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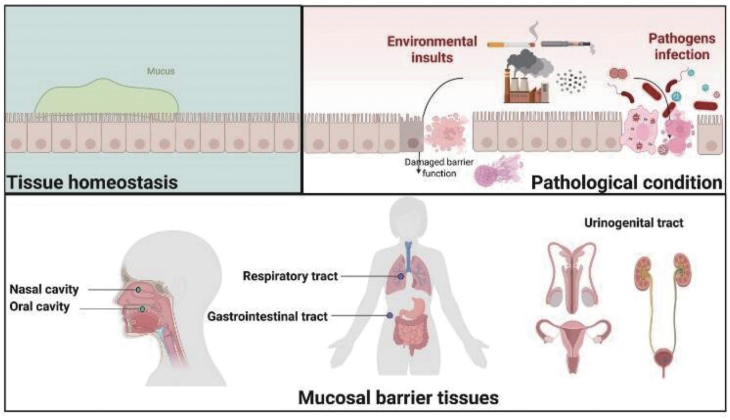
Multilayered molecular architecture orchestrating programmed cell death in mucosal barriers tissues

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ABSTRACT: Mucosal barrier tissues, including the nasal, respiratory, oral, gastrointestinal, and urinogenital tract, constitute the largest interface between the host and the external environment. These surfaces are continuously exposed to pathogen infection and environmental pollutants. Disruption of mucosal barrier integrity leads to various inflammatory and infectious diseases. Emerging evidence suggests that programmed cell death (PCD) plays a crucial role in shaping the integrity of barrier and local immune responses. In recent years, rapid advances have led to the identification of multiple newly characterized PCD, including apoptosis, necroptosis, autosis, pyroptosis, PANoptosis, ferroptosis, cuproptosis, parthanatos, NETosis, disulfidptosis, entosis, anoikis, methuosis, alkaliptosis, oxeiptosis, lysozincrosis, NECSO (necrosis by sodium overload), and mitoxyperiosis. In this review, we summarize recent advances in PCD, emphasizing their morphological features, activation cascades, and regulatory mechanisms, and discuss their implications in mucosal barrier homeostasis. We further examine how dysregulated PCD contributes to epithelial dysfunction, chronic inflammation, and pathogen infection.



KEYWORDS: programmed cell death, epithelial cells, mucosal barrier, tissue injury

1 Introduction

As an irreversible biological process, cell death functions as a double-edged sword in maintenance of tissue homeostasis. When precisely activated and regulated, it facilitates the controlled elimination of damaged, infected, or superfluous cells, thereby preserving tissue integrity. However, its inappropriate or excessive activation can disrupt cellular and tissue homeostasis, leading to the initiation and progression of diverse pathological conditions, including immune disorders, developmental abnormalities, degenerative diseases, and cancers. Cell death is traditionally classified into programmed and non-programmed forms. Over the past years, rapid conceptual and mechanistic breakthroughs have dramatically reshaped our understanding of cell death. A growing spectrum of newly defined and mechanistically distinct programmed cell death (PCD) has been identified, including apoptosis, necroptosis, autosis, pyroptosis, PANoptosis, ferroptosis, cuproptosis, parthanatos,

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NETosis, disulfidptosis, entosis, anoikis, methuosis, alkaliptosis, oxeiptosis, lysozincrosis, NECSO (necrosis by sodium overload), and mitoxyperiosis. Furthermore, several types of cell death previously regarded as non-programmed are now recognized as being subject to precise molecular regulation. For example, mechanical stress-induced plasma membrane rupture (PMR), which involves coordinated signaling rather than representing a purely passive event[1]. These advances are particularly relevant to mucosal tissues, where epithelial cells are constantly exposed to mechanical stress, pathogen infection, and environmental insults. To better understand how PCD contributes to mucosal barrier integrity, it is essential to delineate its defining morphological features as well as the underlying molecular mechanisms governing its activation.

2 The morphological and historical landscape of PCD

PCD is an actively regulated form of biological process controlled by defined genetic programs and signaling cascades[2]. Since the term was first introduced in the 1960s, the understanding of PCD has expanded dramatically, encompassing an increasingly diverse morphological features (Fig. 1)[3,4].

