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REVIEW ARTICLE

# Molecular insights into RIPK-family regulation of programmed cell death in pancreatic pathologies

**Fan Zhang[1,2] and Dingmao Wang[1]***

[1]Department of Gastrointestinal Surgery, Haikou Affiliated Hospital of Central South University Xiangya School of Medicine, Haikou, Hainan, China

[2]Department of Hepatobiliary Surgery, Haikou Affiliated Hospital of Central South University Xiangya School of Medicine, Haikou, Hainan, China

## Abstract

Pancreatic diseases, including acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC), represent significant threats to human health, with programmed cell death (PCD) playing a pivotal role in their pathogenesis and progression. This review provides a comprehensive analysis of the molecular mechanisms by which receptor-interacting protein kinase (RIPK) family members regulate PCD and their pathophysiological roles in various pancreatic diseases. In AP, RIPK3-mediated necroptosis is a key factor in acinar cell damage and the exacerbation of systemic inflammation. In CP, RIPK family members contribute to the progression from chronic inflammation to fibrosis through modulation of the NF-κB pathway and loss of parenchymal cells. In the context of PC, dysregulated expression of RIPK1/3 is strongly linked to tumor progression and chemoresistance, with the induction of necroptosis emerging as a promising strategy to overcome apoptosis resistance. Additionally, this review discusses the potential clinical value of RIPK3 and phosphorylated mixed lineage kinase domain-like pseudokinase as biomarkers for necroptosis, as well as recent advancements in RIPK1 kinase inhibitors in clinical trials. A deeper understanding of the molecular mechanisms governing RIPK-mediated cell death not only sheds light on the pathogenic progression of pancreatic diseases but also lays the groundwork for precision anti-inflammatory interventions and the development of novel therapeutic targets.

***Keywords:*** RIPK family; Programmed cell death; Necroptosis; Pancreatic cancer; Acute pancreatitis; Chronic pancreatitis

***Corresponding author:**
Dingmao Wang
(363881760@qq.com)

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## 1. Introduction

As a critical organ, the pancreas is vulnerable to functional impairment in the setting of acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC). These diseases not only impose a psychological and economic burden on affected individuals but also represent a significant challenge to global public health. A key factor in the development of AP, CP, and PC is the dysregulation of inflammatory responses.[1–3] Inflammation is not merely a secondary feature but often acts as a primary driver of disease initiation and progression. For example, repeated episodes of AP lead to

irreversible pancreatic damage, triggering the transition to CP, which is characterized by acinar cell necrosis, extracellular matrix (ECM) deposition, and fibrosis.[4] CP is also a well-established risk factor for the onset of PC.[5] Therefore, controlling inflammation is central to therapeutic management, and understanding the complex inflammatory mechanisms involved in these diseases is critical for advancing clinical treatments.

The receptor-interacting protein kinase (RIPK) family comprises seven serine/threonine kinases[6], designated RIPK1 through RIPK7. These kinases share a highly conserved catalytic domain and exert functional diversity by forming distinct protein complexes and undergoing various modifications, enabling them to participate in multiple cellular signaling pathways.[7,8] The RIPK family regulates essential biological processes, including cell death, inflammation, and cell proliferation.[6,9] These proteins act as "molecular switches," dictating cellular outcomes—whether survival, inflammation, or death—by activating different signaling pathways depending on the nature of upstream stimuli and the specific cellular context.[10,11] Given that inflammatory dysregulation is a hallmark of many pancreatic diseases, the RIPK family, with its unique regulatory mechanisms, plays a pivotal role in shaping disease outcomes. Therefore, understanding how RIPKs regulate inflammation and cell death in pancreatic diseases is vital for developing targeted therapeutic strategies.

In multicellular organisms, programmed cell death (PCD) is essential for normal development, tissue homeostasis, and the clearance of damaged or infected cells.[12] Apoptosis, the most well-characterized form of PCD, is an active process essential for development, homeostasis, and stress response. Notably, apoptosis is immunologically silent, meaning it does not trigger inflammation.[13] In contrast, necroptosis is a pro-inflammatory form of PCD that induces robust immune responses. It often functions as a "fail-safe" mechanism, activated when apoptotic pathways are impaired, ensuring cellular self-destruction.[14] Necroptosis is marked by plasma membrane rupture, organelle swelling, and cytoplasmic and nuclear disintegration, leading to the release of intracellular contents and the exposure of damage-associated molecular patterns (DAMPs), which provoke strong inflammatory responses.[11,15] Both apoptosis and necroptosis contribute to the pathogenesis of AP, CP, and PC, with the RIPK family playing a key regulatory role in both processes.[10,16] This review explores the PCD pathways involved in these pancreatic diseases, focusing on the molecular mechanisms of RIPK-mediated cell death and their impact on disease progression, thereby providing a theoretical basis for developing effective therapeutic interventions.

## 2. Literature search strategy

This narrative review was prepared based on a literature search of PubMed, Web of Science, and Google Scholar. The search terms included "RIPK," "necroptosis," "programmed cell death," "pancreatitis," "acute pancreatitis," "chronic pancreatitis," "pancreatic cancer," "inflammation," "fibrosis," and "biomarker." Articles published in English from January 2000 to January 2026 were considered. Original research articles, reviews, and clinical studies were selected based on their relevance to RIPK-mediated signaling, PCD, inflammation, fibrosis, and pancreatic diseases. Additional references were identified from the bibliographies of selected articles.

