

PYROPTOSIS

Regulated, inflammatory lytic cell death



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What defines pyroptosis?

Regulated initiation

Caspases mediate an intracellular death pathway.

Lytic execution

Gasdermin D pores culminate in membrane rupture.

Inflammatory output

IL-1 β and other mediators are released.

One process, two linked outcomes

Caspase-dependent GSDMD activation

Cell death

Membrane pores → osmotic
disturbance → rupture

Inflammation

IL-1 β and other mediators reach
extracellular tissue

Why “fiery death”?

- The prefix pyro refers to fever.
- A characteristic inflammatory output is interleukin-1 β (IL-1 β).
- The defining event is lytic cell death coupled to inflammatory mediator release.

Name describes the inflammatory phenotype—not a separate source of heat.

The microbial-infection context

Microbial material enters an infected cell



Intracellular sensing engages a pyroptotic route



Gasdermin pores develop



Infected cell dies and local inflammation follows

Physiologic defense and pathologic excess

Potential host defense

- Responds to intracellular microbial products
- Eliminates an infected cell by lysis
- Alerts adjacent tissue by mediator release

When exaggerated

- Inflammatory injury may become excessive
- Textbook links excess to sepsis
- Autoimmune inflammatory disease is another association

The regulated-cell-death landscape

Feature	Apoptosis	Necroptosis	Pyroptosis
Membrane fate	Usually preserved before clearance	Disrupted	Pore formation → rupture
Core machinery	Apoptotic caspases	RIPK1/RIPK3–MLKL	Inflammatory caspases–GSDMD
Typical reaction	Limited inflammation	Inflammatory lysis	Inflammatory lysis + cytokine release

Pyroptosis is not ordinary apoptosis

Apoptosis

- Cell shrinkage and chromatin condensation
- Apoptotic bodies are rapidly cleared
- Limited release of proinflammatory contents

Pyroptosis

- Membrane-perforating GSDMD oligomers
- Osmotic disturbance and cell rupture
- Inflammatory mediator release

Pyroptosis is not necroptosis

Mechanistic step	Necroptosis	Pyroptosis
Trigger context	TNFR1 or viral signals	Microbial sensing / cytosolic LPS
Activation arm	RIPK1–RIPK3	Caspase-1 or caspases-4/5
Membrane effector	MLKL	Gasdermin D
Shared result	Loss of membrane integrity	Loss of membrane integrity

Pyroptosis is not ferroptosis

Ferroptosis

- Iron-associated lipid peroxidation
- Failure of antioxidant defenses
- Membrane lipid injury dominates

Pyroptosis

- Caspase-dependent GSDMD cleavage
- Oligomeric protein pores
- Inflammatory mediator escape

The decisive questions

Recognition

What intracellular danger is detected?

Activation

Which caspase becomes active?

Execution

How does GSDMD form pores?

Outcome

How does membrane injury produce inflammation?

Two pathways, one membrane effector

Canonical

Inflammasome → caspase-1

Noncanonical

Cytosolic LPS → caspases-4/5

GSDMD cleavage

Oligomers → pores → lysis



Pattern-recognition receptors: The upstream logic

- Innate immunity recognizes conserved microbial structures (PAMPs).
- Injured and necrotic cells supply danger-associated signals (DAMPs).
- Receptors occupy membrane, endosomal and cytosolic compartments.

Intracellular location helps determine which danger-sensing pathways can engage.

PAMPs and DAMPs are not synonymous

PAMP

- Pathogen-associated molecular pattern
- Derived from microbes
- Signals invasion or microbial presence

DAMP

- Damage-associated molecular pattern
- Arises from injured or dying host cells
- Signals cellular damage

Why cytosolic recognition matters

Intracellular microbial products



Cytosolic innate immune receptors



Inflammasome activation (canonical route)



Caspase-1 → gasdermin pores

NOD-like receptors and the inflammasome

- NOD-like receptors (NLRs) are one family of cytosolic sensors.
- They detect microbial products and several signals of damage.
- Some NLRs activate a multiprotein inflammasome.
- The inflammasome activates caspase-1.

