REVIEW

Acta Neurobiol Exp 2026, 86: 211–220
DOI: 10.55782/qj1kb197

Functional relevance and mechanisms of necroptosis in ischemia–reperfusion injury

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Ischemia–reperfusion injury remains a major cause of mortality and disability worldwide, with limited therapeutic options. While reperfusion is essential for tissue salvage, it paradoxically triggers secondary damage, highlighting the need to better understand regulated cell death pathways. Traditionally, apoptosis was considered the dominant mechanism; however, incomplete protection by caspase inhibition revealed a substantial contribution of caspase-independent death. Among these, necroptosis has emerged as a functionally purposeful process, eliminating compromised cells but simultaneously amplifying sterile inflammation through the release of damage-associated molecular patterns. This review synthesizes current knowledge of necroptosis in ischemia–reperfusion injury. We first establish its functional relevance, then examine canonical and non-canonical molecular pathways, including RIPK1–RIPK3–MLKL signaling, mitochondrial dysfunction, and CaMKIIδ-mediated execution. We discuss mechanisms of CASP8 checkpoint weakening and bypass, emphasizing the roles of metabolic collapse, oxidative stress, and ZBP1-mediated signaling. Finally, we highlight the cell-type and temporal dynamics of necroptosis, as well as its translational implications. Recognizing necroptosis as a context-dependent permissive state rather than a simple backup pathway provides a more comprehensive framework for understanding ischemic cell death and its tissue-specific manifestations.

Key words: ischemia-reperfusion, necroptosis, cell death

INTRODUCTION

Ischemic stroke alone accounted for an estimated 7.8 million incident cases and 3.6 million deaths in 2021 (Li et al., 2024), while ischemic heart disease affected approximately 254 million people and caused around 9 million deaths (Jing et al., 2026), together representing one of the largest contributors to the global disease burden. Beyond these, ischemia–reperfusion injury underlies tissue damage in a range of clinical settings, including organ transplantation and resection of the liver and kidney, acute kidney injury, mesenteric ischemia, and retinal vascular disease. In each of these, restoration of blood flow is indispensable for tissue salvage, yet reperfusion paradoxically initiates a second wave of injury: the abrupt return of oxygen provokes a burst of reactive oxygen species, calcium overload, and sterile inflammation that can extend damage beyond the originally ischemic territory. Despite the scale of this problem, therapeutic options remain limited, largely confined to timely restoration of perfusion, and no pharmacological agent is approved to prevent reperfusion injury itself.

Early investigation of ischemic cell death centered on apoptosis, a caspase-dependent form of programmed cell death that was long regarded as the dominant regulated mechanism in the ischemic penumbra. This view was supported by experimental studies in which caspase inhibition proved neuroprotective: pan-caspase inhibitors such as Z-VAD-FMK and the caspase-3-preferring Z-DEVD-FMK, reduced infarct volume and delayed neuronal death in rodent models of focal cerebral ischemia (Hara et al., 1997; Endres et al., 1998), with comparable tissue protection reported in cardiac, hepatic, and intestinal ischemia–reperfu-

Received 9 June 2026, accepted 17 September 2026

sion. Yet the protection afforded by caspase inhibition was consistently incomplete and context-dependent, effective in focal but not global ischemia, and often confined to narrow time windows (Li et al., 2000; Cho et al., 2004), revealing a substantial contribution from caspase-independent death. Indeed, pan-caspase inhibition can itself divert cells toward necroptosis by blocking caspase-8, unmasking the very pathway it was intended to suppress. Among these caspase-independent mechanisms, necroptosis has since emerged as a key regulated pathway across diverse ischemic contexts, including neuronal (Jin et al., 2026), cardiac (Zheng et al., 2025), hepatic (Lin et al., 2025), retinal (Wang et al., 2025), renal (Xie et al., 2025), and intestinal systems (Li et al., 2026b).

Necroptosis is defined as a regulated form of cell death dependent on receptor-interacting serine/threonine-protein kinase 3 (RIPK3) and mixed lineage kinase domain-like pseudokinase (MLKL), distinct from apoptosis by its hallmark plasma membrane rupture and release of damage-associated molecular patterns (DAMPs), which amplify sterile inflammation (Galluzzi et al., 2018). Canonically, necroptosis is suppressed by caspase-8 (CASP8), raising the critical question of how ischemic stress permits its activation.

In this review, we first establish the functional relevance of necroptosis in ischemia, then examine the molecular pathways that mediate it, and also analyze the mechanisms of CASP8 checkpoint weakening and bypass. We next highlight cell-type and temporal dynamics. By integrating molecular mechanisms with tissue context, we propose that necroptosis in ischemia reflects a context-dependent permissive state rather than a simple backup pathway, emphasizing its potential as a therapeutic target within salvageable tissue.