## 3. Regulatory roles of the RIPK family in programmed cell death

Although RIPK family members share a highly conserved N-terminal kinase domain, significant structural divergence in their C-terminal regions underlies the distinct biological functions of each member.[6] This review provides an in-depth exploration of the specific roles of individual RIPK family members in regulating PCD.

Among forms of PCD, RIPK1 and RIPK3 are most directly associated with necroptosis, in which RIPK3 phosphorylates mixed lineage kinase domain-like pseudokinase (MLKL), thereby disrupting membrane integrity. Beyond necroptosis, RIPK1 serves as a signaling hub that regulates cell-fate decisions involving survival, apoptosis, and necroptosis, while RIPK3 can participate in inflammatory cell death crosstalk, including pyroptosis. In contrast, the links between RIPK signaling and ferroptosis, autophagy-dependent cell death, parthanatos, or cuproptosis are generally indirect, context-dependent, and less well established.

### 3.1. RIPK1

Receptor-interacting protein kinase 1 is the most central and extensively studied member of the RIPK family, recognized as a critical hub for determining cell fate. Upon tumor necrosis factor (TNF) binding to its receptor TNFR1, RIPK1 and TNFR1-associated death domain protein (TRADD) are recruited to the death domain (DD) of TNFR.1[17] This is followed by the recruitment of TNF receptor-associated factor 2 (TRAF2) to TRADD, which serves as an anchoring point for cellular inhibitor of apoptosis proteins (cIAPs), specifically cIAP1 and cIAP2.[10] At this stage, RIPK1 undergoes ubiquitination by cIAPs at K48, K63, and M1 linkages, along with TAK1-dependent phosphorylation.[18–21] These modifications activate the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways, promoting

cell survival and the expression of pro-inflammatory cytokines.[22,23] This RIPK1-containing assembly is referred to as Complex I, formed rapidly within seconds of TNF–TNFR1 engagement (**Figure 1**).

When ubiquitination is impaired or TAK1 is inactivated, RIPK1 dissociates from Complex I and translocates to the cytosol, where it binds the adapter protein FAS-associated DD protein (FADD) and caspase-8 to form Complex II. In this complex, RIPK1 functions as both a scaffold and a regulator of kinase activity. The formation of Complex II marks the transition to cell death pathways, highlighting RIPK1's role as a "molecular switch." Notably, the assembly of Complex II does not always result in cell death. The outcome depends on the stoichiometric balance of cellular FLICE-like inhibitory protein (cFLIPL), FADD, caspase-8, and RIPK3. High cFLIPL levels inhibit both caspase-8-mediated apoptosis and RIPK3-dependent necroptosis, promoting cell survival.[24,25] In contrast, low cFLIPL levels enable caspase-8 homodimerization within Complex II, leading to caspase-8-dependent apoptosis.[26,27] Additionally, when caspase-8 activity is inhibited, RIPK1's kinase activity is unleashed, leading to its autophosphorylation and recruitment of RIPK3, thereby initiating necroptosis[28] (Figure 1). In summary, RIPK1 serves as a master regulator of PCD, integrating upstream signals and post-translational modifications to regulate cell-fate and inflammatory outcomes, including survival, inflammation, apoptosis, and necroptosis.

### 3.2. RIPK3

Receptor-interacting protein kinase 3 is the most proximal and critical member of the RIPK family involved in necroptosis, universally recognized as the primary executioner kinase of this process. Unlike RIPK1, which functions as a versatile "molecular switch," RIPK3 has a more specialized role, primarily driving necroptosis through its kinase activity. Additionally, RIPK3 contributes to inflammatory amplification, the regulation of apoptosis, and the indirect modulation of other forms of PCD in specific contexts.[29] The activation of RIPK3 is tightly controlled by phosphorylation, ubiquitination, and caspase-mediated cleavage.[11] Its N-terminal kinase domain, highly homologous to that of RIPK1, facilitates both autophosphorylation and substrate phosphorylation, essential for initiating necroptosis. In contrast, its unique RIP homotypic interaction motif (RHIM) enables interactions with RIPK1, Z-DNA-binding protein 1 (ZBP1), or TIR-domain-containing adapter-inducing interferon beta (TRIF), leading to the formation of the necrosome complex and triggering MLKL-mediated cell death.[30] Typically, RIPK3 activation follows RIPK1 autophosphorylation[31], which recruits RIPK3 through RHIM–RHIM interactions. This is followed by RIPK3 autophosphorylation, necrosome formation[32,33], and the recruitment and phosphorylation of MLKL, culminating in cellular ion imbalance, reactive oxygen species production, and plasma membrane rupture. RIPK3 can