Signals recognized by NLRs

Microbial products

Foreign molecules in the cytosol

Damaged-cell ATP

Extracellular/injury-associated signal

Uric acid

Damage-associated substance

Reduced intracellular K⁺

Ionic perturbation associated with danger

Inflammasome: Functional architecture

Cytosolic sensor (e.g., NLRP3)



Adaptor component



Caspase-1 recruitment / activation



Maturation of IL-1 β and GSDMD cleavage

The three inflammasome modules

Sensor

Recognizes danger-associated signals

Adaptor

Supports multiprotein assembly

Caspase-1

Protease activated within the assembled complex

Caspase-1 is an inflammatory protease

Activated caspase-1

Cytokine processing

Pro-IL-1 β $\rightarrow$ mature IL-1 β

Membrane execution

Gasdermin D cleavage $\rightarrow$ pore
formation

Precursor and mature IL-1 β have distinct roles

Pro-IL-1 β precursor



Caspase-1-mediated proteolytic cleavage



Biologically active IL-1 β



Inflammatory signaling in surrounding tissue

IL-1 synthesis $\neq$ IL-1 maturation

Production of precursor

- Innate receptor stimulation induces IL-1 synthesis
- Builds a precursor cytokine pool
- Does not itself establish mature IL-1 activity

Proteolytic maturation

- Inflammasome activates caspase-1
- Caspase-1 processes the IL-1 precursor
- Active cytokine can participate in inflammation

Canonical pyroptosis: Pathway map

Microbial products sensed by cytosolic innate receptors



Inflammasome activation



Caspase-1 activation



GSDMD cleavage and IL-1 β processing



Membrane pores, inflammatory mediator release, lysis

Canonical initiation occurs inside the cell

- Microbial products enter infected cells.
- Cytoplasmic innate immune receptors recognize these products.
- Inflammasome formation links sensing to an active protease.

Canonical does not simply mean every extracellular bacterial stimulus.