Functional relevance of necroptosis in ischemia

Necroptosis in the context of ischemia–reperfusion injury plays a dual role: it enables rapid elimination of cells that have lost viability, while simultaneously triggering a strong wave of sterile inflammation. Throughout this review, the term sterile inflammation denotes an inflammatory response driven by endogenous danger signals released from dying or damaged cells in the absence of infection, as distinct from pathogen-triggered inflammation. Unlike apoptosis, which culminates in the formation of apoptotic bodies and their silent clearance by phagocytes, necroptosis is characterized by plasma membrane rupture and uncontrolled release of intracellular components that act as DAMPs, activating the immune system (Kaczmarek et al., 2013; Murao et al., 2021). In apoptosis, dying cells expose "eat-me" signals such as phosphatidylserine that promote prompt efferocytosis before their contents can escape, and the process is accompanied by anti-inflammatory mediators that restrain bystander activation, so that injury remains contained. Necroptosis inverts this outcome: membrane rupture spills the same intracellular contents that apoptosis would have sequestered and cleared, so that DAMP release, complement activation, and recruitment of neutrophils and monocytes propagate injury into the surrounding peri-infarct tissue.

The composition and immunogenicity of DAMPs depend on the mode of cell death and include, among other features, the length of the cell-free DNA fragment and the redox state of high-mobility group box 1 (HMGB1). During apoptosis, caspases cleave immunomodulatory molecules such as phospholipase A2 (PLA2) and interleukin-33 (IL-33), thereby limiting their inflammatory potential. Necroptosis, by contrast, lacks caspase activity, allowing the release of intact PLA2, IL-33, and HMGB1, which can further cause secondary tissue damage (Wen et al., 2017).

The functional relevance of necroptosis lies in its role as an overt, signal-generating form of cell death rather than a silent mode of self-elimination. Unlike apoptosis, which removes compromised cells with minimal disturbance, necroptosis is triggered when injury demands broader recognition. Plasma membrane rupture and the release of intracellular contents both eliminate cells that are unable to sustain homeostasis and alert the immune system to critical stress, mobilizing inflammatory and reparative responses (Wu et al., 2024). This alarm-like signaling, however, comes at a cost: uncontrolled discharge of DAMPs and cytotoxic molecules damages adjacent viable cells, expands secondary injury, and limits tissue recovery (Kaczmarek et al., 2013; Zhang et al., 2024). Necroptosis is therefore best understood as a purposeful process whose inflammatory footprint simultaneously announces the severity of damage and constrains regenerative potential (Du et al., 2024; Lin et al., 2025).

Clinical evidence underscores the translational relevance of necroptosis: serum levels of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and RIPK3 in patients with acute ischemic stroke correlate with lesion volume and disease severity (Dong & Xiong, 2024), while MLKL expression is elevated both in the infarct core and peri-infarct regions (Han et al., 2019). Moreover, extracellular RIPK3 may itself act as a novel DAMP, amplifying tissue injury (Zhang et al., 2024).

Thus, necroptosis functions not only as a regulated mechanism of cell death but also as a potent modulator of sterile inflammation, shifting the outcome toward either tissue repair or progressive ischemic injury.

Molecular pathway of necroptosis

Necroptosis proceeds through a regulated signaling cascade that converts stress cues into inflammatory cell death.

Canonically, the pathway begins with Tumor Necrosis Factor alpha (TNF-α) binding to Tumor necrosis factor receptor 1 (TNFR1), which can yield three distinct outcomes depending on cellular context. Under permissive conditions, assembly of membrane-associated signaling Complex I, comprising TNF receptor-associated factor 2 (TRAF2), RIPK1, Cellular Inhibitors of Apoptosis proteins (cIAPs), and the Linear ubiquitin chain assembly complex (LUBAC) ubiquitin ligase, drives pro-survival signaling through NF-κB and MAPK activation (Wu et al., 2024) (Fig. 1). Destabilization of Complex I, particularly due to ischemia, promotes the formation of cytosolic Complex II, which includes RIPK1, FADD, CASP8, and cFLIP. Within this complex, CASP8 triggers the CASP3/CASP7 apoptotic cascade and concurrently suppresses necroptosis. This suppression was long attributed to direct cleavage of RIPK3, but recent genetic evidence indicates that RIPK3 cleavage is dispensable for necroptosis inhibition: mice expressing cleavage-resistant RIPK3 develop normally and their cells show no change in RIPK1, RIPK3, or MLKL phosphorylation in response to necroptotic stimuli, with the cleavage instead serving to restrict NLRP3 inflammasome activation and IL-1β release (Tran et al., 2024). Among the candidate CASP8 substrates, only