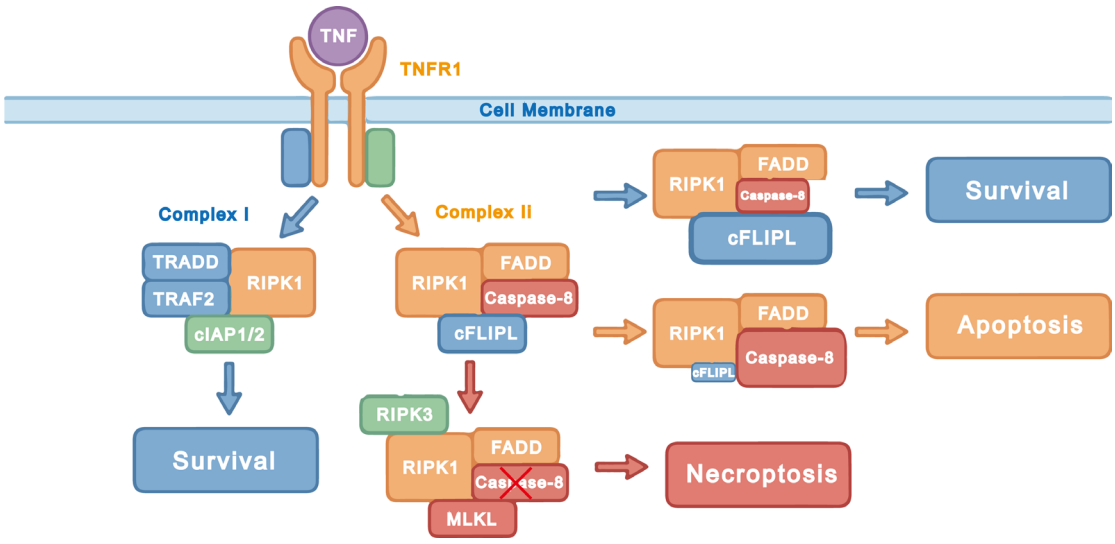


**Figure 1.** The complex pathway of RIPK1. Figure created by authors.

also be activated via RIPK1-independent pathways: ZBP1 can directly activate RIPK3 through RHIM, initiating necroptosis[34,35], and Toll-like receptor 3/4 (TLR3/4) signaling via TRIF can engage RIPK3's RHIM to trigger its activation.[29,36] In summary, RIPK3 activation is tightly regulated by upstream signals and is considered the definitive executioner of necroptosis.

Beyond its canonical role in MLKL-dependent necroptosis, RIPK3 has emerged as an important regulator of inflammatory cell death crosstalk. Under conditions of impaired inhibitor of apoptosis protein signaling, RIPK3 kinase activity has been shown to promote interleukin-1 activation, linking RIPK3 signaling to inflammasome-associated cytokine maturation.[37] In addition, recent studies have shown that, in the absence of inhibitor of apoptosis proteins, lipopolysaccharide triggers RIPK3-mediated activation of caspase-8, thereby promoting apoptosis and activation of the NLRP3–caspase-1 pathway, independently of RIPK3 kinase activity and MLKL. In contrast, when both inhibitor of apoptosis proteins and caspase-8 are absent, RIPK3 kinase activity and MLKL are required for TLR-induced NLRP3 activation. These findings demonstrate that RIPK3 can promote NLRP3 inflammasome activation and inflammatory cell death independently of MLKL, suggesting that RIPK3-mediated inflammatory signaling is not restricted to the canonical necroptosis pathway.[38] In the context of viral infection, Kuriakose *et al.*[39] further demonstrated that ZBP1/DAI activates the NLRP3 inflammasome and multiple PCD pathways, including RIPK3-dependent necroptosis, thereby providing mechanistic evidence for the involvement of RIPK3 in coordinated pyroptosis, apoptosis, and necroptosis. Together, these findings support the concept that RIPK3 is not merely an executor of necroptosis but also an important signaling node connecting necroptosis with pyroptosis-associated inflammatory responses and PANoptotic cell death.

### 3.3. Other RIPK family members

In contrast to the direct roles of RIPK1 and RIPK3 in cell death, RIPK2 and RIPK4 primarily influence cell survival or death indirectly through specific inflammatory pathways. RIPK2 functions predominantly as a scaffold protein and kinase in innate immune signaling, activating MAPK and IRF pathways through the nucleotide-binding oligomerization domain (NOD) signaling axis.[40–42] This results in the production of pro-inflammatory cytokines, such as interleukin (IL)-6, TNF-α, and IL-1β, as well as type I interferons.[43,44] RIPK2's involvement in PCD is relatively indirect, primarily amplifying inflammatory responses rather than directly regulating cell death. Similarly, RIPK4 does not serve as a core executioner of PCD. Its biological roles are more pronounced in the Wnt/β-catenin and NF-κB signaling pathways[45,46], influencing cell survival through the modulation of inflammatory responses rather than directly driving cell death. RIPK5, RIPK6, and RIPK7 remain understudied, with limited or no direct evidence linking them to PCD. However, as members of the RIPK family, their potential roles in modulating cell death may yet be uncovered.

## 4. Roles of the RIPK family in pancreatic diseases

The RIPK family plays a pivotal role in pancreatic diseases, primarily through the modulation of PCD, which influences disease progression. Among RIPK family members, RIPK1 and RIPK3 are the central players, particularly in the context of pancreatic acinar cell injury and necroptosis-associated inflammation. In contrast, the contributions of other RIPK family members to these diseases appear to be relatively minor.

