Targeting pyroptosis to treat aortic aneurysms: From mechanism to drug discovery (Review)

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Abstract. Pyroptosis is a lytic and highly inflammatory type of programmed cell death that is mediated primarily by members of the gasdermin (GSDM) protein family. Upon activation by inflammatory stimuli or danger signals, GSDMs are cleaved to release N-terminal fragments that oligomerize and form pores in the plasma membrane. This disrupts cellular integrity, resulting in osmotic lysis and the release of potent proinflammatory cytokines, such as interleukin (IL)-1β and IL-18. The progression of an aortic aneurysm (AA) is driven by complex pathophysiological processes, with the loss of vascular smooth muscle cells and sustained vascular inflammation being central to disease pathogenesis. Emerging evidence indicates that pyroptosis markedly contributes to AA development by amplifying inflammatory activation and promoting cellular disintegration within the aortic wall. Further preclinical evidence has demonstrated that pharmacological inhibition of key pyroptosis signaling pathways effectively attenuates AA formation in murine models, underscoring its promising therapeutic potential. The present review summarizes the molecular mechanisms of pyroptosis, highlights its pathophysiological role in AAs and discusses novel therapeutic strategies targeting pyroptosis for the treatment of AAs.

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1. Introduction

An aortic aneurysm (AA) is a life-threatening condition characterized by localized or diffuse dilation of the aortic wall, >50% of the normal diameter (1). The high associated mortality rate is primarily due to rupture, with more than one-half of untreated patients succumbing within 5 years (2). Post-rupture mortality rates range from 35 to 67%, underscoring the grave prognosis (3). Often asymptomatic, AAs are frequently undetected until rupture, which is fatal for most patients before they reach medical care, earning them the moniker 'vascular time bombs'. Current management relies exclusively on surgical interventions, such as endovascular or open repair, while effective pharmacotherapies to prevent expansion or rupture remain elusive (4). This urgency drives research into the molecular pathophysiology of AAs to identify novel, druggable targets.

The pathology of AAs features vascular smooth muscle cell (VSMC) depletion, elastic fiber degradation and pervasive inflammatory cell infiltration. These processes collectively undermine aortic wall integrity, leading to dilation and ultimately, dissection or rupture. Persistent VSMC loss is a central hallmark, driven by mechanisms such as senescence, phenotypic switching and regulated cell death, with the latter being a major contributor (5). Emerging evidence also implicates endothelial cell (EC) dysfunction and death in aortic disease development (6). Simultaneously, inflammatory and autoimmune responses at the medial-adventitial junction are critical triggers of aortic destruction and dilation (7). Infiltration of immune cells (for example, macrophages and lymphocytes) into the aortic wall is a hallmark of aneurysm formation (8). Infiltrating macrophages, particularly classically activated M1-type cells, release large amounts of

proinflammatory cytokines, sustaining a proinflammatory microenvironment (9). This persistent vascular inflammation not only initiates aneurysm development but also profoundly accelerates pathological aortic remodeling by triggering VSMC death, inducing pathological phenotypic switching (for example, to a synthetic state), and promoting the secretion of extracellular matrix (ECM)-degrading proteases (10). The suppression of inflammation has been shown to be effective in attenuating aneurysm progression (11).

Multiple types of regulated cell death have been reported, such as necroptosis, ferroptosis, cuproptosis, disulfidptosis and pyroptosis (12). Among these, pyroptosis, which is an exceedingly inflammatory type, has undergone a revolutionary decade of mechanistic elucidation, revealing its dual role in disease: Moderate activation mediates host defense, whereas excessive activation exacerbates tissue damage (13). However, research into specific pyroptosis mechanisms in AAs remains limited. A deeper understanding of pyroptosis in AAs may reveal new therapeutic opportunities to slow disease progression.

The present review summarizes recent advances in the understanding of pyroptosis and its relevance to AAs. A focus is placed on the pyroptotic pathway, the role of pyroptosis in diverse aneurysmal pathologies and the underlying molecular mechanisms, with a particular emphasis on the key effector protein, gasdermin D (GSDMD). Furthermore, a detailed discussion of potential therapeutic strategies targeting pyroptosis for AA intervention is provided.

2. Overview of pyroptosis

Understanding the multilayered molecular signaling pathways that regulate pyroptosis is fundamental to the development of targeted therapies.

Definition and hallmarks of pyroptosis. Pyroptosis is now characterized as a type of regulated, lytic cell death executed by the pore-forming activity of the N-terminal domains of GSDM family proteins in the plasma membrane (14). This process is triggered by infectious stimuli [such as pathogen-associated molecular patterns (PAMPs)] or non-infectious danger signals [such as damage-associated molecular patterns (DAMPs)] (15). Hallmark features include robust proinflammatory activity and pore-dependent execution (16).

Morphologically, pyroptotic cells undergo characteristic changes. The N-terminal domain of GSDM proteins oligomerizes to form 10- to 20-nm pores in the plasma membrane (17). This process induces ionic imbalances (K^+ efflux and Na^+/Ca^{2+} influx) and osmotic lysis, resulting in cellular swelling, organellar edema and eventual plasma membrane rupture with the release of intracellular contents and inflammatory mediators (18,19). The nucleus exhibits chromatin condensation (often marginalized) but lacks the DNA laddering characteristic of apoptosis (20). Molecularly, pyroptosis crucially depends on activated inflammatory caspases, which cleave GSDM proteins to release the active, pore-forming N-terminal domain from autoinhibition (21,22). Caspase activation is typically driven by specific inflammasome complexes upon recognition of PAMPs or DAMPs (23). These caspases also process proinflammatory cytokine precursors [pro-interleukin (IL)-1β and pro-IL-18] into their mature, active forms (24).

Functionally, pyroptosis essentially initiates and amplifies inflammatory responses and plays pivotal roles in immune defense and disease pathogenesis. Membrane rupture leads to the massive release of cellular contents [DAMPs, such as high mobility group box 1 (HMGB1) protein, adenosine triphosphate (ATP), IL-1α and IL-33] and mature IL-1β and IL-18 (25). These alarmins potently activate and recruit neighboring immune cells, amplify the inflammatory cascade and establish an immune defense mechanism for intracellular pathogen clearance (26). However, uncontrolled pyroptosis can drive intense inflammation and serve as a central pathogenic driver in diseases such as autoinflammatory disorders and atherosclerosis (27,28).

GSDM family: Executors of pyroptosis with GSDMD as the pivotal node. The execution of pyroptosis across all known pathways ultimately relies on the GSDM protein family, whose pore formation is the indispensable final common step. In humans, this family comprises GSDMA, GSDMB, GSDMC, GSDMD, GSDME and deafness autosomal recessive 59 (29). GSDM family members A-E consist of a highly differentiated peptide linker domain, a conserved cytotoxic N-terminus (GSDM-N) that forms pores and a conserved C-terminus (GSDM-C) that inhibits GSDM-N (30). A self-locking regulatory mechanism that consists of GSDM-C and GSDM-N ensures that the active GSDM-N domain is released only after specific cleavage by inflammatory caspases, thereby preventing cell damage caused by spontaneous activation (31). GSDM pores use an 'electrostatic sieve' mechanism, orchestrating the selective and efficient release of IL-1β/IL-18. Concurrently, pore-driven K^+ efflux activates the NOD-like receptor family-pyrin domain-containing 3 (NLRP3) inflammasome, initiating a positive feedback loop that amplifies inflammatory responses (32).

GSDM family members exhibit distinct expression patterns and functions. GSDMD is widely expressed and constitutively highly expressed in myeloid cells (for example, neutrophils, macrophages and dendritic cells) (33). GSDMD serves as the most specific and efficient substrate for caspase-1/4/5/11 and is considered the most versatile executor (22). GSDME is widely distributed across the placenta, intestines, thyroid gland and brain (34); it can switch apoptotic stimuli to pyroptotic death stimuli (35). GSDMB is enriched in the gastrointestinal epithelium and in colorectal cancer, and can be cleaved by granzyme A (GzmA) (36,37). GSDMA and GSDMC are predominantly restricted to epithelial surfaces and the skin (38).

Signaling pathways that activate pyroptosis. The multipathway nature of pyroptosis initiation reflects the flexibility of cells in response to various threats, including PAMPs, DAMPs, cytosolic disturbances and bacterial components, such as lipopolysaccharide (LPS) (Fig. 1).

Canonical caspase-1-dependent pathway. The canonical caspase-1-dependent pathway is the most extensively studied pyroptosis pathway, and is primarily activated in immune cells during host defense against pathogens. PAMPs, DAMPs and cytosolic disturbances activate pattern recognition receptors (PRRs) (39). Subsequently, PRRs trigger oligomeric sensors, the adaptor protein apoptosis-associated speck-like protein (ASC)