Canonical pathway: Assembly before execution

Danger recognized



Inflammasome assembles



Caspase-1 becomes active



GSDMD acquires pore-forming activity

Canonical pathway produces two outputs

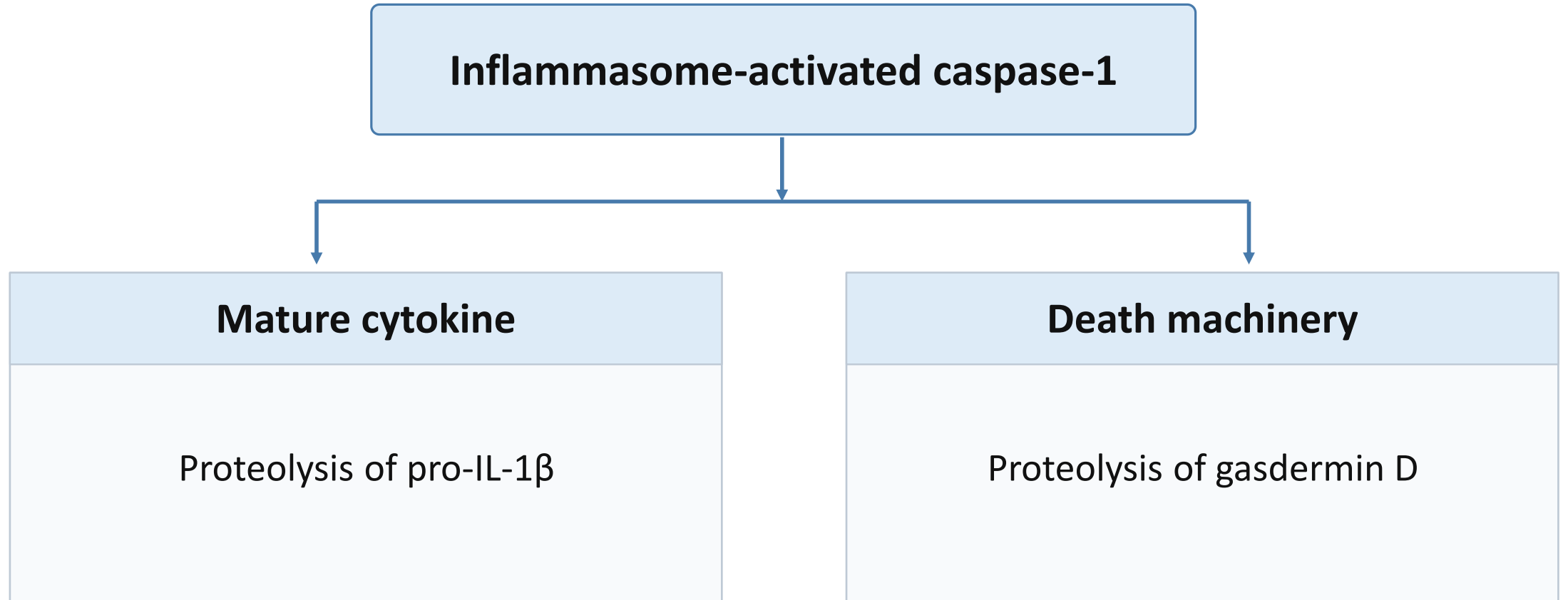
Inflammasome-activated caspase-1

Mature cytokine

Proteolysis of pro-IL-1 β

Death machinery

Proteolysis of gasdermin D



Canonical cytokine arm

Inactive IL-1 β precursor



Caspase-1 cleavage



Mature IL-1 β



Mediator release through pyroptotic membrane injury



Fever and leukocyte recruitment

Canonical membrane-injury arm

Caspase-1 active



GSDMD cleaved



GSDMD oligomerizes



Plasma membrane becomes porous



Osmotic imbalance → lytic death

Canonical case: Interpret the cascade

An infected cell detects a microbial product in its cytoplasm. A multiprotein inflammasome becomes active.

Which protease and membrane effector are expected?

Caspase-1; Cleavage and oligomerization of GSDMD.

The inflammasome engages caspase-1, which processes both IL-1 β precursor and GSDMD.

Noncanonical pyroptosis: Defining trigger

- The textbook specifies intracellular lipopolysaccharide (LPS).
- LPS is produced by gram-negative bacteria.
- This route activates caspases-4 and -5.
- These caspases cleave GSDMD.

Intracellular LPS as a danger signal

Gram-negative bacterial LPS



LPS present in the cytosolic compartment



Caspases-4/5 are activated



Gasdermin D is cleaved

Noncanonical activation bypasses the first canonical step

Canonical entry

- Innate cytosolic receptor sensing
- Multiprotein inflammasome
- Caspase-1 activation

Noncanonical entry

- Intracellular gram-negative LPS
- Caspases-4/5 activation
- Direct convergence on GSDMD cleavage

Noncanonical effector sequence

Intracellular LPS



Caspase-4 or caspase-5



Gasdermin D proteolysis



GSDMD oligomeric pores



Membrane disruption and lysis

Do not confuse cytokine processing with pore activation

Mature IL-1 β

- Caspase-1 processes pro-IL-1 β
- The textbook makes this explicit for canonical activation

GSDMD activation

- Either caspase-1 or caspases-4/5 can cleave GSDMD
- Both branches create the membrane pore-forming effector

Canonical vs noncanonical: Exact distinctions

Step	Canonical route	Noncanonical route
Input	Cytosolic microbial products	Cytosolic gram-negative LPS
Activation	Inflammasome	Caspases-4/5
Initiator protease	Caspase-1	Caspases-4/5
Common effector	GSDMD	GSDMD

Pathway convergence is the central idea

Caspase-1

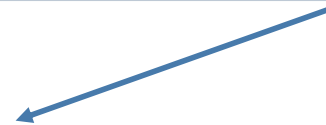
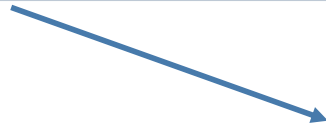
Inflammasome-dependent activation

Caspases-4/5

Intracellular LPS-dependent activation

GSDMD

Pore formation → lytic cell death



Gasdermins are membrane pore-forming proteins

- Gasdermins are the effector family named.
- Gasdermin D (GSDMD) is the best-characterized example.
- Proteolytic cleavage enables its pore-forming activity.

The effector is a membrane protein pore, not an enzyme that digests the entire membrane.

GSDMD cleavage is the commitment step

Inactive/intact GSDMD



Inflammatory caspase cleavage



Activated pore-forming GSDMD component



Multimerization and membrane insertion

Oligomerization creates an effective pore

Cleaved units

Individual activated
GSDMD components

Oligomer

Multiple subunits
assemble

Membrane pore

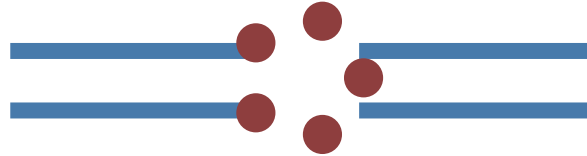
A conductive opening is
formed in plasma
membrane