Importantly, the relationship among RIPK1, RIPK3, and MLKL should not be interpreted as a universally linear cascade across all pancreatic disease settings. Canonical necroptosis is generally characterized by RIPK1-dependent activation of RIPK3 and subsequent MLKL phosphorylation, typically downstream of death receptor signaling. In contrast, non-canonical necroptotic signaling may involve RIPK1-independent RIPK3 activation through upstream innate immune adaptors or sensors, such as TRIF and ZBP1. Therefore, the contribution of individual RIPK members is highly context-dependent and may vary according to disease stage, initiating stimuli, cell type, inflammatory microenvironment, and therapeutic intervention.

### 4.1. Acute pancreatitis

Patients with AP usually develop continuous upper abdominal pain, sometimes radiating to the back, accompanied by marked elevations of serum amylase or lipase to more than three times the upper normal limit.[47] The disease manifests through a spectrum of inflammatory responses, ranging from localized to systemic. In the majority of patients, AP follows a mild clinical course and improves within a week. Nevertheless, nearly 20% of patients develop moderate-to-severe AP, in which pancreatic or peripancreatic necrosis and organ dysfunction substantially increase the risk of death, with mortality reported at 20–40%.[48–50]

The severity and prognosis of AP are primarily determined by two pathological factors: acinar cell necrosis and the extent of the inflammatory response. A recent clinical study employed enzyme-linked immunosorbent

assay (ELISA) to analyze plasma samples from patients with early mild AP (onset < 72 h), severe AP without persistent organ failure at sampling, severe AP with persistent organ failure, late severe AP, and healthy controls.[51] The results revealed that plasma RIPK3 levels were significantly higher in patients with severe AP than in healthy controls and were positively correlated with disease severity. Similarly, plasma MLKL levels were strongly associated with organ failure and were notably elevated even in early mild AP. Interestingly, RIPK1 levels were undetectable in most samples and did not differ significantly among groups, suggesting that circulating RIPK1 may not be a reliable biomarker of AP severity. However, this finding does not necessarily exclude a local or phosphorylation-dependent role of RIPK1 within pancreatic tissue.

Prior work also linked elevated RIPK3 and phosphorylated MLKL (p-MLKL) expression to greater necrotic injury, whereas RIPK1 showed an inverse association.[52] Notably, small interfering RNA (siRNA)-mediated inhibition of RIPK1 increased acinar cell necrosis and suppressed NF-κB activation, yielding a paradoxical finding relative to the conventional view that RIPK1 depletion alleviates AP by mitigating necroptosis. However, other animal models of induced AP demonstrated that RIPK1 inhibition reduced disease severity. For instance, necrostatin-1 (Nec-1), a RIPK1 inhibitor, significantly attenuated pancreatic necrosis and improved survival rates in animal models.[53] Another study confirmed that Nec-1 treatment reduced necrosis, hemorrhage, and edema, with minimal neutrophil infiltration, effectively ameliorating pancreatic injury after 24 h.[54] These findings highlight the conflicting role of RIPK1: while molecular mechanisms and some animal models position RIPK1 as a key pathological regulator, clinical data and alternative experimental evidence suggest it may not be as central as previously thought.

These divergent findings cannot be fully explained by the lack of phosphorylated RIPK1 data alone. Several alternative explanations should be considered. First, different AP models may activate distinct injury and inflammatory pathways[55], leading to variable dependence on RIPK1 kinase activity, RIPK1 scaffold function, RIPK3, and MLKL. Second, genetic or siRNA-mediated RIPK1 depletion and pharmacological RIPK1 inhibition are not mechanistically equivalent. RIPK1 knockdown may impair scaffold-dependent NF-κB survival signaling, thereby exacerbating acinar cell necrosis, whereas Nec-1 may preferentially inhibit RIPK1 kinase-dependent necroptotic signaling within a specific therapeutic window. Third, Nec-1 has potential RIPK1-independent or off-target effects, including reported effects on indoleamine 2,3-dioxygenase.[56] Therefore, its protective effects should not be interpreted as unequivocal evidence of RIPK1-specific pathogenicity. Finally, differences in intervention timing, drug dose, disease stage, and experimental readouts may further contribute to inconsistent conclusions. Together, these findings suggest that RIPK1 has dual and context-dependent functions in AP rather than serving as a uniformly pathogenic upstream driver of the RIPK1–RIPK3–MLKL axis. Future studies should combine tissue-specific genetic models, more selective RIPK1 kinase inhibitors, and parallel detection of phosphorylated RIPK1, RIPK3, and MLKL to distinguish RIPK1 kinase-dependent necroptosis from RIPK1 scaffold-dependent inflammatory or survival signaling.