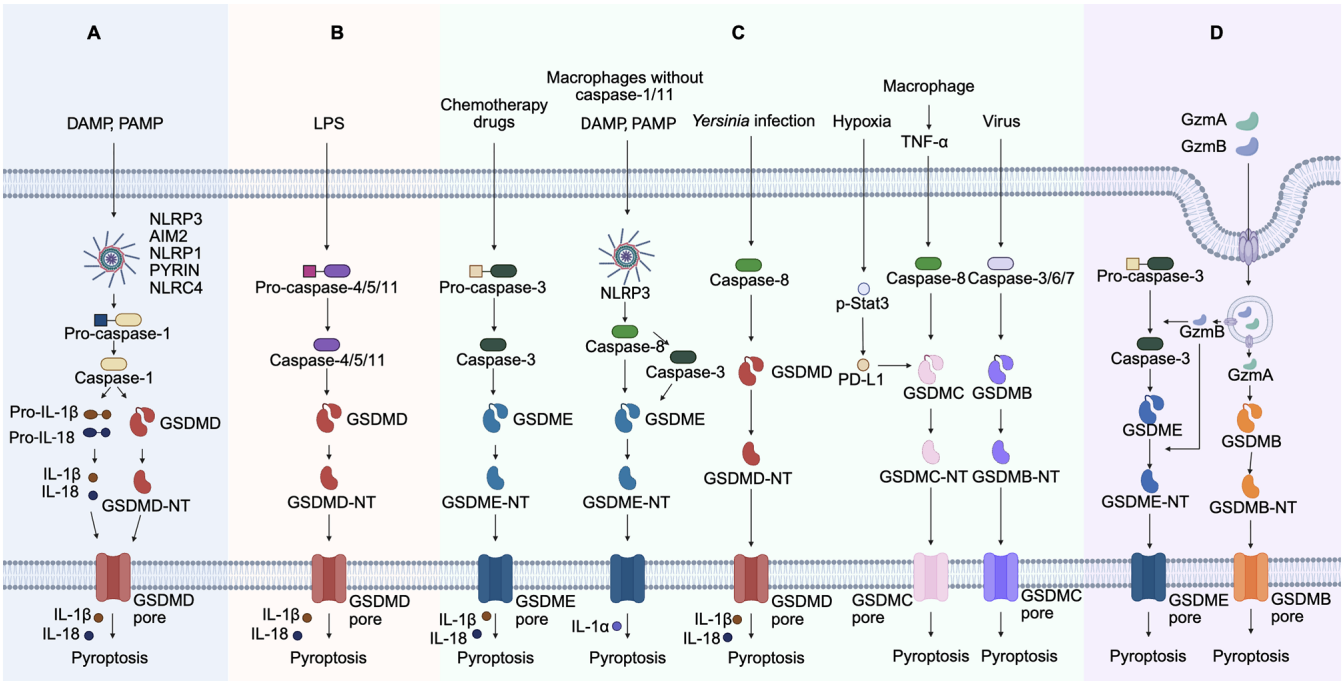

Figure 1. Overview of pyroptotic pathways. Pyroptosis can be broadly categorized into four distinct pathways: The canonical, non-canonical, caspase-3/6/8-mediated and Gzm-mediated pathways. Within the figure, A represents the canonical pathway, in which DAMPs/PAMPs activate the inflammasome, leading to caspase-1 activation that cleaves GSDMD to induce pore formation. B represents the non-canonical pathway: LPS directly activates caspase-4/5/11, which cleaves GSDMD to generate membrane pores. C represents the caspase-3/6/8-mediated pathway: Caspase-3 activates GSDMB/GSDME to trigger pyroptosis; caspase-6 induces pyroptosis via GSDMB cleavage; and caspase-8 activates GSDMC/GSDMD/GSDME to execute pyroptosis. D represents the Gzm-induced pathway: GzmA and GzmB activate GSDMB and GSDME, respectively, to form holes and induce pyroptosis, respectively. Created with Biorender.com. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family pyrin domain containing 3; AIM2, absent in melanoma 2; NLRP1, NOD-like receptor family pyrin domain containing 1; PYRIN, pyrin domain-containing protein; NLRC4, NOD-like receptor family CARD domain containing 4; IL-1β, interleukin-1 beta; Pro-IL-1β, precursor of interleukin-1β; IL-18, interleukin-18; Pro-IL-18 precursor of interleukin-18; GSDMD, gasdermin D; GSDME, gasdermin E; GSDMB, gasdermin B; GSDMC, gasdermin C; -NT, N-terminal; p-Stat3, phosphorylated signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; PD-L1, programmed death-ligand 1; GzmA, granzyme A; GzmB, granzyme B.

and the effector inactive pro-caspase-1 to assemble canonical inflammasomes (40). Five sensor types, NLRP3, absent in melanoma 2 (AIM2), NOD-like receptor family-pyrin domain containing 1, pyrin and NOD-like receptor c4 (NLRC4), primarily mediate the canonical pathway. The caspase recruitment domain (CARD) domain of ASC subsequently engages the CARD domain of pro-caspase-1, triggering self-cleavage of pro-caspase-1 to generate mature caspase-1 (41). Activated caspase-1 then cleaves both GSDMD to generate the pore-forming GSDMD N-terminal (GSDMD-NT) and pro-IL-1β/pro-IL-18 into their mature forms (42). After that, pores in the cell membrane form and pyroptosis occurs.

Non-canonical caspase-4/5/11-dependent pathway. The non-canonical caspase-4/5-dependent pathway in humans and the non-canonical caspase-11-dependent pathway mice responds directly to cytosolicLPSfrom Gram-negative bacteria (30). These caspases are upregulated by type I interferon signaling and are activated upon LPS binding without inflammasome assembly to directly cleave GSDMD to induce pyroptosis (42). Moreover, K^+ efflux mediated by GSDMD pores indirectly activates the NLRP3 inflammasome-caspase-1 canonical pyroptosis pathway (22). This indirect mechanism is recognized as central to non-canonical pathway-induced mature cytokine release and secondary inflammatory amplification. Caspase-4/5/11 cannot directly process pro-IL-1β/pro-IL-18 (43,44). However, recent evidence has demonstrated that LPS-activated human caspase-4 and -5 can cleave pro-IL-18 at sites identical to those targeted by caspase-1 (24). These findings challenge conventional perception, suggesting that non-canonical caspases may have the ability to directly address specific cytokine precursors under specific circumstances.

Caspase-3/6/8-mediated alternative pathways. In the caspase-3-mediated pathway, caspase-3, traditionally designated as the key executioner of apoptosis, can initiate pyroptotic switching under specific stimuli. In GSDME-expressing cells, activated caspase-3 mediates specific cleavage of GSDME, generating its N-terminal pore-forming domain fragment. Subsequent plasma membrane pores and pyroptosis occur thereby executing a modality shift from apoptosis to pyroptosis (35). This process plays a particularly important role in tumor cell killing by chemotherapeutic agents.

In the caspase-8-mediated pathway, caspase-8 is a multifunctional initiator of caspase that promotes pyroptosis through multiple mechanisms; it can directly cleave GSDMD or GSDMC, or activate GSDME via caspase-3, leading to pyroptosis. This process, characterized by the absence of canonical IL-18 release coupled with compensatory IL-1α secretion, has been described as 'incomplete pyroptosis' (45). For instance, *Yersinia* infection triggers the canonical pyroptosis pathway through direct caspase-8 activation, where caspase-8 cleaves GSDMD (46). Under hypoxic conditions in

the tumor microenvironment, tumor necrosis factor-α (TNFα) stimulation causes caspase-8 to cleave GSDMC, shifting the mode of cell death from apoptosis to pyroptosis (47). In caspase-1/11-deficient macrophages, the NLRP3 inflammasome activates caspase-3/8, which subsequently cleaves GSDME to induce pyroptosis. GSDMB can be activated by caspase-3/6/7.

Gzm-mediated pathway. The Gzm-mediated pathway represents a mechanism through which adaptive immune cells (cytotoxic T lymphocytes and natural killer cells) directly induce pyroptosis in target cells. Gzms, serine proteases delivered into target cells via perforin, can directly cleave GSDM proteins. The Gzm family comprises five known human members: GzmA, GzmB, GzmH, GzmK and GzmM (48). Among them, GzmA is the most abundant, while GzmB is distinguished by its potent proapoptotic activity (49,50). GzmB induces pyroptosis through both caspase-3-dependent and caspase-3-independent mechanisms: It rapidly activates caspase-3, which cleaves GSDME, and can also directly cleave GSDME itself (51). By contrast, GzmA directly hydrolyzes and cleaves GSDMB, triggering its pore-forming activity (37). This Gzm-mediated pyroptosis effectively amplifies inflammation in contexts such as antitumor immunity (52).

3. Pathogenic role of pyroptosis in AAs

Multiple aspects of pyroptosis are involved in the pathology of Aas, as described in Fig. 2 and Table I (53-73).

Direct mediator of VSMC loss and wall weakening. Accumulating evidence directly implicates pyroptosis activation in aneurysmal lesions, particularly in VSMCs. Both human AA tissues and mouse models consistently exhibit elevated levels of activated pyroptotic executors, including GSDMD-NT accumulation and mature IL-1β and IL-18, specifically in VSMCs within the lesion wall (53,74). Furthermore, components of the NLRP3 inflammasome are upregulated in AA tissues, with activation markers such as ASC speck formation and cleaved caspase-1 detected specifically in VSMCs (54,58). Functional studies using NLRP3- or caspase-1/11-deficient mice have revealed markedly attenuated vascular dilation, reduced VSMC death and decreased disease incidence across multiple aneurysm models (57,58,75,76). Crucially, abdominal AAs (AAAs) are associated with increased TNFα levels. Wang *et al* (53) observed cell swelling and pore formation in the VSMC membrane under TNFα stimulation by scanning electron microscopy, indicating the pyroptotic lytic death of VSMCs during mouse AAAs. This direct and rapid mode of cell death leads to substantial and irreversible loss of VSMCs, disrupting the cellular foundation required for maintaining aortic wall tension and structural integrity. Thus, pyroptosis represents a key mechanism driving vascular wall thinning, dilation and eventual rupture.

Amplifier of the aortic inflammatory storm. The profound impact of pyroptosis on aneurysmal pathology extends far beyond the direct killing of VSMCs; it triggers and perpetuates a storm of inflammation within the aortic wall.

First, as aforementioned, cellular components and mature and highly bioactive IL-1β and IL-18 secreted from VSMCs undergoing pyroptosis function as potent alarm signals and chemoattractants, robustly recruiting circulating monocytes, neutrophils, T lymphocytes and other inflammatory cells into the vascular wall, particularly at the medial-adventitial junction (77,78). IL-1β and IL-18 directly activate ECs to generate adhesion molecules, facilitating leukocyte rolling, adhesion and transmigration (79). Released ATP acts as an agonist for the purinergic receptor p2x-ligand-gated ion channel 7 (P2X7) receptor on macrophages, thereby activating them, whereas HMGB1 strongly promotes proinflammatory effects via receptor for advanced glycation end product/toll-like receptor (TLR) signaling (80,81).