2.1 Apoptosis

Apoptosis is the earliest identified and most extensively characterized form of PCD. Although physiological cell elimination had been observed previously, the term “apoptosis” was formally introduced in 1972 by Kerr, Wyllie, and Currie to describe a regulated biological process with characteristic morphological features[5]. They defined apoptosis as occurring in a sequence of morphological and biochemical events: initial nuclear and cytoplasmic condensation with fragmentation into membrane-bound apoptotic bodies, followed by their rapid engulfment and lysosomal degradation by neighboring cells or phagocytes, ensuring non-inflammatory clearance. A major breakthrough arose from genetic studies in *C. elegans* by Brenner, Horvitz, and Sulston, which identified key death-causing genes and their mammalian homologues, thereby establishing apoptosis as a genetically regulated and evolutionarily conserved process[6]. Building upon this framework, subsequent study further delineated context-specific apoptosis. In 1994, Anoikis was identified as a form of apoptosis induced by loss of cell-extracellular matrix adhesion, serving as a critical safeguard against inappropriate anchorage-independent survival, and can be suppressed by oncogenic transformation or anti-apoptotic signaling such as Bcl-2 overexpression[7].

2.2 Pyroptosis

Pyroptosis is a pro-inflammatory form of PCD primarily associated with innate immune responses against infection. The earliest observations can be traced back to the year of 1986 when treatment of primary murine macrophages with anthrax lethal toxin was shown to induce rapid cell lysis accompanied by release of intracellular contents[8]. In 2001, the term "pyroptosis" was formally introduced to describe this caspase-1-dependent, pro-inflammatory form of PCD. The name is derived from the Greek word pyro, meaning fire or fever, reflecting its inflammatory nature, and ptosis, meaning falling, to denote a form of cell death[9]. Morphologically, pyroptosis is characterized by progressive cell swelling driven by osmotic imbalance, leading to membrane blebbing with bubble-like protrusions known as pyroptotic bodies, and ultimately culminating in plasma membrane rupture[10]. The loss of membrane integrity results in the release of damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP), as well as cytosolic enzymes such as lactate dehydrogenase (LDH), thereby amplifying local inflammatory responses[11-13].

2.3 Necroptosis

Necroptosis is a regulated form of necrotic cell death that serves as an alternative PCD when apoptosis is inhibited. Early studies showed that caspase inhibition markedly increased the sensitivity of L929 cells to tumor necrosis factor (TNF) -induced necrosis, indicating the existence of a caspase-independent but programmed cell death[14]. A pivotal advance came when Yuan and colleagues demonstrated that this process could be specifically inhibited by the small molecule necrostatin-1 (Nec-1), thereby providing the first direct evidence that necrotic cell death can be genetically and pharmacologically regulated. They subsequently termed this pathway “necroptosis,” establishing it as a distinct and controllable form of PCD[15]. Morphologically, necroptosis resembles classical necrosis, characterized by organelle swelling, minimal nuclear fragmentation, plasma membrane rupture, and the release of intracellular contents[16].

2.4 NETosis

NETosis is a neutrophil-specific form of PCD. Early observations revealed that potent stimulation of human neutrophils with phorbol 12-myristate 13-acetate (PMA) induced rapid cell death distinct from classical apoptosis or necrosis[17]. In 2004, Arturo Zychlinsky and colleagues first reported the formation of neutrophil extracellular traps (NETs), in which neutrophils release chromatin-granule protein complexes that ensnare Gram-positive and Gram-negative bacteria[18]. The term “NETosis” was subsequently introduced in 2007 to define the regulated neutrophil cell death process associated with NET formation in host defense against pathogens[19]. Morphologically, NETosis proceeds in a stepwise manner, beginning with loss of lobulated nuclear morphology and