In contrast to the controversial role of RIPK1, RIPK3 is more consistently associated with necrotic injury and inflammatory amplification in AP, together with MLKL. Evidence from genome-wide siRNA screening highlights RIPK3 and its kinase activity as essential for executing necroptosis.[57] In severe AP, RIPK3-dependent MLKL activation may contribute to acinar cell death, tissue necrosis, DAMP release, and systemic inflammatory amplification, all of which are critical determinants of disease severity.[58] Nevertheless, it is important to distinguish between canonical and non-canonical mechanisms of RIPK3 activation. In the canonical model, RIPK1 interacts with RIPK3 to form the necrosome and subsequently promotes MLKL phosphorylation. However, RIPK3 can also be activated through RIPK1-independent mechanisms, including innate immune adaptor-mediated pathways such as TRIF- or ZBP1-dependent signaling. Thus, although RIPK1 inhibition may attenuate pancreatic injury in some models, persistent RIPK3/MLKL activation could theoretically occur through alternative upstream routes. This pathway redundancy may help explain why RIPK1-, RIPK3-, and MLKL-related findings are not always concordant across clinical samples and experimental AP models. The specialized function of RIPK3, which is primarily dedicated to necroptosis, sets it apart from other family members. Therefore, inhibiting or depleting RIPK3 significantly reduces pancreatic injury *in vivo*, positioning it as a promising therapeutic target for AP.[53]

### 4.2. Chronic pancreatitis

Chronic pancreatitis is a progressive fibroinflammatory disorder of the pancreas[59,60], characterized by excessive apoptosis and necroptosis of parenchymal cells, recruitment of inflammatory leukocytes, and advancing fibrosis.[61,62] Pancreatic fibrosis, a hallmark of CP, contributes to sustained and irreversible damage to the gland. Pancreatic stellate cells (PSCs) are the primary source of ECM deposition during pancreatic injury, and

the persistence of PSC activation plays a critical role in the progression of fibrosis.[63]

Extensive clinical and experimental evidence has established a strong causal link between cell death and fibrosis.[64] Over the past decade, various forms of cell death have been identified, each eliciting distinct biological responses and outcomes in different disease contexts.[65] Recent studies suggest that apoptosis and necroptosis, compared to pyroptosis, ferroptosis, and autophagy, hold greater relevance in the fibrotic process.[66] However, in CP, necroptosis should be considered one component of an integrated injury–inflammation–fibrosis network rather than a single linear driver of disease progression. Repeated acinar cell injury may release DAMPs and inflammatory mediators that promote immune cell recruitment and PSC activation. In this setting, RIPK3/MLKL-dependent necroptosis may amplify inflammation, whereas RIPK1 may exert both kinase-dependent and scaffold-dependent effects on cell death and inflammatory signaling.

Persistent activation of the NF-κB pathway in acinar cells has been identified as a central pathogenic mechanism in CP, independent of trypsinogen activation.[50] Furthermore, Huang *et al.*[67] demonstrated that sustained NF-κB activation exacerbates CP severity. The RIPK family plays a key role in NF-κB regulation in a member-specific manner, with RIPK1, RIPK2, and RIPK4 all contributing to its modulation. For example, the deubiquitinase OTUD1 not only suppresses colonic inflammation by inhibiting RIPK1-mediated NF-κB signaling[68] but also mitigates cerebral ischemic injury by disrupting RIPK2 ubiquitination, thus inhibiting NF-κB activation.[43] Consequently, the RIPK family holds significant therapeutic potential in inflammation-driven diseases. Nevertheless, most evidence connecting RIPK members to CP-associated fibrosis remains indirect. RIPK1 has a plausible mechanistic link to CP because it can regulate both cell death and NF-κB-dependent inflammatory signaling, which may secondarily influence PSC activation through DAMP release, cytokine production, and immune-cell recruitment. By contrast, the roles of RIPK2 and RIPK4 in pancreatic fibrosis are less well established. Although RIPK2 and RIPK4 have been implicated in NF-κB regulation in other inflammatory or epithelial contexts, direct experimental evidence showing that RIPK2 or RIPK4 promotes PSC activation, collagen production, or ECM deposition in CP is currently limited. Therefore, their involvement in pancreatic fibrosis should be regarded as a hypothesis derived from their broader inflammatory functions rather than as a confirmed CP-specific mechanism.

These observations suggest that RIPK members may influence CP through mechanisms beyond classical necroptosis. RIPK1 may regulate inflammatory and survival signaling through NF-κB, RIPK3 may contribute to necroptotic injury and DAMP-driven inflammation, and other RIPK family members may modulate innate immune or stress-response pathways. However, direct evidence defining a causal hierarchy among RIPK1, RIPK3, and MLKL in CP remains limited. In particular, it remains unclear whether fibrosis in CP is driven primarily by canonical RIPK1-dependent necroptosis, by RIPK1-independent RIPK3/MLKL activation, or by necroptosis-independent inflammatory functions of RIPK proteins. However, research specifically linking RIPK members to CP remains limited, and it is expected that the role of RIPK-mediated regulation in CP will receive increasing attention in the near future.