Second, pyroptosis establishes a positive feedback loop that aggravates vascular inflammation. Infiltrating immune cells, particularly macrophages, are strongly activated by pyroptosis-derived factors (especially IL-1β and IL-18) and DAMPs, polarizing toward a proinflammatory M1 phenotype (82). These cells subsequently produce and release large amounts of proinflammatory cytokines (such as TNFα, interleukin-6 and IL-1β), chemokines (such as monocyte chemotactic factor/c-c motif chemokine ligand 2) and reactive oxygen species (ROS) (83,84). Crucially, they may undergo pyroptosis themselves, leading to further release of DAMPs and cytokines. This creates a self-sustaining and amplifying vicious cycle of 'pyroptosis-inflammation-more pyroptosis/inflammation' (72,85). This escalation of the inflammatory milieu not only further damages and kills additional VSMCs (through pyroptosis or other death modalities) but also profoundly affects the other aforementioned key pathological processes, ultimately driving pathological vascular remodeling through the sustained release of proinflammatory cytokines and proteases (86). As shown by Zhang *et al* (85), exosomal lncRNA plasmacytoma variant translocation 1 (PVT1), which originates from M1 macrophages, promotes human aortic vascular smooth muscle cell (HA-VSMC) pyroptosis and inflammation via the miR-186-5p/HMGB1 pathway, upregulating NLRP3 and GSDMD expression, thereby exacerbating AAA progression (85).

Crosstalk with other pathological processes in AA. Pyroptosis does not occur in isolation but is intricately interwoven with other pathological processes in AAs, collectively driving disease progression. The first of these processes is VSMC phenotypic switching. The study by Sun *et al* (87) demonstrated that NLRP3 inhibition prevents platelet-derived growth factor subunit B-induced phenotypic modulation in HA-VSMCs (87). Similarly, the genetic deficiency of NLRP3 attenuates angiotensin II (Ang II)-induced phenotypic switching and vascular remodeling in mouse VSMCs (88). NLRP3 activation contributes to the phenotypic transition and proliferation of rat VSMCs in hypertension (89). Inflammatory mediators and cytokines released during pyroptosis can induce surviving VSMCs to shift from a contractile to a synthetic phenotype (87). This transition impairs contractile function and promotes the secretion of proinflammatory factors and matrix metalloproteinases (MMPs), further disrupting vascular homeostasis and accelerating inflammation and matrix degradation. The second process is ECM degradation. The inflammatory microenvironment triggered by pyroptosis plays a central role in promoting ECM degradation. High levels of cytokines (such as IL-1β

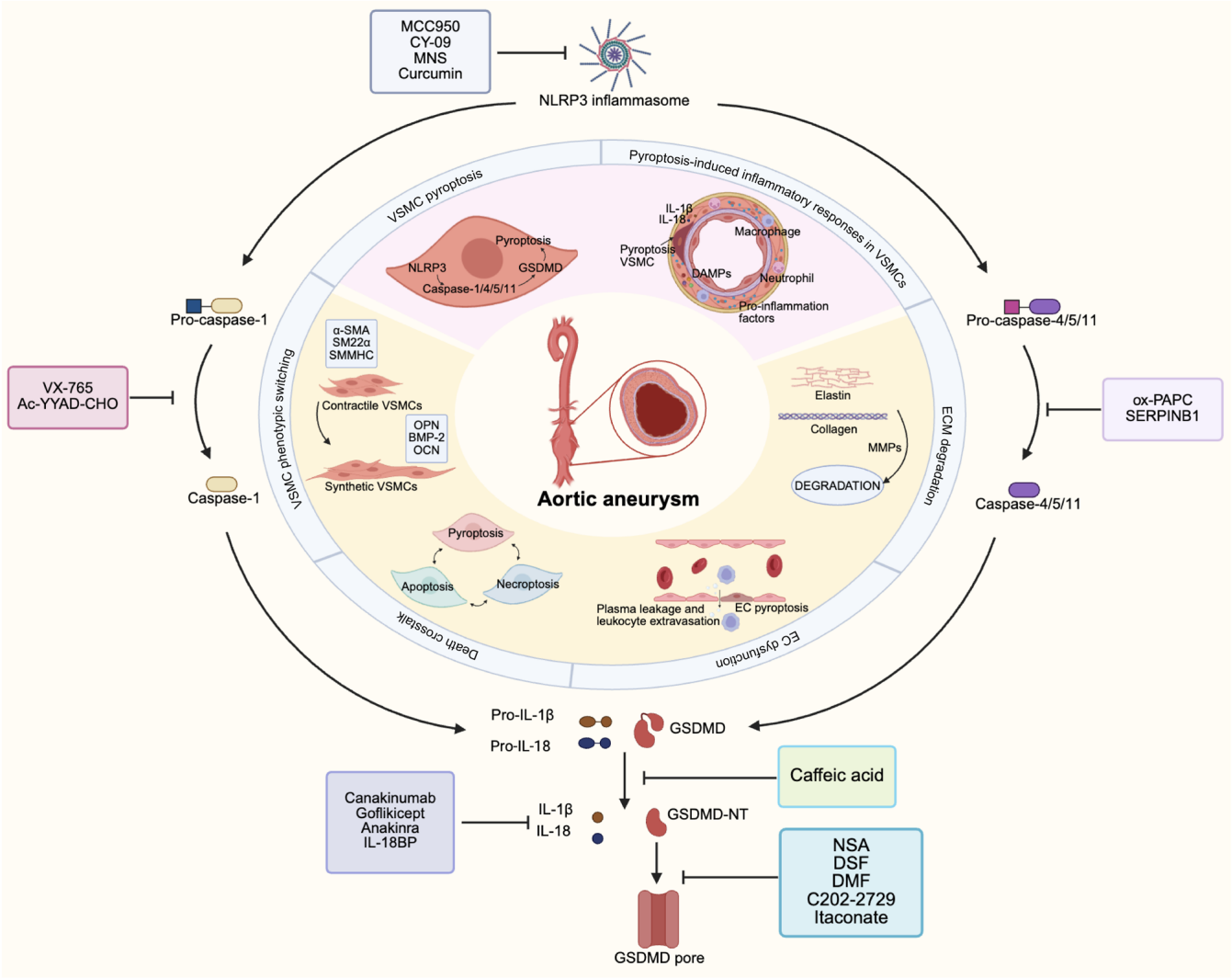

Figure 2. Potential therapeutic strategies targeting pyroptotic pathway for AA and the link between pytoptosis and AA. Inhibitors of NLRP3 inflammasomes: MCC950, CY-09, MNS and curcumin. Inhibitors of caspase-1: VX-765 and Ac-YYAD-CHO. Inhibitors of caspase-4/5/11: ox-PAPC and SERPINB1. Inhibitors of IL-1: Anakinra, Canakinumab and Goflikicept; Inhibitors of IL-18: IL-18BP. Inhibitors that inhibit GSDMD cleavage: Caffeic acid. Inhibitors of GSDMD pore formation: NSA, DSF, DMF, Itaconate and C-202-2729. Created with Biorender.com. AA, aortic aneurysm; NLRP3, NOD-like receptor family pyrin domain-containing 3; MCC950, 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[4-(2-hydroxypropan-2-yl)furan-2-yl]sulfonylurea; CY-09, 4-[[4-Oxo-2-thioxo-3-[[3-(trifluoromethyl)phenyl]methyl]-5-thiazolidinylidene]methyl]benzoic acid; MNS, 3,4-methylenedioxy-β-nitrostyrene; VSMC, vascular smooth muscle cells; GSDMD, gasdermin D; Caspase-1/4/5/11, cysteine-aspartic protease 1/4/5/11; IL-1β, interleukin-1β; IL-18, interleukin-18; DAMPs, damage-associated molecular patterns; α-SMA, α-smooth muscle actin; SM22α, smooth muscle protein 22 α; SMMHC, smooth muscle myosin heavy chain; OPN, osteopontin; BMP-2, bone morphogenetic protein 2; OCN, osteocalcin; VX-765, (S)-1-((S)-2-{[1-(4-Amino-3-chlorophenyl)methanoyl] amino}-3,3-dimethylbutanoyl)pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxotetrahydrofuran-3-yl)amide; Ac-YVAD-CHO, N-Acetyl-L-tyrosyl-L-valyl-N-[(1S)-2-carboxy-1-formylethyl]-L-alaninamide; EC, endothelial cell; MMP, matrix metalloproteinase; ECM, extracellular matrix; ox-PAPC, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; -NT, N-terminal; IL-18BP, interleukin-18 binding protein; NSA, necrosulfonamide; DSF, disulfiram; DMF, dimethyl fumarate; SERPINB1, serine protease inhibitor clade B member 1; C202-2729, a GSDMD N-terminal inhibitor.

and TNFα) upregulate multiple MMPs (including MMP-2 and MMP-9), disrupting the balance between MMPs and their endogenous inhibitors (57). The NLRP3 inflammasome may further directly activate pro-enzymes through cleavage of inhibitory domains (53). Studies have demonstrated that NLRP3 or caspase-1 deficiency significantly reduces elastin degradation and MMP activation during early mouse AAA formation (57,76,90). Activated MMPs degrade critical structural components of the aortic wall, namely, elastic fibers and collagen, resulting in a precipitous loss of tensile strength, decreased wall compliance, and ultimately constituting the biomechanical basis for dilation and rupture. Infiltrating inflammatory cells, such as neutrophils and macrophages, are also major sources of MMPs (91). The third pathological process in AAs is EC dysfunction. Pyroptosis-induced EC death and associated inflammatory factors compromise endothelial integrity, increase vascular permeability, and facilitate plasma leakage and leukocyte extravasation, exacerbating vascular inflammation and edema. Furthermore, pyroptosis-related EC injury may cause dysregulation of the secretion of vasoactive factors (92). A fourth process is crosstalk with other programmed cell death pathways. VSMCs within the aneurysmal microenvironment often undergo multiple forms of programmed cell death simultaneously or sequentially. For instance, in Ang II-induced mouse AAA models, markers of pyroptosis (GSDMD activation), apoptosis (caspase-3

Table I. Role of pyroptosis in AA.