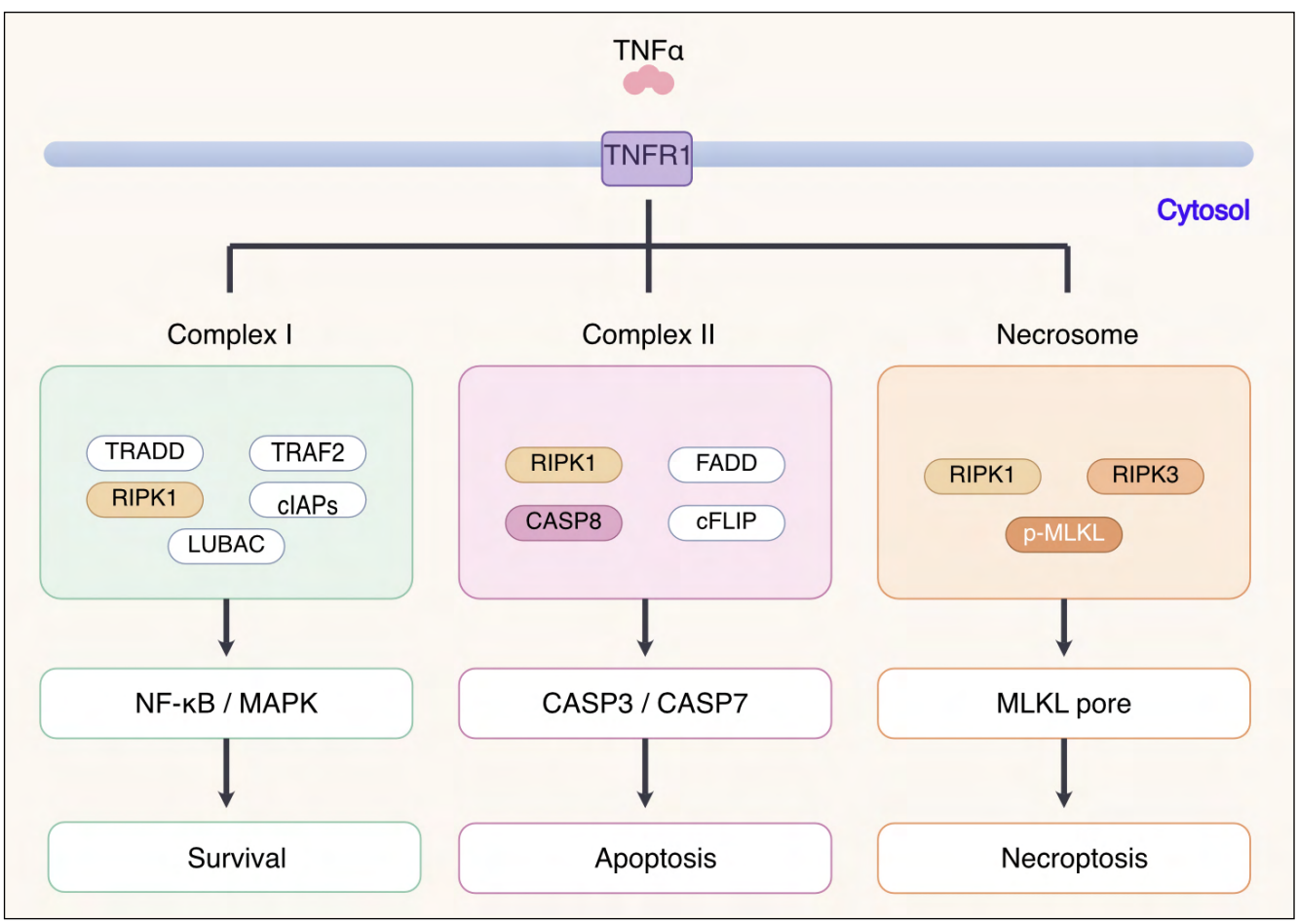

Fig. 1. TNFR1 nucleates three sequential cytosolic complexes that dictate cell fate. The binding of TNFα to TNFR1 at the plasma membrane recruits three mutually exclusive signaling platforms in the cytosol. Complex I, the membrane-proximal scaffold, assembles TRADD, TRAF2, RIPK1, cIAPs and LUBAC; ubiquitylation of RIPK1 within this complex drives NF-κB and MAPK activation and a pro-survival transcriptional output. Following RIPK1 deubiquitylation and dissociation from the receptor, Complex II forms around RIPK1, FADD, caspase-8 (CASP8) and cFLIP, cleaving and activating the executioner caspases CASP3 and CASP7 to commit the cell to apoptosis. When CASP8 activity is lost or insufficient, RIPK1 instead recruits RIPK3 to assemble the necrosome, in which RIPK3 phosphorylates MLKL; oligomeric p-MLKL traffics to the plasma membrane and forms lytic pores, executing necroptosis. cIAPs, cellular inhibitor-of-apoptosis proteins; LUBAC, linear ubiquitin chain assembly complex; cFLIP, cellular FLICE-like inhibitory protein; p-MLKL, phosphorylated mixed-lineage kinase domain-like pseudokinase.

non-cleavable RIPK1 proves embryonic-lethal; this lethality is not prevented by loss of MLKL alone – and is therefore apoptotic rather than necroptotic – identifying RIPK1 cleavage as the physiologically decisive event by which CASP8 restrains death signaling from this complex (Newton et al., 2019). CASP8 thus acts principally upstream, at the level of RIPK1, while its cleavage of RIPK3 calibrates the inflammatory output of the same complex.