### 4.3. Pancreatic cancer

The RIPK family is closely associated with PC, a highly aggressive malignancy characterized by a poor prognosis. Key clinical features of PC include apoptosis resistance, a pro-inflammatory microenvironment, dense fibrotic stroma, and notable chemoresistance.[69] The RIPK family influences tumorigenesis, disease progression, and therapeutic response by modulating necroptotic, apoptotic, and inflammatory signaling pathways. Among the RIPK members, RIPK1 and RIPK3 have been the most extensively studied, and the pharmacological induction of these pathways has emerged as a promising therapeutic strategy. In contrast, the roles of other RIPK family members in PC remain relatively underexplored. However, the biological consequences of RIPK signaling in PC are highly context-dependent. Depending on tumor cell-intrinsic signaling, stromal interactions, immune contexture, and therapeutic pressure, RIPK-mediated pathways may either suppress tumor growth by promoting cancer cell death or support tumor progression by enhancing inflammation, immune evasion, or tissue remodeling.

RIPK1 and RIPK3, key components of the necrosome, are upregulated in PC[70], highlighting the distinct role of the RIPK family in this malignancy. Ando *et al.*[71] confirmed through immunohistochemistry and Western blot analysis that RIPK3 and MLKL expression levels are significantly elevated in PC tissues compared to normal pancreatic tissues. Further research revealed that CHMP4C promotes PC progression by inhibiting necroptosis via the RIPK1/RIPK3/MLKL signaling axis.[72] Salecan, a naturally occurring β-glucan polysaccharide, significantly inhibits PC cell proliferation, with mechanistic studies showing that it suppresses PC progression by inducing necroptosis through the RIPK1/MLKL pathway.[73] Additionally, AdipoRon, an anti-diabetic adiponectin receptor agonist, has been shown to inhibit PC growth by triggering

RIPK1/ERK-dependent necroptosis.[74] Moreover, 6-methoxydihydroavicine, an alkaloid from *Scutellaria baicalensis*, induces RIPK1/caspase-dependent cell death, thereby inhibiting PC development.[75] These findings highlight the therapeutic potential of the RIPK family, particularly RIPK1, in PC.

Although these studies support the therapeutic relevance of RIPK-mediated cell death in PC, they should be interpreted with caution. First, RIPK1-, RIPK3-, and MLKL-associated signaling in cancer does not always represent a simple canonical necroptosis cascade. RIPK1 can regulate apoptosis, necroptosis, NF-κB activation, MAPK signaling, and inflammatory cytokine production, whereas RIPK3 may participate in both MLKL-dependent necroptosis and MLKL-independent inflammatory or metabolic regulation. Second, non-canonical RIPK3 activation may occur under conditions of innate immune sensing, inflammatory stimulation, or therapy-induced cellular stress, potentially bypassing RIPK1. Third, induction of necroptosis in tumor cells may have dual consequences: it can directly eliminate apoptosis-resistant cancer cells, but it may also release DAMPs and cytokines that reshape the tumor microenvironment. Consequently, the development of RIPK-targeted therapeutic strategies and biomarker assays is an emerging research frontier. However, such approaches should distinguish kinase-dependent and scaffold-dependent functions of RIPK1, RIPK3/MLKL-dependent necroptosis, non-canonical RIPK3 activation, and necroptosis-independent inflammatory signaling.

## 5. Biomarker potential of RIPK-family signaling

Mechanistically, RIPK3-mediated necroptosis promotes MLKL phosphorylation, plasma membrane disruption, DAMP release, and inflammatory amplification. These molecular events provide a rationale for exploring RIPK3 and p-MLKL as potential biomarkers of necroptotic activity and inflammatory severity. In AP, increased activation of the RIPK3–MLKL axis may reflect acinar cell injury and sterile inflammation, whereas in PC, altered RIPK signaling may be associated with tumor cell death, immune microenvironment remodeling, and therapeutic responsiveness. Indicators linked to the RIPK signaling pathway have shown significant promise as diagnostic tools for pancreatic diseases. Although RIPK pathway-based diagnostic biomarkers have not yet been widely adopted in clinical practice, ongoing research points to promising developments. The clinical utility of RIPK-related biomarkers lies in their ability to specifically reflect necroptotic activity, which can be leveraged for assessing disease severity, prognostic prediction, therapeutic monitoring, and drug target screening. To date, RIPK3 and p-MLKL are the most well-established biomarkers for necroptosis[51,76], with commercially available ELISA kits already in use. In contrast, due to the complex multifunctional roles of RIPK1, its analysis often requires interpreting its specific phosphorylation status. However, current evidence remains preliminary, and the clinical utility of RIPK3 or p-MLKL as diagnostic or prognostic biomarkers requires validation in larger, multicenter cohorts with standardized detection platforms and clinically meaningful endpoints.

Furthermore, microRNA (miRNA) expression profiling in tissue samples from patients with PC has identified several miRNAs associated with PC pathogenesis.[77] While a direct link between these miRNAs and the RIPK family has not been conclusively established, given the critical roles of RIPK members in cell death and inflammation—processes regulated by miRNAs—it is plausible that RIPK family members may be targeted by these miRNAs. Such interactions could influence the initiation and progression of PC, offering potential molecular targets for its diagnosis. However, this possibility remains speculative until supported by direct target validation experiments.