Authors, year	Models/tissues/cells	Pathological changes of AA	Upstream pathways (effect on pyroptosis)	Pyroptosis pathways	(Refs.)
Wang *et al*, 2024	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *In vitro*: VSMCs	VSMC inflammation, phenotypic switching, pyroptosis	Keap1↑-Nrf2↑-Hmox-1 ↑ (inhibits)	Caspase-1-GSDMD	(53)
Liao *et al*, 2023	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *In vitro*: VSMCs	VSMC inflammation, pyroptosis, oxidative stress, collagen deposition, elastin degradation	NF-κB↑ (promotes)	NLRP3-Caspase-1-GSDMD	(54)
Liu *et al*, 2023	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *In vitro*: macrophages, VSMCs	Macrophages secrete ET-1, VSMC inflammation, pyroptosis and oxidative stress	ET-1↑-ETRA↑-Ca^{+}↑-ROS↑ (promotes)	NLRP3-Caspase-1-GSDMD	(55)
Hu *et al*, 2024	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice, $CaCl_2$-induced AAA in C57BL/6 mice; *in vitro*: RAW264.7 cells	Elastin degradation, macrophage-upregulated MMP9 and MMP2, inflammation, pyroptosis	p38↑-ERK↑-miR145↓-TLR4↑ (promotes)	NLRP3-Caspase-1-GSDMD	(56)
Usui *et al*, 2015	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *in vitro*: macrophages	Elastin degradation, Macrophage-upregulated MMP9 and MMP2, inflammation, pyroptosis, mtROS	AT1R-mtROS↑ (promotes)	NLRP3-Caspase-1-GSDMD	(57)
Wu *et al*, 2017	*In vivo*: Human aortic tissues, Ang II-induced AAA in C57BL/6 wild-type mice; *in vitro*: VSMCs, macrophages	VSMC phenotypic switching, pyroptosis		NLRP3-Caspase-1-GSDMD	(58)
Dihlmann *et al*, 2014	*In vivo*: Human lymphoid tissue	Lymphocyte infiltration and inflammation		AIM2-Caspase-5	(59)
Zhang *et al*, 2024	*In vitro*: Human monocyte THP-1 cell line; human aortic VSMCs	VSMC inflammation and pyroptosis	lncRNA PVT1↑/miR-186-5p inhibition/HMGB1 inhibition (promotes)	NLRP3-Caspase-1-GSDMD	(60)
Cai *et al*, 2025	*In vivo*: Porcine pancreatic elastase-induced AAA in C57BL/6 mice; *in vitro*: macrophages	Elastin degradation, collagen deposition, macrophage inflammation, pyroptosis	TRAF6↑ (promotes)	NLRP3-Caspase-1-GSDMD	(61)
Fu *et al*, 2022	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *in vitro*: MOVAS	Elastin degradation, collagen deposition, VSMC inflammation, pyroptosis, oxidative stress	α7nAChR (promotes)	NLRP3-Caspase-1-GSDMD	(62)
Hu *et al*, 2022	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice; *in vitro*: Raw264.7 cells, adipose-derived mesenchymal stem cells	Elastin degradation, collagen deposition, macrophage inflammation, pyroptosis	miR-17-5p-TXNIP↓ (inhibits)	NLRP3-Caspase-1-GSDMD	(63)
Xie *et al*, 2024	*In vivo*: Human aortic tissues; *in vitro*: THP-1, human aortic VSMCs	Macrophage non-canonical pyroptosis, VSMC phenotypic switching, apoptosis, non-canonical pyroptosis	mtROS-Drp1↑ (promotes)	Caspase-4-GSDMB	(64)

Table I. Continued.

Authors, year	Models/tissues/cells	Pathological changes of AA	Upstream pathways (effect on pyroptosis)	Pyroptosis pathways	(Refs.)
Guo *et al*, 2024	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice	Inflammation, inflammatory cell infiltration, medial elastin breaks, VSMC depletion and collagen deposition		GSDMD	(65)
Liu *et al*, 2019	*In vivo*: $CaCl_2$-induced AAA in C57BL/6 mice; *in vitro*: myelogenous cells	Elastin degradation, inflammatory cell infiltration	CD95/CD95L (promotes)	Caspase-8	(66)
Chi *et al*, 2025	*In vivo*: β-aminopropionitrile fumarate-induced TAA; *in vitro*: MOVAS	Elastin degradation VSMC phenotypic switching, pyroptosis, and upregulated MMP9 and MMP2	CB1 receptor↑-cAMP-PKA↓ (promotes)	NLRP3-Caspase-1-GSDMD	(67)
Huang *et al*, 2025	*In vivo*: Human AAA sample	Inflammatory cell infiltration, VSMC pyroptosis and inflammation	CXCL8↑ (promotes)	NLRP3-Caspase1-GSDMD	(68)
Xiong *et al*, 2024	*In vivo*: Elastase-induced AAA in C57BL/6 mice	Inflammatory neutrophils, extracellular traps and elastin degradation	PI3Kγ↑-cAMP-PKA↓ (promotes)	Caspase-11-GSDMD	(69)
Cai *et al*, 2024	*In vivo*: Human AAA sample, Ang II-induced AAA in ApoE$^{-/-}$ mice; *in vitro*: RAW 264.7 cells	Inflammatory cell infiltration, macrophage inflammation, pyroptosis	miR-146a-5p-TRAF6 inhibition (inhibits)	NLRP3-Caspase-1-GSDMD	(70)
Yao *et al*, 2023	*In vivo*: Ang II-induced AAA	VSMC inflammation, upregulated MMPs, cell death	CARMA3↓-p38↑-mitochondria-endoplasmic reticulum stress↑ (promotes)	NLRP3-Caspase-1-GSDMD	(71)
Sun *et al*, 2023	*In vivo*: Ang II-induced AAA in ApoE$^{-/-}$ mice, $CaCl_2$-induced AAA in C57BL/6 mice; *in vitro*: primary macrophages	Macrophage inflammation, upregulated MMPs, oxidative stress	P2X7 (promotes)	NLRP3-Caspase-1-GSDMD	(72)
Xiong *et al*, 2021	*In vitro*: Human primary VSMCs	VSMC inflammation, upregulated MMPs, pyroptosis, phenotypic switching	PVT1-miR-26a-KLF4 inhibition-PI3K/AKT inhibition (promotes)	Caspase-1	(73)

AA, aortic aneurysm; AAA, abdominal aortic aneurysm; ApoE$^{-/-}$, apolipoprotein E-deficient; VSMC, vascular smooth muscle cell; Ang II, angiotensin II; TAA, thoracic aortic aneurysm; MOVAS, mouse aortic vascular smooth muscle cells; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; Hmox-1, heme oxygenase 1; GSDMD, gasdermin D; GSDMB, gasdermin B; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family-pyrin domain-containing 3; ET-1, endothelin-1; ETRA, endothelin receptor type A; ROS, reactive oxygen species; MMP, matrix metalloproteinase; ERK, extracellular regulated protein kinases; p38, p38 mitogen-activated protein kinase; TLR4, toll-like receptor 4; mtROS, mitochondrial ROS; AT1R, angiotensin II type 1 receptor; AIM2, absent in melanoma 2; HMGB1, high mobility group box 1; PVT1, plasmacytoma variant translocation 1; TRAF6, tumor necrosis factor receptor-associated factor 6; THP-1, T-helper cell line 1; RAW264.7, mouse mononuclear macrophage leukemia cells; α7nAChR, α7 nicotinic acetylcholine receptor; TXNIP, thioredoxin-interacting protein; Drp1, dynamin-related protein 1; CD95, cluster of differentiation 95; CD95L, cluster of differentiation 95 ligand; CB1, cannabinoid receptor 1; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CXCL8, C-X-C motif chemokine ligand 8; PI3Kγ, phosphatidylinositol 3-kinase γ; CARMA3, caspase recruitment domain family member 10; P2X7, purinergic receptor p2x-ligand-gated ion channel 7; KLF4, kruppel-like factor 4; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; miR, microRNA.

cleavage) and necroptosis (mixed lineage kinase domain-like protein phosphorylation) have been detected concurrently in VSMCs (53,93,94). Complex molecular crosstalk occurs among these pathways. The coexistence and interaction of these death mechanisms likely synergistically amplify VSMC loss and inflammatory responses, thereby accelerating aneurysmal progression. The differences and connections between them will be elaborated later in the review.

Non-redundant and central role of GSDMD in AAs. Studies have indicated that cell-specific deletion of GSDMD in either VSMCs or macrophages ameliorates AAA development and progression (74,86). In various AAA induction models, $Gsdmd^{-/-}$ mice consistently exhibited significant and concordant protective effects. Specifically, VSMC-specific GSDMD knockout substantially attenuated aneurysm formation, aortic dilation, VSMC death, inflammatory responses and ECM degradation (74). Research by Ye *et al* (86) further confirmed that macrophage-specific GSDMD deletion also delayed mouse AAA progression (86). These genetic findings are strongly supported by pharmacological interventions: Compounds that specifically inhibit GSDMD pore formation or oligomerization confer therapeutic benefits in AAA mouse models (65). Together, these results underscore GSDMD as a highly attractive and precise therapeutic target for inhibiting pyroptosis in aneurysms.

GSDMD plays a uniquely destructive role in aneurysms, as its ability to mediate pyroptosis is rapid and lytic. Although VSMCs in AAs may be exposed to multiple cell death signals, GSDMD-driven pyroptosis is rapid and lytic, causing complete cellular disintegration and the rapid release of cellular contents. By contrast, apoptosis is generally slower and non-lytic (via phagocytic clearance) and tends to be anti-inflammatory or immunologically silent (12,95). Thus, pyroptosis poses a greater threat due to its acute and inflammatory nature, leading to a substantial net loss of structural cells. Furthermore, as a 'master switch' that initiates and amplifies lethal inflammatory storms, the GSDMD pore-mediated release of inflammatory mediators occurs explosively and at high local concentrations, resulting in a proinflammatory effect far exceeding that of other secretory mechanisms (96). As previously discussed, these mediators further amplify inflammatory signaling and cellular damage (97). Consequently, GSDMD pores essentially control the release of the most potent initial triggers (IL-1β/IL-18) and critical DAMPs in the pro-aneurysmal inflammatory cascade (86). Without GSDMD pore formation, even upon upstream inflammasome activation, the release efficiency of these key factors is substantially compromised, resulting in a failure to ignite or sustain the intense inflammatory storm necessary for driving aneurysm progression (98,99). This establishes GSDMD as an indispensable hub and amplifier connecting upstream danger sensing (inflammasome activation) with widespread downstream inflammatory destruction (immune cell infiltration, activation and cytokine storm).

Beyond GSDMD: Potential roles of other GSDM members in AA. In addition to GSDMD, other GSDM family members, notably GSDMB and GSDME, and potentially GSDMA/GSDMC, have been implicated as pyroptotic executors in aneurysmal vascular remodeling processes (64,100,101).