Plasma-membrane pores: Structural logic

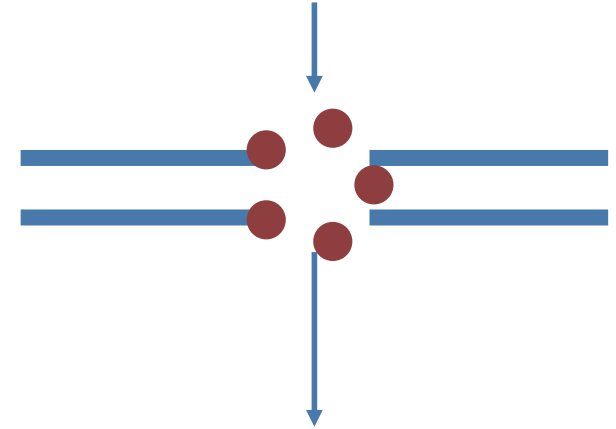
Before cleavage



After GSDMD
oligomerization



Pore-mediated flux



Schematic: Pore-forming proteins interrupt the barrier function of the plasma membrane.

A pore changes permeability before rupture

GSDMD pore in plasma membrane



Disruption of normal membrane barrier



Altered ion/water distribution



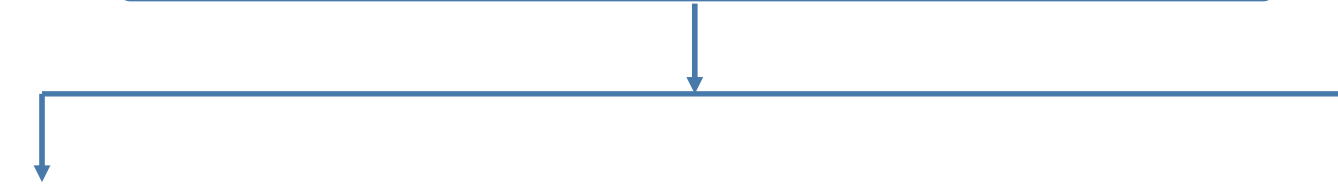
Osmotic disturbance



Membrane rupture

Mediator release and lysis are coupled

GSDMD pore formation



Release

IL-1 β and other inflammatory mediators
leave the cell

Physical failure

Local osmotic gradients become
unstable $\rightarrow$ rupture

Pyroptotic bodies appear before terminal rupture

GSDMD pores form



Osmotic potential becomes disturbed



Pyroptotic bodies develop



Plasma membrane eventually ruptures

The terminal event is lytic cell death

- Membrane integrity ultimately fails.
- Cellular components escape into extracellular space.
- The tissue is exposed to inflammatory mediators.
- The process is regulated upstream despite the necrosis-like endpoint.

Follow the entire injury sequence

Signal recognition



Caspase activation



GSDMD cleavage



Pore oligomerization



Mediator release + osmotic failure



Rupture and local inflammation

How IL-1 β produces local inflammation

Mature IL-1 β is released



Endothelial activation and leukocyte adhesion



Recruitment of leukocytes



Inflammatory response in local tissue

The link between IL-1 β and fever

- IL-1 is a fever-inducing proinflammatory cytokine.
- Caspase-1 maturation enables biologically active IL-1 β .
- Lytic permeability permits release from the pyroptotic cell.
- Fever reflects systemic inflammatory signaling, not cellular heat production.

Why local inflammation amplifies tissue effects

Pyroptotic inflammatory mediators

Leukocyte recruitment

IL-1 supports a coordinated
inflammatory infiltrate

Tissue consequences

Inflammatory response may protect but
also injure tissue

When host defense becomes pathogenic

Useful response

- Recognize intracellular microbes
- Remove infected cells
- Recruit inflammatory defenses

Excessive response

- Lytic death can extend injury
- Released mediators amplify inflammation
- Sepsis is a textbook-associated disorder

Sepsis: Relevance without overclaiming

- Excessive pyroptosis may contribute to sepsis.
- The statement is contributory, not a claim that all sepsis is pyroptosis.
- Gasdermin-mediated lysis provides a plausible inflammatory amplification route.

Do not substitute this mechanism for the broader multifactorial pathogenesis of sepsis.

Autoimmune disease: An association, not a criterion

- Autoimmune disease among conditions linked to excessive pyroptosis.
- This does not establish that GSDMD activation diagnoses autoimmune disease.
- Mechanistic association and validated clinical biomarker are different claims.