When CASP8 activity is insufficient to maintain this checkpoint, the balance shifts toward necroptosis, with RIPK1 and RIPK3 engaging through their RHIM domains to assemble the necrosome. This triggers MLKL recruitment, its phosphorylation-dependent oligomerization, and translocation to the plasma membrane, resulting in permeabilization and lytic death (Seo et al., 2021). Permeabilization and the final rupture that discharges DAMPs are now recognized as separately executed steps, however, so MLKL is the channel-forming effector rather than the direct agent of lysis. Whereas Ninjurin-1 (NINJ1) mediates this rupture across pyroptosis and apoptosis (Kayagaki et al., 2021), in necroptosis the corresponding role is filled by SIGLEC12, which acts downstream of MLKL and is cleaved by the protease TMPRSS4 to drive rupture (Noh et al., 2026). Notably, this SIGLEC12–TMPRSS4 axis appears human-specific, adding a further layer of context dependence to necroptotic execution.

This process not only causes cell rupture but also initiates phosphatidylserine externalization and release of necroptotic extracellular vesicles (NecrEVs), amplifying inflammation (Shlomovitz et al., 2019; Raden et al., 2021). MLKL also targets intracellular organelles, particularly mitochondria, where it interacts with voltage-dependent anion channel 1 (VDAC1), promoting calcium overload, reactive oxygen species (ROS) generation, and mitochondrial failure (Wan et al., 2023, 2024).

Importantly, necroptosis can proceed through alternative MLKL-independent execution routes. RIPK3 directly activates calcium/calmodulin-dependent protein kinase II delta (CaMKIIδ), which opens the mitochondrial permeability transition pore (mPTP) and drives cell death (Zhang et al., 2016; Wang et al., 2022). This highlights necroptosis as a flexible program that can be implemented according to the presence of different tissue-specific stressors (Grootjans et al., 2017).

In summary, necroptosis is not a linear cascade but a modular network: RIPK1–RIPK3–MLKL form its core, while mitochondrial and calcium-dependent pathways provide additional layers of execution. This explains why necroptosis can be engaged differently across tissues and why it exerts such a strong inflammatory impact in ischemia.

CASP8 checkpoint weakening

Under physiological conditions, CASP8 serves as a critical checkpoint that suppresses necroptosis. In ischemic–reperfusion injury, the central question is to elucidate the pathways of suppression of CASP8 activity (Fig. 2). One proposed mechanism is metabolic failure. Because caspase activation and apoptotic execution are energy-dependent, ATP depletion can shift cell death toward necrosis. This occurs with severe and prolonged energy deprivation. Although there are variations across models, oxygen and glucose deprivation have been shown to cause ATP depletion, mitochondrial dysfunction, and increased RIPK3-MLKL signaling, with ATP restoration reducing necroptotic activity (Singh & Chen, 2023; Fan et al., 2024).

Another mechanism is oxidative and nitrosative stress. Hydrogen peroxide reversibly inhibits CASP3 and CASP8, with low concentrations promoting apoptosis but higher levels blocking caspase activity and favoring necroptosis (Hampton & Orrenius, 1997; Borutaite & Brown, 2001). Similarly, hypothiocyanous acid oxidation of CASP8 enables TNF-mediated necroptosis (Bozonet et al., 2023). Nitric oxide can inhibit CASP8 *via* S-nitrosylation, preventing apoptosis and facilitating necroptosis (Kim et al., 2000). Reactive oxygen species (ROS) also promote RIPK1 autophosphorylation and necrosome formation (Zhang et al., 2017a). In neonatal hypoxia–ischemia with hyperglycemia, mitochondrial ROS were necessary and sufficient to drive a shift from apoptosis to necroptosis, reversible by a mitochondria-targeted ROS inhibitor (Deragon et al., 2020).

A third factor is microenvironmental acidosis resulting from ischemia-induced lactic acid accumulation, lowering intracellular pH. In neurons, low pH induces necroptosis *via* a direct interaction between RIPK1 and Acid-sensing ion channel 1a (ASIC1a), independent of its ion conductance (Wang et al., 2015). Interestingly, the low pH environment does not impair CASP8 activity in endothelial cells, highlighting a divergence in pH-dependent cell death signaling (Zhang et al., 2017b).

The factors described create a permissive environment in which CASP8 no longer acts as a binary switch but rather as a vulnerable node within a broader stress-responsive network. This weakening of the checkpoint explains how necroptosis can be engaged even in the absence of genetic CASP8 deficiency, highlighting the importance of metabolic and redox context in ischemic cell death. Thus, these findings show that CASP8 suppression during ischemia is a context-dependent process, shaped by metabolic collapse, redox imbalance, and microenvironmental conditions.