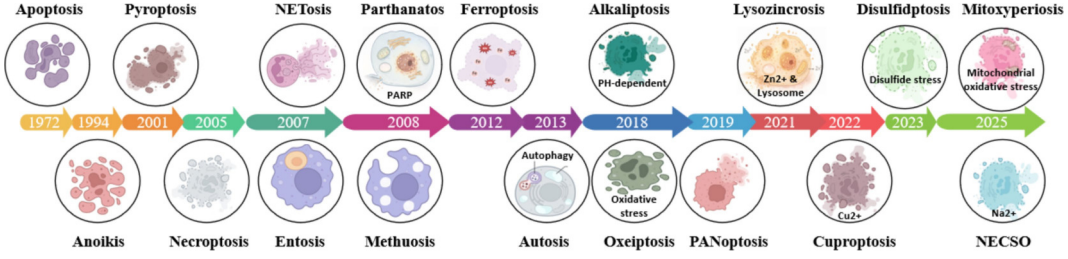


Figure 1 Historical timeline of programmed cell death. Timeline of the terms used in programmed cell death, including apoptosis, anoikis, pyroptosis, necroptosis, NETosis, entosis, parthanatos, methuosis, ferroptosis, autosis, alkaliptosis, oxeiptosis, PANoptosis, lysozincrosis, cuproptosis, disulfidptosis, NECSO, and mitoxyperiosis.

the distinction between eu- and heterochromatin, followed by disappearance of internal membranes and allows NET components to mix. The process culminates in plasma membrane rupture and extracellular release of NET[20].

2.5 Entosis

Entosis is a unique form of cell death characterized by the invasion of one living cell into another, resulting in the formation of "cell-in-cell" structures. It was first described in 2007 during studies of epithelial cancer cells detached from the extracellular matrix, where investigators observed that suspended cells actively invaded neighboring cells rather than undergoing classical apoptosis. This previously unrecognized phenomenon was subsequently named "entosis"[21]. Morphologically, entosis is defined by the presence of intact "cell-in-cell" structures, in which the internalized cell retains a relatively normal nuclear morphology and a majority were negative for cleaved caspase-3 staining[22].

2.6 Parthanatos

Parthanatos is a PCD driven by excessive activation of poly (ADP-ribose) polymerase-1 (PARP-1) in response to severe DNA damage. Unlike apoptosis, parthanatos is caspase-independent and is primarily mediated by the accumulation of poly(ADP-ribose) (PAR) polymers, which trigger an unique cell death cascade. The conceptual foundation of this biological process can be traced back to the early 1990s with the formulation of the "PARP suicide hypothesis". This hypothesis proposed that extensive DNA strand breaks activate PARP-1, leading to massive poly(ADP-ribose) (PAR) synthesis and depletion of its substrate nicotinamide adenine dinucleotide (NAD^+), ultimately resulting in cellular energy failure and cell death[23]. Building upon these observations, subsequent mechanistic studies led by Valina L. Dawson, Ted M. Dawson and their colleagues revealed that excessive PAR formation triggers the mitochondrial release of apoptosis-inducing factor (AIF), which translocates to the nucleus and induces large-scale DNA fragmentation in a caspase-independent manner[24-26]. In 2008, this PARP-1-dependent cell death pathway was termed “parthanatos”. The name, derived from “PAR” and Thanatos-the personification of death in Greek mythology-reflects its dependence on poly(ADP-ribose) polymerases, particularly PARP-1, which accounts for the majority of cellular PARP activity[27]. The morphological signature of parthanatos includes nuclear shrinkage, chromatin condensation, and early plasma membrane permeability, as indicated by rapid propidium iodide uptake[27].

