621−47.
137. Ma X, Li SJ, Liu Y, Zhang T, Xue P, Kang Y, et al. Bioengineered nanogels for cancer immunotherapy. *Chem Soc Rev* 2022;**51**:5136−74.
138. Huang G, Shen H, Xu K, Shen Y, Jiale J, Chu G, et al. Single-cell microgel encapsulation improves the therapeutic efficacy of mesenchymal stem cells in treating intervertebral disc degeneration *via* inhibiting pyroptosis. *Research (Wash D C)* 2024;**7**:0311.
139. Quazi MZ, Park N. Nanohydrogels: advanced polymeric nanomaterials in the era of nanotechnology for robust functionalization and cumulative applications. *Int J Mol Sci* 2022;**23**:1943.
140. Zhu SW, Ye M, Ma X, Wu ZZ, Wan SC, Yang SC, et al. pH-Responsive nanoprodrugs combining a Src inhibitor and chemotherapy to potentiate antitumor immunity *via* pyroptosis in head and neck cancer. *Acta Biomater* 2022;**154**:497−509.
141. Guo W, Li Z, Huang H, Xu Z, Chen Z, Shen G, et al. VB12-sericin-PBLG-IR780 nanomicelles for programming cell pyroptosis *via* photothermal (PTT)/photodynamic (PDT) effect-induced mitochondrial DNA (mitoDNA) oxidative damage. *ACS Appl Mater Inter* 2022;**14**:17008−21.
142. Zhou J, Ma X, Li H, Chen D, Mao L, Yang L, et al. Inspired heat shock protein alleviating prodrug enforces immunogenic photodynamic therapy by eliciting pyroptosis. *Nano Res* 2022;**15**:3398−408.
143. Chen DR, Gao Y, Xiao Y, Wan SC, Wu ZZ, Wang S, et al. Engineered nanogels simultaneously implement HDAC inhibition and chemotherapy to boost antitumor immunity *via* pyroptosis. *Appl Mater Today* 2022;**26**:101363.
144. Xiong H, Ma X, Wang X, Su W, Wu L, Zhang T, et al. Inspired epigenetic modulation synergy with adenosine inhibition elicits pyroptosis and potentiates cancer immunotherapy. *Adv Funct Mater* 2021;**31**:2100007.
145. Zhang MJ, Liang MY, Yang SC, Ma XB, Wan SC, Yang QC, et al. Bioengineering of BRAF and COX2 inhibitor nanogels to boost the immunotherapy of melanoma *via* pyroptosis. *Chem Commun* 2023;**59**:932−5.

146. Ji P, Zhang S, Liu P, Li X, Bao W, Cui X, et al. Modulation of mitochondrial electron transport chain by pyroptosis nanoagonists for photoresponsive tumor destruction. *Nano Today* 2022;**44**:101511.
147. Xu J, Qiu W, Liang M, Ye M, Hu J, Ma X, et al. Dual-stimulus phototherapeutic nanogel for triggering pyroptosis to promote cancer immunotherapy. *J Control Release* 2023;**358**:219−31.
148. Wang S, Jing H, Yang R, Heger Z, Krizkova S, Zhou Y, et al. Magnetocaloric responsive hydrogel nanoarchitectonics for pyroptosis relay immunotherapy to suppress post-operation tumor recurrence and metastasis. *Adv Funct Mater* 2024;**34**:2314194.
149. Wu Q, Ma Q, Ma J, Chen J, Zhuang B, Yang S, et al. Cascade amplification of pyroptosis and apoptosis for cancer therapy through a black phosphorous-doped thermosensitive hydrogel. *Pharmaceutics* 2023;**15**:1830.
150. Zhou Z, Yang R, Dong J, Di Y, Yang Y, Huang Y, et al. Pore forming-mediated intracellular protein delivery for enhanced cancer immunotherapy. *Sci Adv* 2022;**8**:eabq4659.
151. Wang X, Wang Y, Zhang W, Zhu X, Liu Z, Liu M, et al. Biomimetic gasdermin protein expressing nanoplatform mediates tumor-specific pyroptosis for cancer immunotherapy. *J Control Release* 2024;**367**:61−75.
152. Yang J, Guo W, Huang R, Bian J, Zhang S, Wei T, et al. Self-assembled albumin nanoparticles induce pyroptosis for photodynamic/photothermal/immuno synergistic therapies in triple-negative breast cancer. *Front Immunol* 2023;**14**:1173487.
153. Jin J, Yuan P, Yu W, Lin J, Xu A, Xu X, et al. Mitochondria-targeting polymer micelle of dichloroacetate induced pyroptosis to enhance osteosarcoma immunotherapy. *ACS Nano* 2022;**16**:10327−40.