CASP8 bypass

While CASP8 is a recognized "gatekeeper" that limits necroptosis, it is not the exclusive regulator, as noted above. Even when CASP8 activity is preserved, necroptosis can be engaged through alternative signaling routes that bypass its inhibitory function (Tran et al., 2024). These non-canonical pathways highlight the adaptability of necroptotic machinery.

Accumulating evidence supports non-canonical upstream entry routes into necroptosis, with Z-DNA binding protein 1 (ZBP1) being the most studied. ZBP1 senses Z-conformation nucleic acids *via* its Zα domains and engages RIPK3 (Fig. 2). In hepatic ischemia–reperfusion, hypoxia-induced mitochondrial damage and Z-DNA accumulation activate ZBP1/RIPK3-dependent necroptosis, while mitochondrial protection or DNA removal attenuates this pathway (Lin et al., 2025). However, the extent to which ZBP1 acts independently of RIPK1 appears context- and species-dependent: murine studies support a RIPK1-independent route, whereas human cell data indicate that RIPK1 is required to stabilize the ZBP1–RIPK3 complex (Amusan et al., 2025).

These bypass mechanisms demonstrate that necroptosis is not strictly dependent on CASP8 inhibition but can be initiated through diverse molecular cues. This flexibility explains its occurrence across different tissues and time points in ischemia, reinforcing the concept of necroptosis as a context-dependent permissive state rather than a linear backup pathway.