These paralogs share a common execution mechanism, yet their upstream activating signals are markedly different. GSDMB is cleaved by lymphocyte-derived GzmA at Lys244 and is upregulated in human AAA tissues in parallel with caspase-4 (102). A functional study has demonstrated that GSDMB knockdown attenuates macrophage pyroptosis via the mitochondrial ROS (mtROS)-dynamin-related protein 1 (Drp1)-caspase-4 axis, subsequently suppressing VSMC phenotypic switching and apoptosis, and implicating GSDMB in AA pathogenesis through immune-VSMC crosstalk (64). By contrast, GSDME activation is intimately linked to the apoptosis-pyroptosis continuum: In both human and murine aneurysmal tissues, GSDME mediates non-canonical pyroptosis and modulates inflammatory responses and senescence following VSMC phenotypic transition (100). Moreover, AMP-activated protein kinase-mediated phosphorylation of GSDME suppresses its proinflammatory activity, revealing a regulatory interface between metabolic homeostasis and cell death (103). Although direct evidence linking GSDMA or GSDMC to AAs is currently lacking, their non-canonical activation mechanisms in other systems, including streptococcal toxin-mediated GSDMA cleavage and GzmB-induced GSDMC pyroptosis in melanoma cells, offer exciting clues for potential alternative activation pathways in the vasculature (104,105). Furthermore, the non-proteolytic activation modes observed in lower eukaryotes, such as dimer dissociation-dependent activation of Tricho-GSDMs in *Trichoplax adhaerens*, suggest at an even broader diversity of GSDM regulatory mechanisms that may extend beyond current paradigms (106).

At the cellular level, emerging evidence has revealed a preliminary division of labor among GSDM family members within the aortic wall. GSDMD is ubiquitously expressed in macrophages, T lymphocytes, VSMCs and ECs, and functions as a multilineage pyroptosis executor (65,74,86,107). GSDMB is predominantly enriched in macrophages, indirectly shaping VSMC fate through immune modulation (64), and GSDME is preferentially upregulated in VSMCs, potentially serving as a molecular switch that governs the apoptosis-pyroptosis transition (100). This functional segregation suggests that GSDMD and GSDMB may synergistically orchestrate immune defense in AAs, whereas GSDME governs VSMC death modality decisions. Although direct evidence for functional redundancy or complementarity among GSDM members remains elusive, these observations provide a conceptual framework for deciphering the spatiotemporal coordination of multicellular and multipathway death programs during AA progression.

Distinction of pyroptosis from other regulated cell death pathways in AA. As aforementioned, AA progression involves the concurrent or competing activation of multiple regulated cell death pathways, among which pyroptosis, apoptosis, necroptosis and ferroptosis exhibit distinct triggers, execution mechanisms, inflammatory consequences and cell-type preferences, collectively constituting a complex regulatory network that governs vascular cell fate.

Pyroptosis, the central focus of this review, has previously been characterized in detail in AAs. By contrast, apoptosis plays a dual role in AA pathobiology that is highly context dependent. As a non-lytic death modality, apoptosis is initiated

by intrinsic mitochondrial pathways (Bcl-2 associated X protein/Bcl-2 antagonist/killer 1-caspase-9) or extrinsic death receptor pathways [fas cell surface death receptor (Fas)-fas ligand-caspase-8], culminating in caspase-3/7-mediated cellular dismantling and phagocytic clearance without eliciting inflammation (108-110). During early AA formation, physiological apoptosis contributes to vascular remodeling; however, in progressive stages, excessive VSMC apoptosis leads to medial thinning and elastic fiber depletion, whereas uncleared macrophage apoptosis may undergo secondary necrosis, exacerbating local inflammation (111). Notably, apoptosis-pyroptosis transformation has recently garnered attention. For instance, caspase-8 can initiate apoptosis and under certain conditions, cleave GSDMD or activate NLRP3. Apoptotic bodies generated during apoptosis may be phagocytosed by macrophages, triggering further inflammation and pyroptosis. In addition, cytokines released during pyroptosis can induce apoptosis in neighboring cells (112,113). This mechanism was preliminarily validated in aneurysmal VSMCs (64).

Necroptosis, a prototypical type of necrosis pathway, is triggered by death receptors (tumor necrosis factor receptor 1 and Fas) or PRRs (TLR3/4) under conditions of caspase-8 inhibition, which are executed via the receptor interacting serine/threonine kinase 1 (RIPK1)-RIPK3-mixed lineage kinase domain-like cascade to form plasma membrane pores and release cellular contents, with the intensity of inflammation intermediate between that of apoptosis and pyroptosis (114,115). In AAs, necroptosis has been documented in both macrophages and VSMCs and is associated with MMP activation and vascular wall remodeling (116). However, its shared upstream signals with pyroptosis (for example, RIPK1 involvement in inflammasome regulation) and similar lytic morphology suggest potential functional overlap or compensatory mechanisms.

Ferroptosis is characterized by iron-dependent lipid peroxidation, resulting from inactivation of the system X_c^-/glutathione/glutathione peroxidase 4 antioxidant axis or disruption of the ferroptosis suppressor protein 1/CoEnzyme Q10 pathway (117-120). Morphologically, it features mitochondrial shrinkage with initially preserved plasma membrane integrity, culminating in membrane rupture and the release of DAMPs (121). In AAs, iron deposition and lipid peroxidation products are markedly elevated; VSMC ferroptosis has been shown to be involved in medial degeneration and potentially cross talks with pyroptosis. Ferroptosis-derived lipid peroxides activate the NLRP3 inflammasome, while pyroptosis-released heme exacerbates iron overload (122).

In summary, in the aneurysmal context, pyroptosis, apoptosis, necroptosis and ferroptosis do not occur in isolation but instead form an integrated programmed cell death network through shared triggers, competition for caspase resources and reciprocal modulation of inflammatory outputs. Pyroptosis is a network hub with a potent proinflammatory capacity; apoptosis promotes basal cellular turnover but can be switched to pyroptosis to amplify pathology, while necroptosis serves as an alternative lytic pathway when caspases are compromised, and ferroptosis is involved in positive feedback with pyroptosis through lipid peroxidation and oxidative stress. The cell-type preferences, temporal dynamics and functional consequences of these four death modalities in AAs are summarized comparatively in Table II (38,86,122-132).

Upstream signaling regulation of pyroptotic pathways in AA. The initiation of pyroptosis in AAs is governed by a multilayered network of upstream signaling cascades (Fig. 3). This architecture can be deconstructed into four hierarchical tiers, including the triggering level, transduction level, effector level and regulatory level. At the triggering level, a repertoire of membrane receptors, including α7 nicotinic acetylcholine receptor (α7nAChR), cannabinoid receptor type 1, P2X7, endothelin receptor type A and Ang II's type 1 receptor, senses danger signals within the aneurysmal microenvironment (55,57,62,67,72). At the transduction level, signals from receptors are transduced to the intracellular level via the modulation of key second messengers, such as cyclic adenosine monophosphate (cAMP)/protein kinase A, nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), p38 mitogen-activated protein kinase (p38)/extracellularly regulated protein kinases (ERK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 and Ca^{2+} influx. Next, these intracellular signals converge on the effector level, namely the NLRP3 inflammasome assembly (53-56,67,69,73). Parallel kinase pathways, such as p38/ERK and PI3K/AKT, are engaged by effectors such as caspase recruitment domain family member 10 deficiency, further amplifying inflammasome assembly and crosstalk with the endoplasmic reticulum and mitochondrial stress (71). Non-canonical pyroptosis in AAs involves caspase-4/11-mediated GSDMB/GSDMD cleavage, which is driven by the mtROS-Drp1 or PI3Kγ-cAMP axis (64,69). Superimposed upon this core cascade is the regulatory level mediated by epigenetic mechanisms, where lncRNAs (such as PVT1) and miRNAs (such as miR-186-5p, miR-146a-5p, miR-17-5p and miR-26a) fine-tune signaling intensity by targeting key nodal molecules, including tumor necrosis factor receptor-associated factor 6 (TRAF6), thioredoxin interacting protein, HMGB1 and krüppel-like factor 4 (63,70,73,85). Furthermore, the cluster of differentiation 95 ligand-cluster of differentiation 95 axis induces caspase-8-mediated pyroptosis, whereas the kelch-like ECH-associated protein 1-Nrf2 pathway provides antioxidative counter-regulation (53,66).

The aforementioned levels are illustrated by specific examples in AA; for example, at the triggering and signal transduction level, TRAF6 promotes macrophage pyroptosis and accelerates mouse AAAs through NLRP3 inflammasome engagement (61). The endothelin-1/Ca^{2+} axis similarly drives VSMC pyroptosis and mouse AAA formation via NLRP3 and GSDMD activation (55). Conversely, α7nAChR activation suppresses NLRP3 and GSDMD activity, limiting pyroptosis and attenuating mouse AAAs (62). At the regulatory level, exosomal miR-17-5p from adipose-derived mesenchymal stem cells alleviates mouse AAAs by inhibiting thioredoxin-interacting protein-NLRP3 signaling and GSDMD-NT expression (63).

Collectively, these intertwined upstream signals precisely orchestrate canonical and non-canonical pyroptosis pathways in vascular cells, fueling the sustained inflammation and

Table II. Distinction of regulated cell death in AA.