154. Liu Y, Zhang M, Bu W. Bioactive nanomaterials for ion-interference therapy. *View* 2020;**1**:e18.
155. Wang G, Li B, Tian H, Xie L, Yan J, Sang W, et al. A metal-phenolic nanocoordinator launches radiotherapeutic cancer pyroptosis through an epigenetic mechanism. *Adv Funct Mater* 2023;**33**:2213425.
156. Zhang Q, Shi D, Guo M, Zhao H, Zhao Y, Yang X. Radiofrequency-activated pyroptosis of bi-valent gold nanocluster for cancer immunotherapy. *ACS Nano* 2023;**17**:515−29.
157. Li Z, Mo F, Wang Y, Li W, Chen Y, Liu J, et al. Enhancing gasdermin-induced tumor pyroptosis through preventing ESCRT-dependent cell membrane repair augments antitumor immune response. *Nat Commun* 2022;**13**:6321.
158. Zhang Y, Jia Q, Li J, Wang J, Liang K, Xue X, et al. Copper-bacteriochlorin nanosheet as a specific pyroptosis inducer for robust tumor immunotherapy. *Adv Mater* 2023;**35**:e2305073.
159. Zhao F, Liang L, Wang H, Wang C, Su D, Ying Y, et al. H_2S-activated ion-interference therapy: a novel tumor targeted therapy based on copper-overload-mediated cuproptosis and pyroptosis. *Adv Funct Mater* 2023;**33**:2300941.
160. Niu Q, Liu Y, Zheng Y, Tang Z, Qian Y, Qi R, et al. Co-delivery of nigericin and decitabine using hexahistidine-metal nanocarriers for pyroptosis-induced immunotherapeutics. *Acta Pharm Sin B* 2022;**12**:4458−71.
161. Su X, Wang WJ, Cao Q, Zhang H, Liu B, Ling Y, et al. A carbonic anhydrase IX (CAIX)-anchored rhenium (I) photosensitizer evokes pyroptosis for enhanced anti-tumor immunity. *Angew Chem Int Ed Engl* 2022;**61**:e202115800.
162. Zhou JY, Wang WJ, Zhang CY, Ling YY, Hong XJ, Su Q, et al. Ru(II)-modified TiO_2 nanoparticles for hypoxia-adaptive photoimmunotherapy of oral squamous cell carcinoma. *Biomaterials* 2022;**289**:121757.
163. Hu J, Dong Y, Ding L, Dong Y, Wu Z, Wang W, et al. Local delivery of arsenic trioxide nanoparticles for hepatocellular carcinoma treatment. *Signal Transduct Target Ther* 2019;**4**:28.
164. Liu K, Zhang L, Lu H, Wen Y, Bi B, Wang G, et al. Enhanced mild-temperature photothermal therapy by pyroptosis-boosted ATP deprivation with biodegradable nanoformulation. *J Nanobiotechnology* 2023;**21**:64.
165. Wan SC, Ye MJ, Yang QC, Zhang T, Zhang MJ, Ma XB, et al. Diselenide-based dual-responsive prodrug as pyroptosis inducer potentiates cancer immunotherapy. *Adv Healthc Mater* 2023;**12**:e2202135.
166. Wu Z, Chen H, Zhang H, Ye L, Ke J, Liu Y, et al. Construction of tumor-cell nucleus targeting lanthanide nano-prodrugs with lutetium-177 labelling for high-efficient tumor fluorescence-localization and radionuclide therapy. *Nano Today* 2024;**55**:102214.
167. Wei FM, Liang JZ, Tan ZS, Tang SX, Xu H, Liang H, et al. Rhenium(I) coordinated carbon nitride as type II immunogenic cell death inducers for enhancing photoimmunotherapy against triple-negative breast cancer. *Chem Eng J* 2024;**485**:150154.
168. Liu L, Lei H, Hou G, Zhang L, Chen Y, Lu Y, et al. Gas-amplified metalloimmunotherapy with dual activation of pyroptosis and the STING pathway for remodeling the immunosuppressive cervical cancer microenvironment. *ACS Nano* 2024;**18**:12830−44.
169. Chen H, Ding B, Zheng P, Liu B, Tan J, Meng Q, et al. Cysteine depletion-initiated redox imbalance evokes ferroptosis and pyroptosis for enhanced pancreatic cancer therapy. *ACS Mater Lett* 2024;**6**:1103−11.
170. Wang B, Wang T, Jiang T, Li S, Zhang L, Zhao X, et al. Circulating immunotherapy strategy based on pyroptosis and STING pathway: Mn-loaded paclitaxel prodrug nanoplatform against tumor progression and metastasis. *Biomaterials* 2024;**306**:122472.