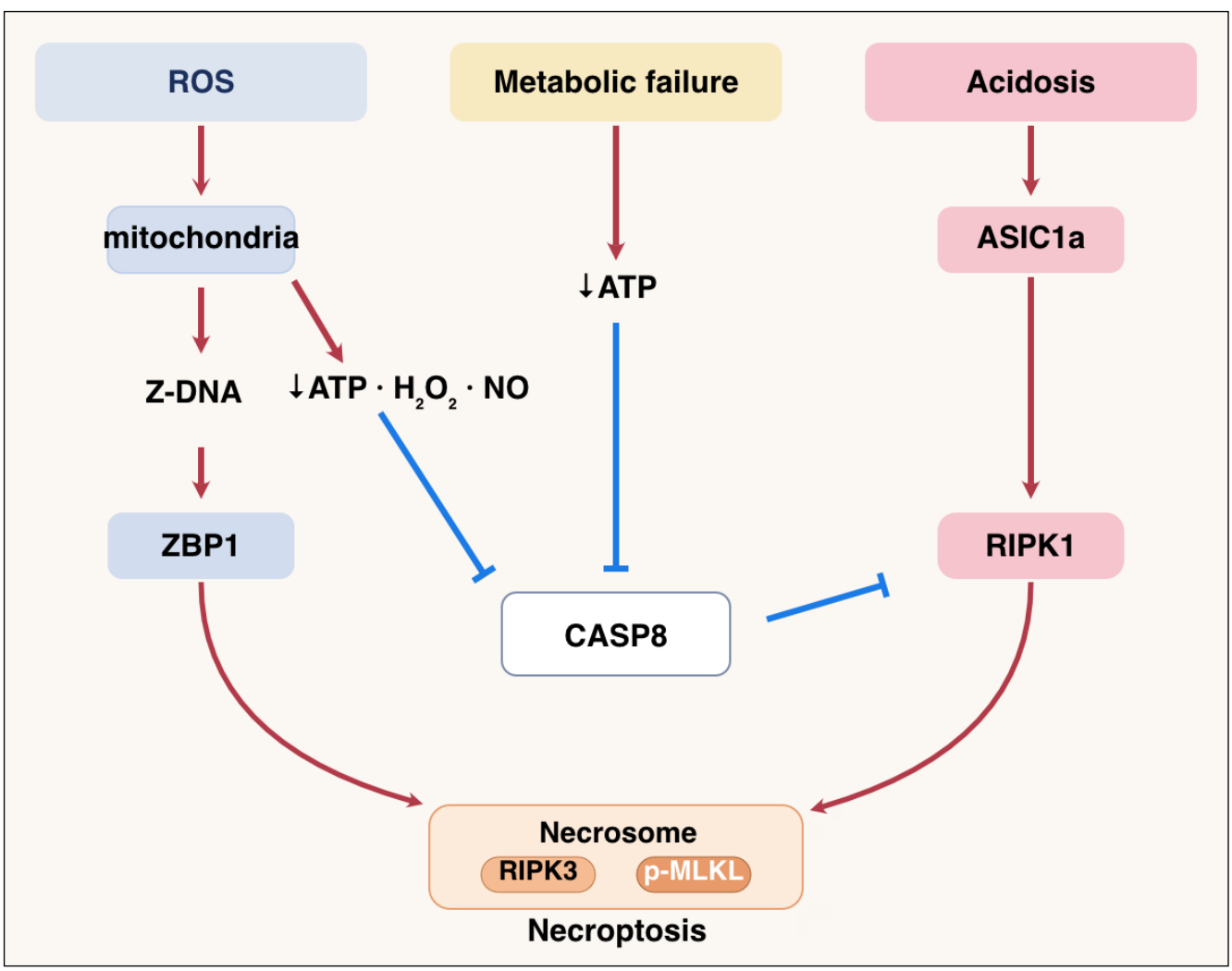

Fig. 2. Convergent non-canonical triggers of necroptosis. Three injury-associated inputs feed the necrosome (RIPK3·p-MLKL) independently of canonical TNFR1 ligation. Red arrows denote activating relationships; blue T-bars denote inhibition. (i) Mitochondrial reactive oxygen species (ROS) promote the accumulation of cytosolic Z-form nucleic acids, which are sensed by ZBP1 and license necrosome assembly. (ii) Metabolic failure and mitochondrial dysfunction collapse intracellular ATP and raise H_2O_2 and NO; together, these suppress CASP8, removing the cleavage-based brake that CASP8 normally imposes on RIPK1 and thereby permitting necroptosis. (iii) Tissue acidosis activates the proton-gated channel ASIC1a, which scaffolds RIPK1 and routes it into the necrosome. ASIC1a, acid-sensing ion channel 1a; ZBP1, Z-DNA binding protein 1.

PANoptosis

A further layer of complexity is introduced by PANoptosis, an inflammatory form of regulated cell death in which pyroptosis, apoptosis, and necroptosis are engaged concurrently through a shared multiprotein scaffold termed the PANoptosome (Malireddi et al., 2019). This platform is assembled from upstream sensors such as ZBP1, AIM2, or NLRP3, the adaptors ASC and FADD, and the catalytic effectors RIPK1, RIPK3, CASP1, and CASP8 (Christgen et al., 2020). Because CASP8 is itself a core component of this complex, PANoptosis is best understood not as a route that circumvents the CASP8 checkpoint but as a convergent program in which necroptotic execution proceeds alongside, rather than in place of, caspase activity.

In ischemia-relevant settings, ZBP1 has been identified as the principal sensor nucleating PANoptosome assembly, linking the non-canonical entry route discussed above to this integrated death program. PANoptosis has been reported in hippocampal neurons and in cerebral and myocardial ischemia–reperfusion, where targeting the ZBP1–RIPK3 axis attenuates neuronal injury and reduces infarct size (Shu et al., 2025; Li et al., 2026a). Its engagement across cell types and organs is consistent with the context-dependent activation of necroptotic machinery emphasized throughout this review.

Nonetheless, the relevance of PANoptosis to ischemia–reperfusion remains an emerging concept. Direct demonstration of an assembled PANoptosome in ischemic tissue is still lacking, and much of the supporting evidence derives from infection models or in vitro systems. A detailed analysis of PANoptosome biology is beyond the scope of this review. We note it as a convergent outcome downstream of the described signaling pathways, rather than an established mechanism of ischemic cell death.

Cell-type- and time-resolved engagement of the necroptotic machinery

Despite extensive research, the engagement of necroptosis in ischemia-reperfusion injury is markedly heterogeneous. Evidence from neuronal, glial, and hepatic models shows significant variations driven by cellular composition, differentiation states, and specific experimental contexts.

Current consensus suggests that necroptosis and ferroptosis peak early during reperfusion, whereas apoptosis develops later. MLKL and phosphorylated RIPK3 remain elevated within hours of reperfusion before declining (Naito et al., 2020; Du et al., 2024). The early activation of signaling molecules establishes a framework for the progressive recruitment of various cell types into necroptosis. Neurons dominate necroptosis in the first 3 days, astrocytes peak around day 5, and pericytes show maximal engagement at day 7 in blood–brain barrier compartments (Yang et al., 2018; Xu et al., 2025) (Fig. 3).

Contradictions across studies often reflect tissue specificity and timing rather than fundamental disagreement. For example, MLKL expression has been reported primarily in microglia in spinal cord injury (Fan et al., 2015), while pMLKL colocalization with neurons was documented in postmortem stroke tissue (Han et al., 2019).

In hepatocytes, findings are also divergent. Earlier work suggested poor RIPK3 expression due to epigenetic silencing (Preston et al., 2022), but more recent studies show dynamic remodeling: RIPK3 expression rapidly appears under stress, enabling hepatocyte necroptosis during ischemia–reperfusion (Lin et al., 2025). This highlights the importance of epigenetic regulation in determining necroptotic susceptibility.

This temporal and cellular variability underscores that necroptosis is not a single, synchronized event but a dynamic process shaped by tissue context. Such heterogeneity explains why therapeutic interventions may show differential efficacy depending on the target cell population and timing of administration.