Parameter	Pyroptosis	Apoptosis	Necroptosis	Ferroptosis	(Refs.)
Main triggers	PAMPs/DAMPs; pathogenic infection	TNFR; DNA damage; growth factor withdrawal	TNFR1; TLR	Cystine deficiency; GPX4 inactivation; iron overload	(123,124)
Key molecules	Caspase-1/4/5/11; GSDMD/ GADMB/GSDME	Caspase-3/6/7/8/9; Bax/Bak	RIPK1; RIPK3; MLKL	GPX4; FSP1	(123)
Plasma membrane integrity	Early rupture (GSDM pores)	Maintained until phagocytosis	Early rupture (MLKL pores)	Early rupture (lipid peroxidation)	(38,125,126)
Morphological features	Cell swelling; plasma membrane pores	Cell shrinkage; nuclear fragmentation; apoptotic bodies	Plasma membrane rupture; moderate chromatin condensation	Mitochondrial shrinkage; outer membrane rupture	(127)
Inflammatory response	Strongly pro-inflammatory (release of IL-1β, IL-18, DAMPs); neutrophil recruitment	Non/low-inflammatory	Moderately pro-inflammatory (DAMP release)	Pro-inflammatory (DAMP release)	(127)
Potential role in AA	Drives inflammatory death of macrophages and VSMCs, amplifies immune responses, promotes medial degeneration	Contributes to vascular remodeling in early stages; excessive VSMC apoptosis leads to medial thinning; defective macrophage clearance may lead to secondary necrosis	Compensatory activation when caspase activity is inhibited; mediates VSMC and macrophage death; promotes MMP release	VSMC ferroptosis contributes to medial degeneration, forming a vicious cycle with oxidative stress	(86,128-130)
Interplay with pyroptosis	-	Convertible: Caspase-3 cleaves GSDME, switching apoptosis to pyroptosis	Parallel or compensatory: RIPK1 induces NLRP3 activation; may serve as alternative lytic pathway	Synergistic amplification: Lipid peroxides activate NLRP3; pyroptosis-released heme exacerbates iron overload	(122,131, 132)

PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TNFR, tumor necrosis factor receptor; TNFR1, tumor necrosis factor receptor 1; TLR, Toll-like receptor; caspase, cysteine-aspartic protease; GSDM, gasdermin; Bax, Bcl-2-associated X protein; Bak, Bcl-2 antagonist/killer; RIPK1, receptor-interacting protein kinase 1; RIPK3, receptor-interacting protein kinase 3; MLKL, mixed lineage kinase domain-like protein; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; NLRP3, NOD-like receptor family-pyrin domain-containing 3; IL-1β, interleukin-1β; IL-18, interleukin-18; VSMC, vascular smooth muscle cell; MMP, matrix metalloproteinase; AA, aortic aneurysm.

matrix degradation that characterize aneurysm progression. Related studies are shown in Table I (53-73).

4. Medicinal chemistry strategies for targeting pyroptosis in AAs

Given the central role of pyroptosis in AAs, the development of specific inhibitors has emerged as a promising therapeutic frontier. The pathway offers multiple nodes for pharmacological intervention, from upstream sensors to downstream inflammatory effectors (Fig. 2; Table III) (54,65,66,133-151). This section will systematically review these strategies and evaluate the mechanisms, advantages and limitations of their main representative compounds from the perspective of medicinal chemistry.

Targeting inflammasome assembly and activation. Inflammasomes, particularly NLRP3, are attractive upstream targets.

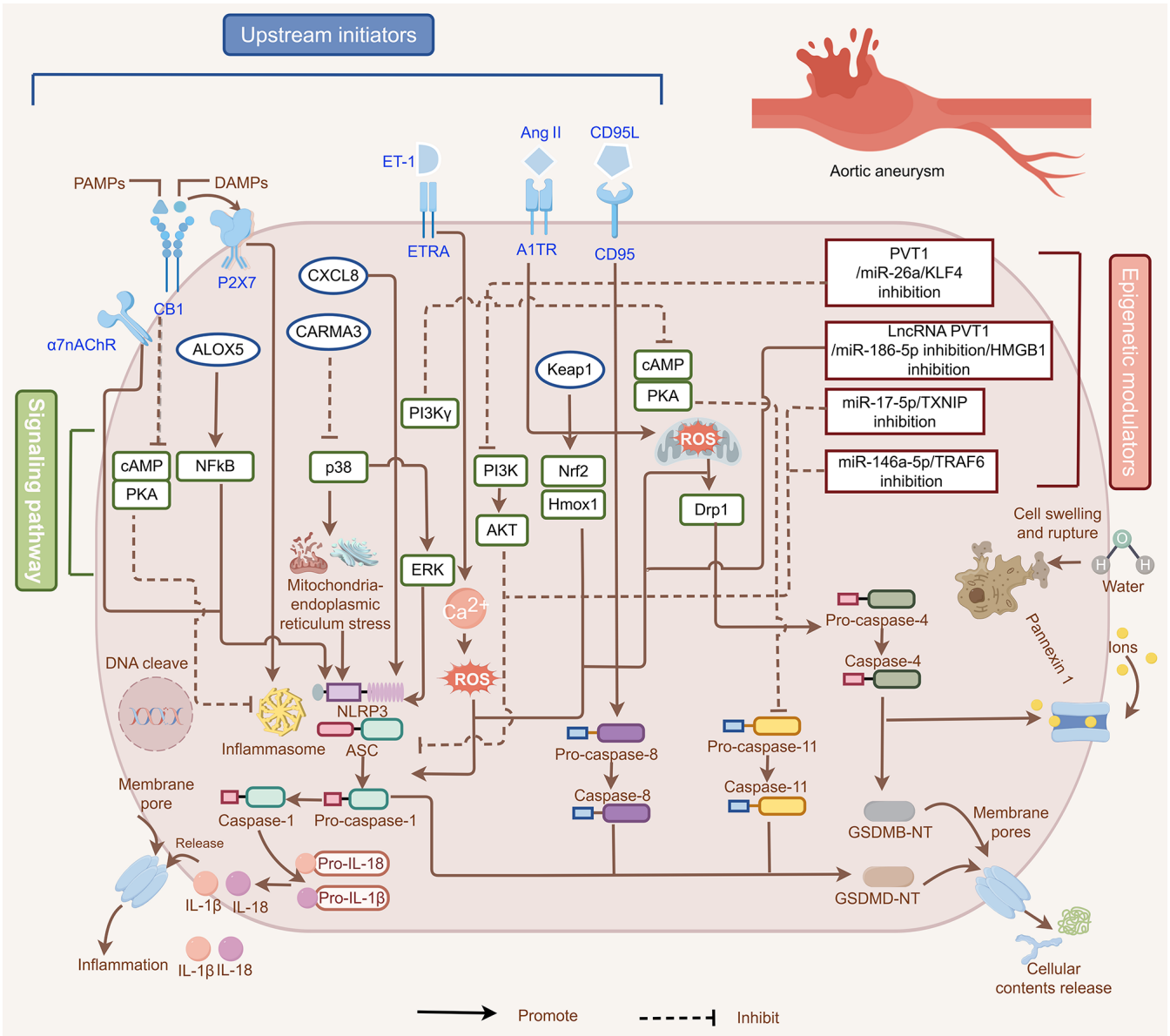

Figure 3. Upstream regulation signaling of pyroptotic pathways in AA. Diverse upstream initiators activate specific signaling pathways, while epigenetic modulators fine-tune the process. These signals converge on NLRP3 inflammasome-induced canonical pyroptosis or caspase4/11-induced non-canonical pyroptosis activation, triggering the execution phase characterized by GSDMD or GSDMB cleavage. This leads to pyroptotic cell death, inflammation and ultimately, aneurysm progression. The solid arrows represent promoting effects, while the dotted short horizontal lines indicate inhibitory effects. Created with Figdraw.com. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; ET-1, endothelin-1; AnGII; angiotensin II; CD95L, cluster of differentiation 95 ligand; 7nAChR, α7 nicotinic acetylcholine receptor; CB1, cannabinoid receptor 1; P2X7, purinergic receptor p2x-ligand-gated ion channel 7; ETRA, endothelin receptor type A; AT1R, angiotensin II type 1 receptor; CD95, cluster of differentiation 95; ALOX5, arachidonate 5-lipoxygenase; CARMA3, caspase recruitment domain family member 10; CXCL8, C-X-C motif chemokine ligand 8; Keap1, Kelch-like ECH-associated protein 1; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; p38, p38 mitogen-activated protein kinase; PI3Kγ, phosphatidylinositol 3-kinase γ; ERK, extracellular regulated protein kinases; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Nrf2, nuclear factor erythroid 2-related factor 2; Hmox-1, heme oxygenase 1; ROS, reactive oxygen species; Drp1, dynamin-related protein 1; NLRP3, NOD-like receptor family-pyrin domain-containing 3; ASC, apoptosis-associated speck-like protein; Caspase-1/4//8/11, cysteine-aspartic protease 1/4//8/11; Pro-caspase-1/4//8/11, cysteine-aspartic protease 1/4//8/11, precursor of cysteine-aspartic protease 1/4//8/11; IL-1β, interleukin-1 beta; IL-18, interleukin-18; GSDMD, gasdermin D N-terminal; GSDMB, gasdermin B N-terminal; PVT1, plasmacytoma variant translocation 1; KLF4, kruppel-like factor 4; HMGB1, high mobility group box 1; TXNIP, thioredoxin-interacting protein; TRAF6, tumor necrosis factor receptor-associated factor 6; miR-26a, microRNA-26a; miR-186-5p, microRNA-186-5p; miR-17-5p, microRNA-17-5p; miR-146-5p, microRNA-146-5p.

NLRP3 inhibitors. MCC950 is a potent and selective small-molecule inhibitor of NLRP3; it binds to the NACHT domain of NLRP3, inhibiting its ATPase activity and thereby preventing inflammasome oligomerization and activation (152). Notably, MCC950 suppresses NLRP3 activation through both canonical and non-canonical pathways (153). In apolipoprotein E-deficient (ApoE$^{-/-}$) mice fed a Western diet, MCC950 delayed atherosclerosis progression and reduced IL-1β and IL-18 secretion (133). Although direct evidence in AA models needs accumulation, its potent anti-inflammatory effects suggest considerable therapeutic potential in AAs, including the alleviation of vascular inflammation and

Table III. Potential therapies targeting pyroptosis for AA.