2.7 Ferroptosis

Ferroptosis is a distinct form of iron-dependent PCD characterized by the accumulation of lipid peroxides and oxidative membrane damage. In 2003, Brent R. Stockwell and colleagues employed synthetic lethal high-throughput screening of 23,550 compounds and discovered that oncogenic alterations sensitized tumorigenic cells to a distinct nonapoptotic cell death process induced by erastin, laying the foundation for the later identification of ferroptosis[28]. Subsequently, two additional compounds, designated RAS-selective lethal 3 (RSL3) and RAS-selective lethal 5 (RSL5), were found to exhibit enhanced cytotoxicity in cells harboring oncogenic rat sarcoma virus (RAS)[29]. In 2012, Stockwell and colleagues termed “ferroptosis” to describe it as an iron-dependent form of PCD that is distinct from apoptosis, necrosis, and autophagy. Furthermore, they identified ferrostatin-1 as a specific inhibitor of this process and demonstrated that erastin induces ferroptosis by blocking cystine uptake, thereby triggering iron-dependent lipid peroxidation[30]. Morphologically, ferroptosis is characterized by increased mitochondrial membrane densities, reduced or absent mitochondrial cristae, rupture of the outer mitochondrial membrane, and preservation of nuclear integrity[31].

2.8 Autosis

Autosis is a distinct form of autophagy-dependent PCD that occurs independently of apoptosis and necroptosis. Early studies reported that dying cells frequently contained abundant autophagosomes, which led to the early classification of autophagy as a form of cell death[32,33]. In 2013, Beth Levine and colleagues showed that Tat-Beclin1 induces dose-dependent autophagy-associated cell death that is regulated by sodium/potassium- adenosine triphosphatase (Na^+/K^+-ATPase) and inhibited by cardiac glycosides, establishing it as a genetically controlled and targetable pathway. They coined the term “autosis” to describe this mechanistically distinct PCD driven by excessive or dysregulated autophagy[34]. Morphologically, autosis proceeds in two phases. Phase 1 features nuclear convolution with moderately condensed chromatin, electron-dense mitochondria, dilated and fragmented endoplasmic reticulum, and accumulation of autophagosomes and autolysosomes. A hallmark event is focal swelling of the perinuclear space along the inner nuclear membrane. Phase 2 is marked by pronounced ballooning of the perinuclear space with nuclear concavity, generalized organelle swelling, and reduced autophagic structures, producing a morphology resembling necrosis. The dynamic expansion of the perinuclear space distinguishes autosis from other forms of PCD[34].

2.9 PANoptosis

PANoptosis is a form of PCD that integrates key components of pyroptosis, apoptosis, and necroptosis into a coordinated death program. The concept of PANoptosis was proposed in 2019 by Thirumala-Devi Kanneganti and colleagues following the identification of Z-DNA-binding protein 1 (ZBP1) as a innate immune critical sensor mediating influenza-induced inflammatory cell death[35]. Their findings demonstrated that activation of ZBP1 triggers simultaneous engagement of caspases, receptor-interacting protein (RIP) kinases, and inflammasome components, suggesting that these pathways can function in a highly interconnected manner rather than as isolated mechanisms[36,37]. Morphologically, PANoptotic cells exhibit overlapping features of multiple death modalities, including membrane pore formation and cellular swelling reminiscent of pyroptosis, chromatin condensation characteristic of apoptosis, and membrane rupture typical of necrotic death[38]. The coexistence of these hallmarks reflects its hybrid and integrative nature. Although PANoptosis incorporates fundamental elements of individual cell death pathways, it represents a coordinated and mechanistically distinct process that cannot be adequately explained by any single modality alone.

2.10 Cuproptosis

Cuproptosis is a recently defined form of PCD driven by intracellular copper accumulation and proteotoxic stress. Unlike apoptosis, necroptosis, or pyroptosis, cuproptosis is not primarily mediated by caspases or membrane pore formation, but instead results from copper-induced disruption of mitochondrial metabolic processes. Initial evidence linking copper-dependent cell death to mitochondrial metabolism emerged in 2019, when Todd R. Golub

and colleagues demonstrated that the small molecule elesclomol targets the mitochondrial reductase ferredoxin 1 (FDX1) and induces a distinct copper-dependent cytotoxicity[39]. Building upon this mechanistic foundation, the same group formally introduced the concept of "cuproptosis" in 2022, showing that copper directly binds to lipoylated components of the tricarboxylic acid (TCA) cycle, promoting their aggregation and the subsequent loss of iron-sulfur cluster proteins. This cascade results in proteotoxic stress and subsequent cell death[40]. Morphologically, cuproptosis manifests as mitochondrial shrinkage, plasma membrane rupture, and endoplasmic reticulum damage[41].