Morphology: What the supplied passage supports

Explicitly described

- Membrane pores and osmotic disruption
- Formation of pyroptotic bodies
- Eventually plasma-membrane rupture

Not established by this excerpt

- Unique diagnostic H&E pattern
- Specific organ-level gross morphology
- Validated histologic cutoff or test threshold

Apoptosis and pyroptosis: Fate of cell contents

Event	Apoptosis	Pyroptosis
Cell outline	Shrinks; apoptotic bodies form	Osmotic injury; pyroptotic bodies
Membrane integrity	Usually retained until clearance	Perforated; finally ruptures
Contents	Phagocytic clearance	Inflammatory mediator release
Inflammation	Usually limited	Intrinsic to the process

Necroptosis and pyroptosis: Different pores

Feature	Necroptosis	Pyroptosis
Signaling	RIPK1/RIPK3 kinases	Inflammatory caspases
Effector	Phosphorylated MLKL	Proteolytically cleaved GSDMD
Final membrane event	Membrane disruption	Protein pore formation → rupture
Inflammatory result	Cell contents released	Cytokine + other mediator release

Ferroptosis and pyroptosis: Different injury chemistry

Feature	Ferroptosis	Pyroptosis
Dominant trigger	Iron/ROS and impaired antioxidant defense	Microbial products / intracellular LPS
Effector change	Lipid peroxidation	GSDMD pore formation
Membrane defect	Peroxidized membrane lipids	Oligomeric membrane pores
Regulation	Iron-dependent pathway	Caspase-dependent pathway

Integrated differential of lytic death

Necrosis

Uncontrolled injury → swelling/rupture

Necroptosis

RIPK1/RIPK3–MLKL → rupture

Pyroptosis

Caspase–GSDMD → rupture + IL-1 β

Ferroptosis

Iron-linked lipid peroxidation → death

Clinical application: Inflammasome route

A microbial product is sensed in an infected cell. Caspase-1 is activated, and mature IL-1 β appears.

Which form of pyroptosis is represented?

Canonical pyroptosis.

Cytosolic sensing → inflammasome → caspase-1, with GSDMD downstream.

Clinical application: Cytosolic LPS

Intracellular LPS from gram-negative bacteria activates caspases-4 and -5 in a model cell.

Which branch and effector are expected?

Noncanonical pathway; GSDMD activation.

The initiating caspases differ from canonical pyroptosis, but the pore effector is shared.

Mechanistic application: Block GSDMD cleavage

A hypothetical intervention prevents inflammatory caspases from cleaving GSDMD, while upstream danger sensing remains intact.

What downstream event would the mechanistic model predict to be reduced?

GSDMD oligomeric pore formation and consequent membrane lysis.

Inference from the textbook causal pathway; This is not a claimed clinical treatment effect.

Common conceptual errors

- “Pyroptosis is the same as apoptosis.” — It is lytic and inflammatory.
- “Every pathway uses caspase-1 first.” — Noncanonical initiation uses caspases-4/5.
- “Caspases are the membrane pores.” — The pore-forming effector is GSDMD.
- “IL-1 β alone defines cell death.” — GSDMD-mediated lysis is central.

Mechanism recap: Two entries, one exit

Canonical

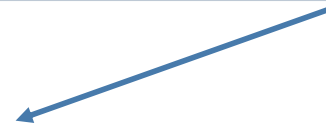
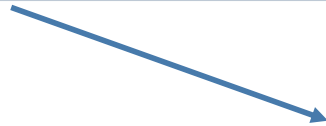
Inflammasome → caspase-1

Noncanonical

Intracellular LPS → caspases-4/5

GSDMD membrane pores

Mediator release + osmotic failure → lytic death



Essential teaching conclusions

- Pyroptosis is regulated, pore-mediated, inflammatory lytic cell death.
- Canonical activation links the inflammasome to caspase-1.
- Noncanonical activation involves cytosolic LPS and caspases-4/5.
- Both cleave GSDMD; Pore formation causes cytokine release and membrane rupture.
- Excessive activation may contribute to sepsis and autoimmune inflammation.

Principal textbook sources

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 2: Other Mechanisms of Cell Death; “Pyroptosis,” p. 45.

Same textbook, Chapter 6: Cellular Receptors for Microbes and NOD-like Receptors and the Inflammasome.

Same textbook, Chapter 3: Recognition of Microbes and Damaged Cells; Tumor Necrosis Factor and Interleukin-1.