171. Lu Y, Chen Y, Hou G, Lei H, Liu L, Huang X, et al. Zinc-iron bimetallic peroxides modulate the tumor stromal microenvironment and enhance cell immunogenicity for enhanced breast cancer immunotherapy therapy. *ACS Nano* 2024;**18**:10542−56.
172. Zan G, Wu Q. Biomimetic and bioinspired synthesis of nanomaterials/nano-structures. *Adv Mater* 2016;**28**:2099−147.
173. Li A, Zhao Y, Li Y, Jiang L, Gu Y, Liu J. Cell-derived biomimetic nanocarriers for targeted cancer therapy: cell membranes and extracellular vesicles. *Drug Deliv* 2021;**28**:1237−55.
174. Chen W, Tang C, Chen G, Li J, Li N, Zhang H, et al. Boosting checkpoint immunotherapy with biomimetic nanodrug delivery systems. *Adv Healthc Mater* 2024;**13**:e2304284.
175. Su W, Qiu W, Li SJ, Wang S, Xie J, Yang QC, et al. A dual-responsive STAT3 inhibitor nanoprodrug combined with oncolytic virus elicits synergistic antitumor immune responses by igniting pyroptosis. *Adv Mater* 2023;**35**:e2209379.
176. Liu Y, Lu Y, Ning B, Su X, Yang B, Dong H, et al. Intravenous delivery of living listeria monocytogenes elicits gasdermin-dependent tumor pyroptosis and motivates anti-tumor immune response. *ACS Nano* 2022;**16**:4102−15.
177. Xu X, Fan H, Yang Y, Yao S, Yu W, Guo Z, et al. Virus-like particle-induced cGAS-STING activation and AIM2 inflammasome-mediated pyroptosis for robust cancer immunotherapy. *Angew Chem Int Ed Engl* 2023;**62**:e202303010.
178. Zhang S, Zhang Y, Feng Y, Wu J, Hu Y, Lin L, et al. Biomineralized two-enzyme nanoparticles regulate tumor glycometabolism inducing tumor cell pyroptosis and robust antitumor immunotherapy. *Adv Mater* 2022;**34**:e2206851.
179. Chang M, Wang Z, Dong C, Zhou R, Chen L, Huang H, et al. Ultrasound-amplified enzyodynamic tumor therapy by perovskite nanoenzyme-enabled cell pyroptosis and cascade catalysis. *Adv Mater* 2023;**35**:e2208817.
180. Hu C, Man R, Li H, Xia M, Yu Z, Tang B. Near-infrared triggered self-accelerating nanozyme camouflaged with a cancer cell membrane for precise targeted imaging and enhanced cancer immunotherapy. *Anal Chem* 2023;**95**:13575−85.
181. Song X, Huang H, Xia L, Jia W, Yang S, Wang C, et al. Engineering 2D multienzyme-mimicking pyroptosis inducers for ultrasound-augmented catalytic tumor nanotherapy. *Adv Sci* 2023;**10**:e2301279.
182. Chen J, Tang Y, Lin Y, Lu X, Wei L, Xia S, et al. Dual-coordinated atomically dispersed Pt nanozymes evoke efficient pyroptosis for cancer immunotherapy. *Chem Eng J* 2024;**483**:149312.
183. Wang X, Ge X, Zhang M, Sun J, Ouyang J, Na N. A dynamic cascade DNA nanocomplex to synergistically disrupt the pyroptosis checkpoint and relieve tumor hypoxia for efficient pyroptosis cancer therapy. *Chem Sci* 2024;**15**:7079−91.

184. Wang W, Zhang L, Zhang Y, Liu X, Song A, Ren J, et al. A self-adaptive pyroptosis inducer: optimizing the catalytic microenvironment of nanozymes by membrane-adhered microbe enables potent cancer immunotherapy. *Adv Mater* 2024;**36**:e2310063.
185. Zhao P, Wang M, Chen M, Chen Z, Peng X, Zhou F, et al. Programming cell pyroptosis with biomimetic nanoparticles for solid tumor immunotherapy. *Biomaterials* 2020;**254**:120142.
186. Long Y, Fan J, Zhou N, Liang J, Xiao C, Tong C, et al. Biomimetic prussian blue nanocomplexes for chemo-photothermal treatment of triple-negative breast cancer by enhancing ICD. *Biomaterials* 2023;**303**:122369.