Translational implications

Necroptosis inhibition protects tissue in many experimental models of ischemia–reperfusion injury in which it has been tested. Despite this breadth, no inhibitor of the necroptotic machinery has to date entered a clinical trial in any ischemia–reperfusion indication. Clinical development of RIPK1 inhibitors has instead proceeded within chronic inflammatory and neurodegenerative disease, where outcomes have been consistently disappointing: DNL104 and SAR443060 (DNL747) were abandoned on toxicological grounds despite the latter proving safe and demonstrably target-engaging in patients (Grievink et al., 2020; Vissers et al., 2022), and although the brain-penetrant successor SAR443820 (DNL788) achieved near-complete target engagement in healthy volunteers (Hincelin-Mery et al., 2024), the phase II HIMALAYA trial in amyotrophic lateral sclerosis did not meet its primary endpoint of change in the ALSFRS-R and was discontinued (ClinicalTrials.gov: NCT05237284); earlier trials of the RIPK1 inhibitor GSK2982772 in rheumatoid arthritis and ulcerative colitis were likewise negative (Weisel et al., 2021b, 2021a). This record is often read as a verdict on the pathway.

We would read it differently: sustained suppression of a kinase whose pathological activity in ischemia is concentrated within the first hours of reperfusion tests a different hypothesis from the one advanced here.

What separates this experimental record from the clinic is, in each instance, an unresolved question of mechanism rather than a failure of pharmacology. The dose-limiting toxicities arose under chronic exposure and proved compound - rather than target-specific (Vissers et al., 2022), leaving open what acute inhibition timed to reperfusion would achieve. Species specificity is increasingly pressing: the terminal rupture step downstream of MLKL appears to be executed in human cells by SIGLEC12 following TMPRSS4 cleavage, with no murine equivalent (Noh et al., 2026), while ZBP1-driven necroptosis requires RIPK1 in human but not murine cells (Amusan et al., 2025), so that the events most directly responsible for DAMP release may not be faithfully modelled in rodents. Timing and cellular heterogeneity further constrain any single-agent approach, since neurons, glia, and pericytes enter the pathway on distinct schedules (Fig. 3) and the permissive window opens at reperfusion. Determining which cells engage the pathway, at which moment, and through which execution route is therefore not preliminary to translation but its substance; on present evidence it points toward acute administration timed to revascularization or to cardiac surgery, and toward *ex vivo* delivery during organ preservation, a setting in which perfusion of discarded human livers with a pan-caspase inhibitor has already been shown to dampen innate immune activation (Raigani et al., 2022).