From a clinical perspective, RIPK-related molecules may help stratify patients according to disease severity, inflammatory activity, or treatment susceptibility. For example, in AP, activation of the RIPK3–MLKL pathway may indicate extensive acinar cell injury and sterile inflammation, potentially contributing to early risk assessment. In CP, RIPK-associated inflammatory pathways may be linked to fibroinflammatory remodeling, although direct evidence for a causal role in fibrosis remains limited. In PC, RIPK signaling may influence tumor cell death, immune cell recruitment, and responses to chemotherapy, radiotherapy, or immunotherapy. Therefore, integrating RIPK-related markers with established clinical parameters may provide a more refined approach to patient stratification, although prospective validation is still needed.

## 6. Drug development targeting the RIPK family

Within the RIPK family, RIPK1 and RIPK3 are the primary therapeutic targets for drug discovery. To date, several compounds have advanced to clinical trials, primarily targeting conditions such as inflammatory disorders, neurodegenerative diseases, and malignancies. Although a few inhibitors targeting RIPK2 are also under development, RIPK4–RIPK7 remain largely unexplored in therapeutic applications, with no drug candidates reported to date.

In diseases such as AP, inhibiting RIPK kinase activity is critical for mitigating necroptosis and the subsequent inflammatory response. For example, Nec-1 suppresses necroptotic signaling pathways, reducing necrotic cell death during disease progression.[78] This compound has been shown to significantly reduce pancreatic necrosis and improve survival rates in multiple animal models.[53] Another promising candidate is GSK2982772[79], although its specific efficacy in AP models requires further investigation. In contrast to RIPK1, the development of RIPK3 inhibitors has been relatively limited, and their therapeutic benefits in the context of AP remain unvalidated. The effects of inhibitors such as GSK872[80] and GSK2983559 on AP progression are yet to be fully explored.

In PC, GSK3145095 binds potently to RIPK1 with exceptional kinase specificity and effectively blocks RIPK1 kinase-dependent cellular responses, highlighting its potential as a novel oncological therapy. Additionally, this inhibitor has been shown to promote a tumor-suppressive T-cell phenotype in PC tissue cultures. Currently, GSK3145095 is undergoing Phase I clinical trials for the treatment of PC and other selected solid malignancies.[81] However, not all compounds reported to modulate RIPK-associated signaling in PC should be considered RIPK-specific agents. For example, Salecan and AdipoRon have been shown to suppress PC cell growth and to affect necroptosis-related markers, but their mechanisms are heterogeneous and may involve RIPK-independent pathways. Salecan may exert broader effects on cellular stress and immune-related signaling, whereas AdipoRon, as an adiponectin receptor agonist, can influence ERK signaling, AMP-activated protein kinase–related metabolic regulation, mitochondrial function, and tumor metabolism. Given that metabolic reprogramming is a prominent feature of pancreatic ductal adenocarcinoma, as supported by metabolomic studies identifying altered metabolites in early-stage pancreatic ductal adenocarcinoma[82], the antitumor effects of these agents should not be attributed solely to RIPK-mediated necroptosis.

Despite these translational opportunities, several limitations remain. First, most clinical associations between RIPK-related molecules and disease outcomes are derived from small or retrospective cohorts. Second, detection methods for RIPK3, MLKL, and p-MLKL, including immunohistochemistry, Western blotting, ELISA, and transcriptomic analyses, are not standardized across studies. Third, the functional meaning of RIPK expression may differ by cell type, disease stage, and treatment context. Future studies should incorporate prospective multicenter cohorts, standardized biomarker assays, longitudinal sampling, and integration with clinical severity scores, imaging findings, and therapeutic outcomes. Such efforts will be necessary to determine whether RIPK-related markers can be translated into clinically useful diagnostic, prognostic, or therapeutic tools.

## 7. Discussion

Future research on pancreatic diseases offers both significant challenges and substantial opportunities. In basic research, it is crucial to further elucidate the detailed molecular mechanisms of RIPK-dependent and -independent pathways in pancreatic pathologies, including the intricate interactions between these pathways and their crosstalk with other signaling networks. These insights will be instrumental in identifying novel therapeutic targets and developing more precise treatment strategies. Simultaneously, a key focus of future investigations should be the creation of sophisticated animal and *in vitro* models that more accurately replicate the initiation and progression of human pancreatic diseases, providing a stronger foundation for mechanistic studies and drug screening.

The biological and clinical significance of RIPK signaling is highly context-dependent and may vary across disease types, disease stages, cell populations, and patient backgrounds. In AP, activation of the RIPK3–MLKL axis may primarily reflect acinar cell necroptosis, DAMP release, and sterile inflammatory amplification, particularly during the early phase of tissue injury. In CP, sustained RIPK-associated inflammatory signaling may contribute to fibroinflammatory remodeling, although direct evidence linking RIPK family members to fibrosis remains limited. In PC, RIPK signaling may have dual and stage-dependent functions: it may promote tumor cell death and antitumor immune activation under certain conditions, whereas chronic RIPK-associated inflammation may also support immune suppression, stromal remodeling, tumor progression, or therapeutic resistance. In addition to disease-stage specificity, RIPK signaling should be interpreted in a cell-type-specific manner. In pancreatic acinar cells, RIPK3–MLKL activation may directly mediate necroptotic injury. In immune cells, RIPK1/RIPK3 signaling can regulate cytokine production, inflammasome activation, and inflammatory cell death crosstalk. In PSCs and fibroblasts, RIPK-associated inflammatory pathways may indirectly influence ECM deposition and fibrotic remodeling. In tumor cells, the expression and activation status of RIPK3, MLKL, and related molecules may determine susceptibility to necroptosis or therapy-induced cell death. Patient-level factors, including disease etiology, clinical severity, metabolic status, genetic background, immune microenvironment, and prior