187. Wang Q, Qin W, Qiao L, Gao M, Zhou M, Zhang H, et al. Biomimetic nanophotosensitizer amplifies immunogenic pyroptosis and triggers synergistic cancer therapy. *Adv Healthc Mater* 2023;**12**:e2301641.
188. Yu Z, Cao W, Han C, Wang Z, Qiu Y, Wang J, et al. Biomimetic metal-organic framework nanoparticles for synergistic combining of SDT-chemotherapy induce pyroptosis in gastric cancer. *Front Bioeng Biotechnol* 2022;**10**:796820.
189. Huang Y, You X, Wang L, Zhang G, Gui S, Jin Y, et al. Pyridinium-substituted tetraphenylethylenes functionalized with alkyl chains as autophagy modulators for cancer therapy. *Angew Chem Int Ed Engl* 2020;**59**:10042−51.
190. Pellegrini P, Strambi A, Zipoli C, Hägg-Olofsson M, Buoncervello M, Linder S, et al. Acidic extracellular pH neutralizes the autophagy-inhibiting activity of chloroquine: implications for cancer therapies. *Autophagy* 2014;**10**:562−71.
191. Zhang W, Liu Z, Zhu J, Liu Z, Zhang Y, Qin G, et al. Bioorthogonal disruption of pyroptosis checkpoint for high-efficiency pyroptosis cancer therapy. *J Am Chem Soc* 2023;**145**:16658−68.
192. Sun S, He Y, Xu J, Leng S, Liu Y, Wan H, et al. Enhancing cell pyroptosis with biomimetic nanoparticles for melanoma chemo-immunotherapy. *J Control Release* 2024;**367**:470−85.
193. Lin W, Liu Y, Wang J, Zhao Z, Lu K, Meng H, et al. Engineered bacteria labeled with iridium(III) photosensitizers for enhanced photodynamic immunotherapy of solid tumors. *Angew Chem Int Ed Engl* 2023;**62**:e202310158.
194. Deng Y, Jia F, Jiang P, Chen L, Xing L, Shen X, et al. Biomimetic nanoparticle synchronizing pyroptosis induction and mitophagy inhibition for anti-tumor therapy. *Biomaterials* 2023;**301**:122293.
195. Li Y, Wu J, Qiu X, Dong S, He J, Liu J, et al. Bacterial outer membrane vesicles-based therapeutic platform eradicates triple-negative breast tumor by combinational photodynamic/chemo-/immunotherapy. *Bioact Mater* 2023;**20**:548−60.
196. Zheng C, Zhang D, Kong Y, Niu M, Zhao H, Song Q, et al. Dynamic regulation of drug biodistribution by turning tumors into decoys for biomimetic nanoplatform to enhance the chemotherapeutic efficacy of breast cancer with bone metastasis. *Explor (Beijing)* 2023;**3**:20220124.
197. Wu L, Xie W, Li Y, Ni Q, Timashev P, Lyu M, et al. Biomimetic nanocarriers guide extracellular ATP homeostasis to remodel energy metabolism for activating innate and adaptive immunity system. *Adv Sci* 2022;**9**:e2105376.
198. Liu K, Zan P, Li Z, Lu H, Liu P, Zhang L, et al. Engineering bimetallic polyphenol for mild photothermal osteosarcoma therapy and immune microenvironment remodeling by activating pyroptosis and cGAS-STING pathway. *Adv Healthc Mater* 2024;**13**:e2400623.
199. Li H, Zang W, Mi Z, Li J, Wang L, Xie D, et al. Tailoring carrier-free nanocombo of small-molecule prodrug for combinational cancer therapy. *J Control Release* 2022;**352**:256−75.
200. Zhang X, Li N, Zhang S, Sun B, Chen Q, He Z, et al. Emerging carrier-free nanosystems based on molecular self-assembly of pure drugs for cancer therapy. *Med Res Rev* 2020;**40**:1754−75.
201. Li L, Tian H, Zhang Z, Ding N, He K, Lu S, et al. Carrier-free nanoplatform *via* evoking pyroptosis and immune response against breast Cancer. *ACS Appl Mater Inter* 2023;**15**:452−68.
202. Ali W, Kulsoom Wang F. Molecular probes for monitoring pyroptosis: design, imaging and theranostic application. *Apoptosis* 2024;**29**:1038−50.
203. Wang X, He S, Cheng P, Pu K. A dual-locked tandem fluorescent probe for imaging of pyroptosis in cancer chemo-immunotherapy. *Adv Mater* 2023;**35**:e2206510.
204. Hu B, Zhang Q, Gao X, Xu K, Tang B. Monitoring the activation of caspases-1/3/4 for describing the pyroptosis pathways of cancer cells. *Anal Chem* 2021;**93**:12022−31.