2.11 Disulfidptosis

Disulfidptosis is a recently identified form of PCD driven by disulfide stress under conditions of aberrant glucose metabolism. The earliest defining study reported that although solute carrier family 7 member 11 (SLC7A11)-mediated cystine uptake suppresses ferroptosis[42], it paradoxically promotes cell death in SLC7A11 high cells during glucose deprivation. This death process was found to be distinct from both apoptosis and ferroptosis and was subsequently named "disulfidptosis"[43]. Morphologically, disulfidptosis is characterized by rapid collapse of the actin cytoskeleton, cell shrinkage, and F-actin contraction[44].

2.12 Others

Beyond the well-characterized PCD described above, an expanding spectrum of additional cell death has been reported, further broadening the conceptual landscape of PCD. In 2008, methuosis was termed to describe a necrosis-like PCD triggered by dysregulation of macropinocytosis, characterized by massive accumulation of non-acidic, macropinosome-derived cytoplasmic vacuoles, cell detachment and rupture, and caspase activation without classical apoptotic chromatin condensation[45]. Subsequently, mechanistically distinct stress-responsive death programs were identified. In 2018, Alkaliptosis was described as a pH-dependent form of PCD characterized by intracellular alkalinization, and mechanistically distinct from apoptosis, necroptosis, ferroptosis, and autophagy, leading to selective cytotoxicity in cancer cells[46]. In the same year, oxeiptosis was characterized as a reactive oxygen species (ROS)-sensitive, caspase-independent, and non-inflammatory form of PCD, serving as a protective mechanism to limit excessive inflammation during oxidative stress[47]. More recently, ion- and organelle-centered death mechanisms have emerged. In 2021, lysozincrosis was defined as a lysosomal Zn^{2+}-dependent necrotic cell death driven by transient receptor potential cation channel, mucolipin 1 (TRPML1i)-mediated zinc release, leading to mitochondrial swelling, ATP depletion, and selective destruction of metabolically stressed cancer cells while sparing normal cells[48,49]. In 2025, NECSO was identified as a regulated necrotic cell death triggered by transient receptor potential cation channel subfamily M member 4 (TRPM4)-mediated Na^+ influx, in which intracellular sodium accumulation suppresses mitochondrial oxidative phosphorylation, leading to energy exhaustion, Na^+/K^+-ATPase inactivation, ionic imbalance, cellular swelling, and lysis[50,51]. Also in 2025, mitoxyperiosis was described as a lytic, caspase-independent form of PCD triggered by the synergism of innate immune activation and metabolic disruption, in which BCL2-associated X protein/BCL2 homologous antagonist/killer 1/BH3 interacting-domain death agonist (BAX/BAK1/BID)-dependent mitochondrial oxidative stress drives prolonged mitochondria-plasma membrane contact, causing localized oxidative membrane damage and culminating in membrane lysis in an mammalian target of rapamycin complex 2 (mTORC2)-regulated manner[52]. Overall, these emerging PCD underscore a paradigm shift from classical caspase-centered models toward metabolically, ionically, and organelle-driven regulatory networks, highlighting the intricate interplay between cellular stress sensing, metabolic status, and structural integrity in determining cell fate (Table 1).

3 Activation of programmed cell death in mucosal system

Mucosal barrier systems, including the respiratory, gastrointestinal, oral, and genitourinary epithelia, constitute the largest interface between the host and the external environment[53]. As the first line of defense against pathogens infection, environmental challenge, and mechanical stress, these mucosal barrier systems must maintain structural integrity. Disruption of this integrity can lead to epithelial erosion, barrier leakage, and tissue dysfunction. In this context, PCD serves as a fundamental regulatory mechanism that removes damaged or infected cells while coordinating tissue renewal and stress adaptation.