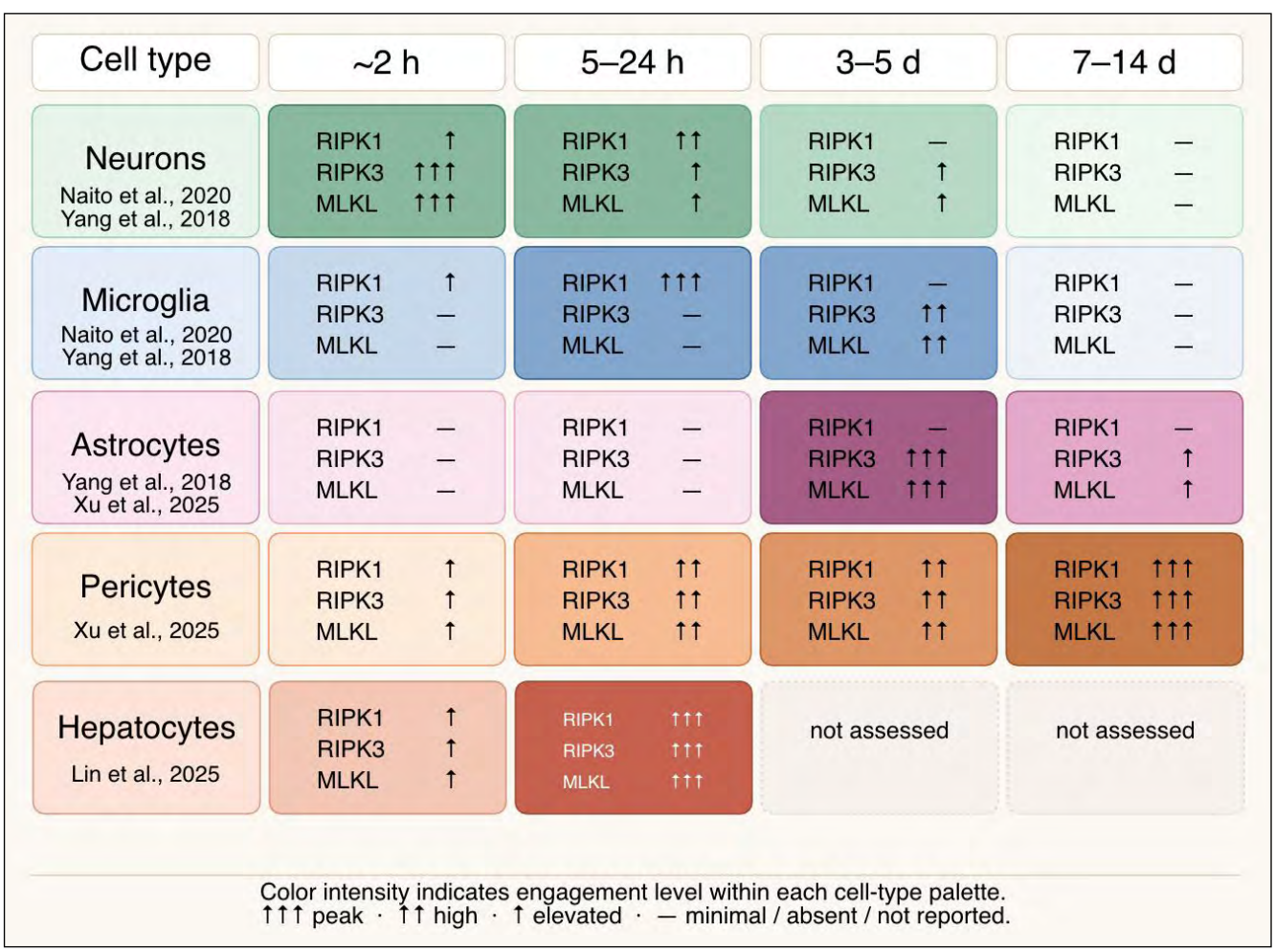

Fig. 3. Cell-type- and time-resolved engagement of the necroptotic machinery. Semi-quantitative summary of RIPK1, RIPK3 and MLKL engagement across five cell populations over four post-injury intervals (≈2 h, 5–24 h, 3–5 d, 7–14 d). Within each cell-type palette, colour intensity scales with engagement level: ↑↑↑, peak; ↑↑, high; ↑, elevated; —, minimal, absent or not reported. Neurons and hepatocytes engage the pathway rapidly, with all three components peaking by 5–24 h. Microglia showed early RIPK1 induction (peak 5–24 h) but delayed MLKL commitment (3–5 d). Astrocytes engage almost exclusively in the 3–5 d window and decline thereafter. Pericytes display progressively rising engagement of all three components across the full time course, peaking at 7–14 d. Hepatocyte responses at 3–5 d and 7–14 d were not assessed in the source studies (dashed cells).

Currently, the most immediate application of the new information considered is diagnostic and prognostic, rather than therapeutic. Serum RIPK1 and RIPK3 in patients with acute ischemic stroke scale with infarct volume and clinical severity and carry predictive value for outcome (Dong & Xiong, 2024). In particular, plasma RIPK3 measured after percutaneous coronary intervention was associated with adverse cardiac events across discovery and validation cohorts, consistent with extracellular RIPK3 acting as a DAMP that amplifies injury (Zhang et al., 2024). Such markers require no new drug to be useful. Because they report on the pathway rather than on tissue loss alone, they offer a means of estimating in an individual patient the extent to which the permissive state described in this review has actually been entered - informing prognosis at the bedside, distinguishing patients in whom necroptotic signaling is active from those in whom it is not, and supplying the enrichment strategy that a first trial of necroptosis inhibition in ischemia–reperfusion will almost certainly require deeper mechanistic account developed in this review has an immediate clinical corollary: each newly defined node of the pathway is also a candidate marker of the state it defines.

CONCLUSION

The traditional view of necroptosis as a mere backup cell death pathway activated upon CASP8 inhibition is insufficient to explain its role in ischemia. Instead, current evidence supports a model in which necroptosis emerges from a permissive cellular state shaped by metabolic stress, redox imbalance, and altered signaling networks. In this framework, CASP8 does not function as a simple on–off switch but as part of a broader regulatory landscape that determines whether necroptotic signaling can proceed.

Non-canonical activation routes such as ZBP1-mediated signaling further challenge linear models of necroptosis and underscore its adaptability to different tissue contexts. PANoptosis is better understood not as a further bypass route but as a convergent program: because CASP8 is itself a core component of the PANoptosome, necroptotic execution there proceeds alongside, rather than in place of, caspase activity, although direct demonstration of an assembled PANoptosome in ischemic tissue is still lacking. Moreover, the cell-type and temporal specificity of necroptosis—neurons early, microglia and astrocytes at intermediate stages, pericytes later, and hepatocytes under dynamic epigenetic regulation highlights that necroptosis is not uniform but context-dependent.

Recognizing necroptosis as a context-dependent and functionally purposeful process provides a more accurate conceptual basis for understanding ischemic cell death. It explains why necroptosis can both eliminate compromised cells and amplify inflammation, shaping the balance between tissue salvage and secondary injury. This perspective may guide the development of targeted therapeutic strategies, including inhibitors of RIPK1-RIPK3-MLKL, antioxidants, and modulators of mitochondrial permeability, aimed at selectively restraining necroptosis within salvageable tissue compartments.

ACKNOWLEDGMENT

During the preparation of this work, the authors used Claude (Anthropic) for English language editing and improving readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication. This work was supported by the National Research Foundation of Ukraine (grant number 2023.05/0023).

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