Targets and agents	Disease model	Findings	(Refs.)
NLRP3			
MCC950	Atherosclerosis in mouse	Reduces plaque size and plaque volume	(133)
CY-09	Aortic valve stenosis and calcification in mouse	Improves aortic valve function and reduces valve calcification deposition	(134)
MNS	Burn/trauma in mouse	Ameliorates burn wound progression and promotes wound healing	(135)
Curcumin	Aortic valve stenosis and calcification in mouse	Reduces atherosclerotic plaque area, plaque cap thickness and blood lipid levels	(136)
AIM2			
Pristimerin	Tendinopathy in mouse	Alleviates the progression of tendinopathy	(137)
Caspase-1			
VX-765	Atherosclerosis in mouse	Reduces lipid burden	(138)
	Vascular calcification in chronic kidney disease rats	Decreases calcified vascular tissue	(139)
	Acute myocardial infarction in mouse	Alleviates hypoxia-induced inflammation	(140)
Ac-YVAD-CHO	Endotoxemia in rats	Reduces the release of proinflammatory mediators	(141)
Caspase-4/11			
ox-PAPC	Septic shock in macrophages	Inhibits LPS-induced pyroptosis	(142)
Caspase-1/4/5/11			
SERPINB1	Cardiac hypertrophy in mouse	Attenuates cardiac remodeling	(143)
Caspase-8			
Z-IETD-FMK	AAA in mouse	Blocks aneurysm development	(66)
GSDMD			
NSA	AAA in mouse	Preserves aortic structural integrity	(65)
DSF	AAA in mouse	Ameliorates collagen deposition and elastin degradation	(54)
DMF	AAA and TAD in mouse	Improves the stretchability of the aortic wall	(144)
Itaconate	AAA in mouse	Suppresses AAA formation	(145)
C202-2729	Endotoxin shock and EAE mouse	Suppressed macrophage and T cell-associated immune inflammation	(146)
Caffeic acid	LPS-challenged mice	Alleviates sepsis	(147)
IL-1β receptor			
Anakinra	Sepsis patients with features of macrophage activation syndrome	Improve survival of patients with sepsis and concurrent hepatobiliary dysfunction/disseminated intravascular coagulation	(148)
IL-1β			
Canakinumab	People with previous myocardial infarction	Reduces recurrent cardiovascular events	(149)
IL-1β and IL-1α			
Goflikicept	People with idiopathic recurrent pericarditis	Reduces the risk of recurrent pericarditis	(150)
IL-18			
IL-18BP	Autoimmune diabetes in NOD mice	Reduced the cumulative incidence of diabetes	(151)

AA, aortic aneurysm; NLRP3, NOD-like receptor family-pyrin domain-containing 3; MCC950, 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[4-(2-hydroxypropan-2-yl)furan-2-yl]sulfonylurea; CY-09, 4-[[4-Oxo-2-thioxo-3-[[3-(trifluoromethyl)phenyl]methyl]-5-thiazolidinylidene]methyl]benzoic acid; MNS, 3,4-Methylenedioxy-β-nitrostyrene; AIM2, absent in melanoma 2; Caspase-1/4/5/8/11, cysteine-aspartic protease 1/4/5/8/11; VX-765, (S)-1-((S)-2-{[1-(4-Amino-3-chlorophenyl)methanoyl]amino}-3,3-dimethylbutanoyl)pyrrolidine-2-carboxylicacid((2R,3S)-2-ethoxy-5-oxotetrahydrofuran-3-yl)amide; Ac-YVAD-CHO, N-Acetyl-L-tyrosyl-L-valyl-N-[(1S)-2-carboxy-1-formylethyl]-L-alaninamide; ox-PAPC, oxidized 1-palmitoyl-2-arachidonyl-phosphatidylcholine; SERPINB1, serine protease inhibitor clade B member 1; Z-IETD-FMK, benzyloxycarbonyl-Ile-Glu(OMe)-Thr-Asp(OMe)-fluoromethylketone; GSDMD, gasdermin D; NSA, necrosulfonamide; DSF, disulfiram; DMF, dimethyl fumarate; LPS, lipopolysaccharide; AAA, abdominal aortic aneurysm; TAD, thoracic aortic dissection; C202-2729, a GSDMD N-terminal inhibitor; EAE, experimental autoimmune encephalomyelitis; IL-1β, interleukin-1 beta; IL-1α, interleukin-1 alpha; IL-18, interleukin-18; IL-18BP, interleukin-18 binding protein; NOD, non-obese diabetic.

VSMC dysfunction. MCC950 has entered clinical trials for several autoinflammatory diseases; however, its development was halted in one trial due to hepatotoxicity, and structural optimization efforts are ongoing to improve its safety profile (154-156). Similar to MCC950, CY-09 and 3,4-methylenedioxy-β-nitrostyrene (MNS) also bind directly to the NACHT domain of NLRP3, competitively inhibiting ATP binding and blocking NLRP3 activation (134,157). CY-09 has been shown to alleviate aortic valve stenosis and calcification by suppressing proinflammatory cytokine expression through NLRP3 inhibition, whereas MNS improved outcomes in murine colitis (134,157). The natural compound curcumin modulates NLRP3 inflammasome activation by regulating NF-κB signaling, attenuating K^+ efflux, blocking Ca^{2+} influx and preventing ASC oligomerization with NLRP3, and has been demonstrated to reduce endothelial damage and atherosclerosis in mice (136,158).

Targeting other inflammasomes. Beyond NLRP3, specific inhibitors for AIM2 or NLRC4 are less developed but represent a future direction. For instance, pristimerin has been shown to inhibit AIM2 and ameliorate tendonopathy in mice (137).

Targeting inflammatory caspases. Direct caspase inhibition provides a strategy to block pyroptosis execution.

Caspase-1 inhibitors. VX-765 is an orally bioavailable, reversible and selective caspase-1 inhibitor; it is a prodrug that is hydrolyzed *in vivo* to its active form, VRT-043198 (159). By inhibiting caspase-1, VX-765 reduces the production of IL-1β and IL-18, thereby mitigating inflammatory tissue damage. Li *et al* (138) demonstrated that VX-765 attenuated plaque formation and inflammation in an atherosclerosis model. In a vascular calcification model, it alleviated VSMC calcification via suppression of STAT3 signaling (139). Moreover, VX-765 protects against acute myocardial infarction by mitigating pyroptosis, hypoxia-induced cardiomyocyte injury, oxidative stress, apoptosis and inflammation (140). These findings suggest its potential benefit in AA-related vascular remodeling. Notably, VX-765 has been evaluated in clinical trials for psoriasis (NCT00205465) and epilepsy (NCT01048255; EudraCT 2011-004156-19), although its long-term use may raise safety concerns.

Other caspase-1 inhibitors also represent promising therapeutic candidates. For instance, Ac-YVAD-CHO is a peptide-based irreversible caspase-1 inhibitor widely used in basic research; it reduces the plasma levels of the caspase-1-dependent cytokines IL-1β and IL-18 in endotoxemic rats. Inhalation of Ac-YVAD-CHO concurrently downregulates inducible nitric oxide synthase gene expression in alveolar macrophages and cyclooxygenase-2 expression in lung tissues, supporting the potential of inhaled caspase inhibitors for treating inflammatory diseases (141). However, owing to its peptide nature, Ac-YVAD-CHO has poor pharmacokinetic properties and is unsuitable for systemic administration, although it serves as a valuable lead compound for inhibitor design.

Caspase-4/5/11 inhibitors. Targeting caspases involved in the non-canonical pyroptosis pathway is an emerging area of research. Several molecules have been reported to directly bind and inhibit caspase-4/11. For instance, oxidized 1-palmitoyl-2-arachidonyl-phosphatidylcholine binds directly to caspase-4/11, competing with LPS to suppress pyroptosis, IL-1β release and septic shock (142). However, its potential as a drug candidate remains limited. Serine protease inhibitor B1 (SERPINB1) functions as a critical endogenous inhibitor of pyroptosis; its suppression promotes spontaneous activation of caspase-1/4/5/11, while its presence helps minimize inflammatory damage (160). Specifically, SERPINB1 restricts caspase activity by inhibiting CARD oligomerization and enzymatic activation. Choi *et al* (160) demonstrated that its C-terminal CARD-binding motif suppresses the activation of pro-caspase-1/4/5/10. Furthermore, a study has indicated that SERPINB1 attenuates pathological cardiac hypertrophy and remodeling through its antipyroptotic effects (143). These findings offer a rationale for the development of novel inhibitors that mimic this mechanism.

Other caspase inhibitors. Additional inhibitors targeting caspases implicated in pyroptosis include Ac-DEVD-CHO, caspase-6b and Z-IETD-FMK.

Ac-DEVD-CHO is a specific caspase-3 inhibitor that suppresses endothelial apoptosis and promotes cerebrovascular spasms. Zhou *et al* (161) demonstrated that selective caspase-3 inhibition blocks downstream signaling of caspase-8, even when caspase-8 is activated within the caspase cascade. Caspase-6b, an isoform generated by alternative splicing of the melanin-concentrating hormone receptor 2 gene, acts as a natural caspase-6-specific inhibitor; it selectively prevents caspase-6 autoactivation without affecting its preactivated form (162).

Z-IETD-FMK is a broad-spectrum, irreversible caspase inhibitor commonly used in scientific research; it mitigates the interplay between NLRP3 inflammasome activation, pyroptosis and apoptosis, thereby conferring protection against oxidative stress-induced lung injury (163). In a $CaCl_2$-induced mouse AAA model, intraperitoneal administration of Z-IETD-FMK reduced the incidence of AAAs. This protective effect is attributed to the role of the CD95/CD95L system in recruiting inflammatory cells to injury sites and promoting the phenotypic switching of aortic smooth muscle cells via caspase-8 signaling, processes that are involved in AAA pathogenesis (66). However, owing to its lack of selectivity and associated toxicity, Z-IETD-FMK is unsuitable for clinical use.

Targeting the core executor GSDMD. Directly inhibiting GSDMD pore formation is considered a highly specific strategy that potentially blocks pathological inflammation while sparing upstream immune surveillance.

Covalent inhibitors. These inhibitors function by covalently modifying specific cysteine residues on GSDMD, thereby blocking its oligomerization and pore formation.

Necrosulfonamide (NSA) covalently binds to GSDMD (Cys191/Cys192 in humans/mice) to inhibit oligomerization and pore formation, thereby inhibiting inflammasome-dependent pyroptosis (164). A distinctive feature of NSA is its ability to directly target GSDMD while preserving other cell death pathways, such as those involved in TLR signaling-mediated cell death (165). However, studies indicate that it also impedes inflammasome priming and caspase-1 activation (166-168).

Owing to its extreme hydrophobicity and immunocyte toxicity, NSA exhibits unfavorable pharmacokinetics *in vivo*. To address this limitation, Boersma *et al* (169) developed a porous nanoparticle-based delivery system for targeted NSA delivery to phagocytes, improving its targeting and safety. Recent evidence has demonstrated that NSA ameliorates Ang II-induced AAA progression in ApoE$^{-/-}$ mice (65).