treatment exposure, may further modify the role of RIPK signaling. For example, tumor genotype, immune-cell infiltration, stromal abundance, and prior chemotherapy or radiotherapy may influence whether RIPK-mediated cell death contributes to antitumor immunity or tumor-promoting inflammation. These heterogeneities have important translational implications, suggesting that RIPK-related biomarkers and RIPK-targeted therapies should not be interpreted using a one-size-fits-all approach. Future studies should incorporate disease-stage stratification, longitudinal sampling, cell-type-resolved analyses, and patient subgroup validation to determine when and in whom RIPK signaling is clinically relevant.

Current diagnostic innovations centered on the RIPK pathway are focused on refining biomarker detection methodologies. At the molecular level, advances in genomic sequencing and protein analysis have significantly enhanced the sensitivity and throughput of assays targeting RIPK-related genes and proteins. For example, next-generation sequencing allows for the precise identification of mutations within the RIPK signaling axis, offering a powerful tool to uncover the molecular foundations of pancreatic diseases. In parallel, the development of proteomic technologies enables a comprehensive qualitative and quantitative characterization of the RIPK-related proteomic landscape, which is essential for discovering novel diagnostic markers.[83] While specific RIPK-targeted medical imaging modalities are not yet available, emerging functional techniques such as functional magnetic resonance imaging and positron emission tomography enable the assessment of pancreatic pathologies from metabolic and functional perspectives. Biological processes linked to the RIPK pathway, such as cellular metabolic shifts and inflammatory responses, may manifest indirectly through these imaging modalities, providing complementary diagnostic insights. For instance, combining positron emission tomography-based metabolic activity assessments with RIPK-related biomarker analysis could offer a more holistic evaluation of disease status in patients with PC.[84]

The development of novel therapeutic agents targeting the RIPK pathway is a critical frontier in managing pancreatic diseases. Although several RIPK inhibitors have been developed, they face challenges such as suboptimal specificity and significant adverse effects. Future efforts must focus on optimizing inhibitor design to improve both selectivity and binding affinity for RIPK targets. Advances in structural biology and computer-aided drug design will be vital for gaining deeper insights into the three-dimensional structure of RIPK proteins, aiding in the rational design of small-molecule inhibitors. Such precision could minimize off-target interactions, reducing side effects.[85] Furthermore, combinatorial therapeutic strategies have emerged as a primary research focus. Given the complexity of pancreatic pathologies, monotherapy often provides limited clinical benefits. Integrating RIPK inhibitors with conventional chemotherapy, targeted therapies, or immunotherapies may produce synergistic effects, enhancing overall therapeutic efficacy. For example, combining RIPK1 inhibitors with poly ADP ribose polymerase inhibitors in PC treatment could potentiate antitumor activity by blocking both cell survival signaling and DNA damage repair pathways. Additionally, developing multi-node inhibition strategies within the RIPK pathway itself could provide a more comprehensive suppression of pathway activity, improving treatment outcomes. It is worth noting that necroptosis can promote the release of DAMPs and inflammatory mediators, which may enhance antitumor immune activation under certain conditions. Conversely, chronic necroinflammation may support tumor progression, immune suppression, and stromal remodeling. Therefore, the role of RIPK3-mediated necroptosis in cancer therapy is likely context-dependent. Assessing RIPK3, MLKL, and p-MLKL status may help clarify whether a tumor is more susceptible to necroptosis-inducing strategies or whether RIPK-associated inflammation contributes to therapeutic resistance.

Therapeutically, the RIPK1–RIPK3–MLKL axis represents a potential target for modulating necroptosis-driven inflammation and tissue injury. RIPK1 inhibitors, such as Nec-1/Nec-1s and several clinically developed small molecules, have shown protective effects in preclinical inflammatory disease models by limiting necroptotic cell death and inflammatory cytokine release. Experimental RIPK3 inhibitors and MLKL inhibitors have also been used to dissect the contribution of necroptosis to tissue damage. In pancreatic diseases, such approaches may be particularly relevant for acute inflammatory injury, where excessive necroptosis can amplify sterile inflammation. However, therapeutic translation requires caution, as RIPK signaling also contributes to host defense, tissue repair, and antitumor immunity. Thus, the timing, disease stage, and cellular context of RIPK inhibition need to be carefully defined before clinical application.

## 8. Conclusion

In conclusion, RIPK family members play central roles in regulating PCD, inflammation, fibrosis, and tumor progression in pancreatic diseases. RIPK-mediated signaling may serve as a source of valuable biomarkers and promising therapeutic targets for AP, CP, and PC.

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## Conflict of interest

The authors declare no conflicts of interest related to this work.

## Author contributions

*Conceptualization:* Fan Zhang
*Visualization:* Fan Zhang , Dingmao Wang
*Writing–original draft:* All authors
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## Ethics approval and consent to participate

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