3.1 Activation of programmed cell death in respiratory epithelia

In respiratory epithelia, viral infection represents a major trigger of PCD, and pyroptosis is increasingly recognized as a common epithelial response to viral invasion[13]. Pyroptosis is a lytic and highly inflammatory form of PCD initiated by inflammasome activation[12]. In rhinovirus infected-airway epithelial cells, viral RNA or replication intermediates are sensed by pattern-recognition receptors, including cytosolic RNA sensors such as DEAD-box helicase 33 (DDX33) and DEAD-box helicase 58 (DDX58), which subsequently trigger activation of the NLR family pyrin domain containing 3(NLRP3)- apoptosis-associated speck-like protein containing a CARD(ASC) - cysteinyl aspartate specific proteinase 1(caspase-1) -gasdermin D (GSDMD) axis. This cascade induces pyroptotic cell death, promotes interleukin-1β (IL-1β) release, and enhances mucin 5AC (MUC5AC) overproduction, thereby linking inflammasome-driven epithelial pyroptosis to airway inflammation and remodeling[54]. Similarly, in SARS-CoV-2 infection, viral 3C-like protease (3CL) proteases cleave NLR family pyrin domain containing 1 (NLRP1) at Glutamine 333 (Q333) site in human lung epithelial cells, triggering inflammasome assembly and cell death that limits viral replication. Although viral proteases can inactivate GSDMD, airway epithelial cells switch to a caspase-3-GSDME-dependent pyroptosis, leading to epithelial injury and disease severity[55]. Beyond GSDMD- and gasdermin E (GSDME)-dependent pyroptosis, gasdermin B (GSDMB), one of the top asthma genetic determinant also functions as an epithelial pyroptotic executor in the airway. Caspase-1 cleaved GSDMB drives epithelial pyroptosis, possibly contributing to epithelial damage seen in asthmatic airways[56]. Together with its roles in mitochondrial antiviral-signaling protein-TANK-binding kinase 1 (MAVS-TBK1) and cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling that drive inflammatory cytokines production, GSDMB-mediated pyroptosis constitutes a feed-forward inflammatory circuit that amplifies airway epithelial injury[57-60]. Importantly, once initiated, this epithelial pyroptotic

Table 1 The morphological features of PCD.

PCD	Features	PCD	Features
Apoptosis	Nuclear and cytoplasmic condensation Formation of membrane-bound apoptotic bodies Phagocytic degradation	NETosis	Neutrophil-specific Lobulated nuclear loss Internal membrane disintegration Final membrane rupture releasing NETs complexes
Necroptosis	Organelle swelling Mild nuclear fragmentation Plasma membrane rupture with intracellular content release Classical necrosis-like morphology	Disulfidptosis	Rapid actin cytoskeleton collapse and contraction Cell shrinkage Driven by disulfide stress
Autosis	Hallmark of focal perinuclear space swelling generalized organelle swelling	Entosis	Formation of cell-in-cell structures Normal nuclear morphology of internalized cells
Pyroptosis	Osmotic imbalance-induced cell swelling Membrane blebbing forming pyroptotic bodies Final membrane rupture releasing DAMPs	Anoikis	Apoptosis subtype Classical apoptotic morphology triggered by ECM detachment
PANoptosis	Hybrid morphology with pyroptosis, apoptosis and necrosis features Membrane pore formation Chromatin condensation Plasma membrane rupture	Methuosis	Massive non-acidic macropinocytic vacuoles in cytoplasm Cell detachment and rupture Caspase activation without apoptotic chromatin condensation
Ferroptosis	Increased mitochondrial membrane density and cristae absence Outer mitochondrial membrane rupture Intact nuclear structure Lipid peroxidation-induced membrane damage	Alkaliptosis	Intracellular alkalinization, Selective cytotoxicity to cancer cells
Cuproptosis	Mitochondrial shrinkage, plasma membrane rupture Endoplasmic reticulum damage	Oxeiptosis	No specific morphology ROS-sensitive, caspase-independent, non-inflammatory Serves as an oxidative stress protective mechanism
Parthanatos	Nuclear shrinkage and chromatin condensation Early plasma membrane permeability Accumulation of poly(ADP-ribose) (PAR) polymers	Lysozincrosis	Mitochondrial swelling and ATP depletion Selective damage to metabolically stressed cancer cells No obvious damage to normal cells
NECSO	Intracellular sodium accumulation-induced swelling and lysis Suppressed mitochondrial oxidative phosphorylation Ionic imbalance		