Disulfiram (DSF), a Food and Drug Administration-approved drug for alcohol dependence, is metabolized *in vivo* to S-methyl-N, N-diethylthiocarbamate sulfoxide, which covalently modifies GSDMD at Cys191/Cys192, effectively inhibiting pore formation (170). DSF significantly reduces IL-1β secretion from activated macrophages and attenuates systemic inflammatory responses (171). Liao *et al* (54) reported that oral DSF administration in Ang II-infused mice reduces AAA incidence while ameliorating collagen deposition and elastin degradation within the aortic wall. The repurposing potential of DSF supports its rapid clinical translation. However, its multitarget nature, including inhibition of aldehyde dehydrogenase, may lead to off-target effects, necessitating careful dose and indication exploration.

Dimethyl fumarate (DMF), a drug used for multiple sclerosis, inhibits pyroptosis by succinylating GSDMD at Cys192, thereby blocking its processing and oligomerization (172). Wang *et al* (144) reported that DMF restored v-src sarcoma/focal adhesion kinase signaling and collagen transport in aortic VSMCs, and mitigated aortic injury in mouse aneurysm and dissection models. As an approved drug, DMF has a well-established safety profile, facilitating its translational research in AAs.

Itaconate and its derivatives function as potent cysteine modifiers (173). GSDMD Cys77 is the modification target of itaconate. Bambouskova *et al* (174) demonstrated that endogenous itaconate post-translationally modifies GSDMD to prevent its processing and inhibit pyroptosis. Moreover, itaconate also protects against AAA formation by inducing and activating Nrf2 expression (145).

Non-covalent inhibitors and natural compounds. Additional non-covalent inhibitors and natural compounds suppress pyroptosis by blocking GSDMD pore formation. C202-2729, a small molecule identified through high-throughput screening, non-covalently binds to the GSDMD N-terminal domain, preventing its membrane association and pore formation. C202-2729 has demonstrated efficacy in a sepsis model (146). Caffeic acid, a natural phenolic compound found in coffee and various fruits and vegetables, inhibits lipoxygenase activity and has antioxidant and anti-inflammatory effects (175); it has been shown to bind GSDMD and inhibit its cleavage by caspase-1, thereby reducing pyroptosis (147).

Mechanistic and translational differences between covalent and non-covalent inhibitors. The two strategies targeting GSDMD possess distinct pharmacological profiles and clinical applications (176). Covalent inhibitors irreversibly modify active site cysteines to block pore formation, offering potent and sustained inhibition suitable for acute inflammatory conditions (165,177). However, their broad-spectrum electrophilic nature confers off-target effects, and irreversible modification may increase their immunogenicity (176,178). Non-covalent inhibitors reversibly bind the GSDMD N-terminal domain through conformational complementarity, theoretically providing higher selectivity and lower off-target toxicity, making them preferable for chronic disease intervention (179,180). However, their efficacy is highly dependent on target conformational stability; activation-induced conformational rearrangements may diminish binding affinity, posing challenges for *in vivo* persistence (181).

From a translational perspective, strategy selection should align with therapeutic windows. Acute progressive stages in AAs warrant covalent inhibitors with targeted delivery to mitigate off-target effects. Chronic settings favor non-covalent inhibitors with optimized pharmacokinetics through medicinal chemistry. Future directions include integrating both approaches, namely, the development of reversible covalent modifiers or non-covalent inhibitors targeting intermediate GSDMD conformations.

Targeting downstream inflammatory cytokines. Given that the detrimental effects of pyroptosis largely result from the release of IL-1β and IL-18, directly neutralizing these cytokines represents another effective therapeutic strategy.

Anakinra, a recombinant IL-1 receptor antagonist, blocks the signaling of both IL-1α and IL-1β; its efficacy has been demonstrated in macrophage activation syndrome with markedly elevated IL-18 levels, and it is already used to treat autoinflammatory diseases (148). Canakinumab is a humanized monoclonal antibody against IL-1β. In a randomized trial involving postmyocardial infarction patients conducted by Ridker *et al* (149), canakinumab markedly reduced cardiovascular events, providing strong clinical evidence for the role of IL-1β in human vascular disease. Additionally, the IL-1 inhibitor goflikicept notably reduced recurrence rates in idiopathic recurrent pericarditis and improved patient quality of life (150). These findings indirectly support the therapeutic potential of IL-1-targeting agents in AAs. IL-18 binding protein, a natural inhibitor of IL-18, is also under development as a recombinant therapeutic.

Each of the aforementioned strategies presents distinct advantages and limitations. Upstream inhibitors (for example, MCC950) may broadly suppress multiple downstream effects but risk interfering with essential host defense mechanisms. Downstream cytokine inhibitors (for example, canakinumab) have well-defined targets but are often costly and require parenteral administration. Direct targeting of GSDMD is regarded as a strategy to precisely 'defuse the bomb', blocking pathological lytic cell death and inflammatory release while potentially preserving upstream immune sensing functions. This approach has thus become a major focus in contemporary medicinal chemistry.

5. Challenges and future perspectives

Targeting pyroptosis in AAs presents translational potential, yet several challenges remain. The predominant focus on GSDMD has also left other GSDM family members largely unexplored. Furthermore, the extensive crosstalk among pyroptosis, apoptosis and necroptosis is poorly understood; inhibiting one cell death pathway may trigger compensatory activation of another. The relative contributions of pyroptosis in VSMCs, macrophages and ECs to AA progression also require clarification to enable cell-specific targeting. Finally,

the specificity and long-term safety of pyroptosis inhibitors, particularly the risk of immunosuppression, warrant careful evaluation.

Current research is limited by an over-reliance on murine models and a paucity of human data for validation. Throughout this review, findings supported by direct evidence from human aneurysmal tissues have been distinguished from those inferred solely from animal studies. For instance, while GSDMD upregulation in macrophages within human AA tissues has been corroborated by multiple studies, the mechanism by which GSDMB regulates macrophage pyroptosis via the mtROS-Drp1-caspase-4 axis is currently largely determined through cellular experiments and murine models, with limited direct confirmation in human tissues. Similarly, although preliminary evidence has shown that GSDME-mediated apoptosis-to-pyroptosis switching occurs in both human and murine specimens, its upstream regulatory networks are derived predominantly from mouse genetic studies. The vast majority of mechanistic studies have employed Ang II-infused murine AAA models. While these models effectively recapitulate the inflammatory infiltration and VSMC loss observed in human AA, their disease progression timeline (days to weeks) fundamentally differs from that of the chronic, insidious course of human AAs (years to decades). Moreover, murine vascular wall biomechanics and immune microenvironments differ substantially from those of humans. Critically, intrinsic species differences in pyroptosis pathways must be acknowledged: In humans, non-canonical pyroptosis is mediated by caspase-4/5, whereas in mice, it relies on caspase-11; moreover, the tissue distribution and regulatory mechanisms of GSDM family members also exhibit interspecies variation. These differences suggest that the efficacy of pyroptosis inhibitors identified through murine screens (such as compounds targeting caspase-11) may show attenuated efficacy in humans due to the structural divergence in target proteins, and that the cell type-specific pyroptosis phenotypes observed in mice may not faithfully recapitulate human pathology. Therefore, future investigations must explicitly acknowledge the inferential nature of animal-derived data and incorporate human tissue validation as an essential component of mechanistic studies.

Future efforts should focus on the following: i) Deepening mechanistic insight. Single-cell and spatial transcriptomics of human AA specimens can be used to map all GSDMs and identify novel targets and subtypes. Proteomic approaches may identify specific pyroptosis-related biomarkers (for example, circulating GSDMD-NT) for diagnosis and monitoring. ii) Innovative drug development. Structure-based design should aim to develop more potent and selective GSDM inhibitors, such as non-covalent compounds or proteolysis-targeting chimeras. Chemical optimization of existing inhibitors (such as NSA) can improve pharmacokinetics, whereas nanoparticle-based or microenvironment-responsive delivery systems may enhance targeting and reduce systemic exposure. iii) Exploring combination therapies. Combining pyroptosis inhibitors with existing treatments (such as Ang II receptor blockers) may yield synergistic benefits. iv) Advancing clinical translation. The efficacy and safety of pyroptosis-targeting strategies should be rigorously evaluated in large animal models (for example, porcine or canine aneurysm models), whose vascular dimensions, hemodynamics and immune backgrounds more closely approximate human conditions. Concurrently, proof-of-concept clinical trials for repurposed drugs (such as DSF and DMF) incorporating pyroptosis biomarkers for patient stratification should be conducted, paving the way for precision medicine approaches.

6. Conclusion

Pyroptosis has firmly established its core role in the pathogenesis of AAs. By directly mediating the lytic death of VSMCs and initiating a powerful, self-amplifying inflammatory response, it acts as a key pathological engine driving AA initiation and progression. Multiple nodes in this signaling pathway, from the NLRP3 inflammasome to the final GSDMD pore, have been validated as effective intervention targets in preclinical models.

The present review, while summarizing existing knowledge, critically highlights the limited understanding of GSDM members beyond GSDMD, non-canonical pathways and complex intercellular cross-talk. From a medicinal chemistry perspective, various strategies have been systematically evaluated, with direct inhibition of the terminal executor GSDMD (for example, by DSF and DMF) emerging as a particularly attractive and precise therapeutic direction.

However, translating these promising targets into clinical reality faces hurdles, including understanding human disease heterogeneity, ensuring inhibitor specificity and safety, and managing long-term risks. Future research, integrating multiomics technologies, structural biology, nanotechnology and intelligent drug design, holds the promise of developing safer and more effective pyroptosis-targeted therapies. Ultimately, through well-designed clinical trials, these novel agents, either alone or in combination with existing strategies, may enable a paradigm shift from purely surgical repair to active pharmacological intervention, potentially improving the prognosis and reducing the societal burden of this devastating disease.

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Availability of data and materials

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Authors' contributions

JM drafted the original manuscript. ML conceptualized and designed the paper, provided the methodology, and reviewed and edited the manuscript. JM and ML used Figdraw.com and Biorender.com to create the figures. LR and CZ proposed the study concept, provided funding support, contributed to the interpretation of the literature and were involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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