process is not solely governed by intrinsic signal but is further shaped by the surrounding inflammatory microenvironment. For example, activation of the cGAS-STING pathway enhances interleukin‐17 (IL-17) production[61]. IL-17A subsequently promotes extracellular signal‐regulated kinase (ERK)-dependent NLRP3/caspase-1 activation in nasal epithelial cells, enhancing pyroptosis and contributing to steroid resistance in chronic airway inflammation[62] (Fig. 2).

In addition to pyroptosis, viral infections are well-established triggers of epithelial apoptosis. In airway epithelial cells, apoptosis is primarily regulated through intrinsic and extrinsic pathways. The intrinsic pathway is triggered by intracellular stressors and is governed by B-cell lymphoma 2 (BCL-2) family proteins that control mitochondrial outer membrane permeabilization (MOMP), leading to cytochrome c release, apoptosome formation (Apaf-1-caspase-9 complex), and activation of effector caspases. In contrast, the extrinsic pathway is initiated by ligand binding to death receptors such as Fas or TNFR, resulting in formation of the death-inducing signaling complex (DISC) and caspase-8 activation. Both pathways converge on effector caspases (particularly caspase-3/6/7), which execute apoptosis by cleaving structural and nuclear substrates, producing characteristic features such as chromatin condensation and phosphatidylserine externalization, with cleaved caspase-3 serving as a key biomarker of irreversible apoptotic commitment[63]. During virus infection, SARS-CoV-2 induces mitochondrial dysfunction in airway epithelial cells by promoting Drp1-mediated mitochondrial fission, electron transport chain suppression, mitochondrial permeability transition pore (mPTP) opening, and AIF/caspase-7-dependent apoptosis, thereby impairing bioenergetics and contributing to hypoxemia in coronaviral pneumonia[64]. Similarly, pediatric airway epithelial cells exhibit heightened susceptibility to respiratory syncytial virus (RSV)-induced cell apoptosis due to impaired signal transducer and activator of transcription 3 (STAT3) activation, promoting viral shedding and disease severity, whereas enhancing STAT3 signaling or inhibiting apoptosis limits viral spread[65]. Environmental and toxic exposures also robustly activate epithelial apoptosis. For example, Heat-not-burn (HnB) tobacco product aerosol exposure causes marked airway epithelial apoptosis and barrier impairment[66]. Copper oxide nanoparticle exposure exacerbates asthma by promoting thioredoxin interacting protein (TXNIP)-dependent airway inflammation and markedly increasing the expression of apoptotic markers in lung epithelia[67]. Furthermore, inhaled diacetyl induces caspase-mediated cleavage of integrin-β 4 in airway epithelial cells, triggering adhesion-dependent apoptosis (anoikis) that contributes to epithelial injury[68]. Conversely, endogenous protective factors can restrain epithelial apoptosis. Inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) protects airway epithelial cells from particulate matter- and oxidative stress-induced apoptosis by suppressing c-Jun N-terminal kinase (JNK) activation and preserving β-catenin signaling[69].

Beyond pyroptosis and apoptosis, viral infections also robustly activate necroptosis in respiratory epithelial cells. Notably, SARS-CoV-2 primarily induces necroptosis in directly infected epithelial cells, while apoptosis and pyroptosis are preferentially engaged in neighboring bystander cells or during the late inflammatory phase

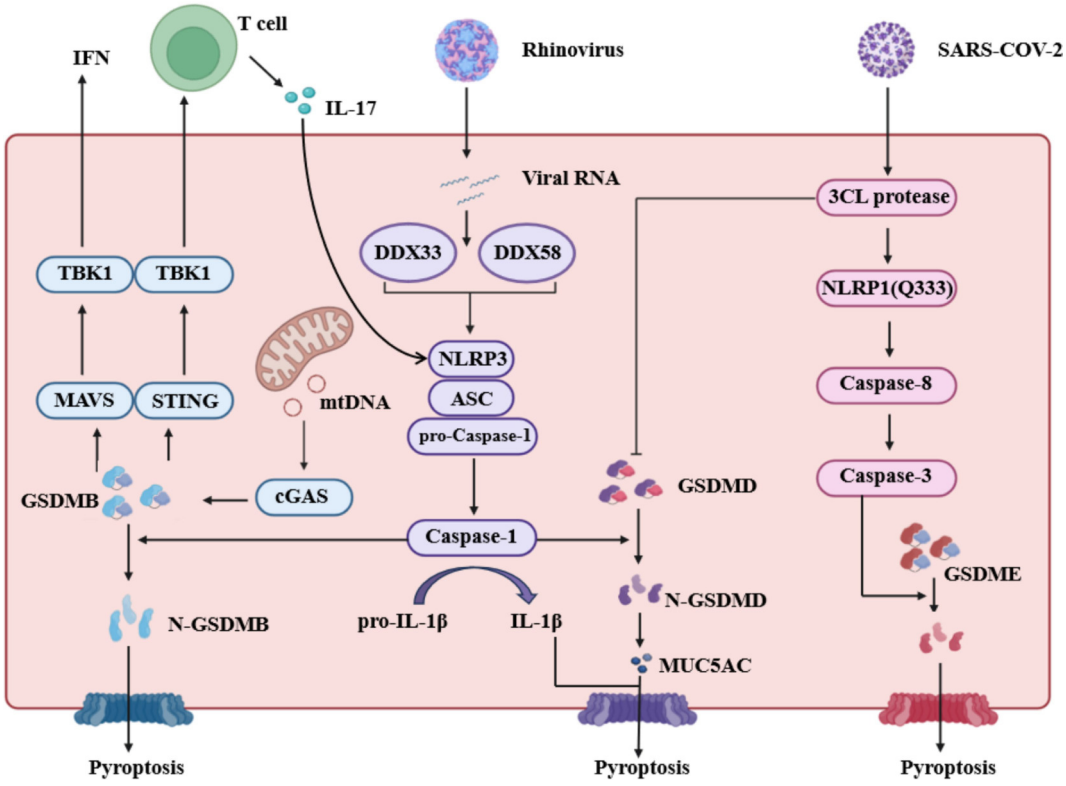


Figure 2 Distinct viral and inflammatory signaling pathways activate pyroptosis in airway epithelial cells. Viral RNA from rhinovirus is detected by cytosolic sensors DDX33 and DDX58, promoting NLRP3 inflammasome assembly and activation of caspase-1, which cleaves gasdermin D (GSDMD) and processes pro-IL-1β into IL-1β, leading to membrane pore formation and pyroptotic cell death. In parallel, inflammatory signaling through the GSDMB-MAVS-STING-TBK1 pathway and mtDNA-cGAS-GSDMB-STING activation further amplifies inflammasome signaling. SARS-CoV-2 infection can also induce pyroptosis through 3CL protease-mediated activation of NLRP1 (Q333), triggering a caspase-8-caspase-3 cascade that cleaves gasdermin E (GSDME). These pathways converge on gasdermin activation to promote pyroptosis and inflammatory responses in airway epithelial cells.

of infection[70]. Necroptosis is commonly initiated through death receptor signaling. Upon TNF-α recognition, Tumor necrosis factor receptor 1 (TNFR1) recruits adaptor proteins including TNF receptor-associated death domain protein (TRADD), receptor-interacting serine/threonine-protein kinase 1 (RIPK1), TNF receptor-associated factor 2/5 (TRAF2/5), and cellular inhibitor of apoptosis protein 1/2 (cIAP1/2) to form membrane-associated complex I. When RIPK1 is polyubiquitinated within complex I, downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling is activated, promoting cell survival and inflammatory gene transcription. However, upon deubiquitination and dissociation from complex I, RIPK1 interacts with RIPK3, fas-associated death domain protein (FADD), and caspase-8 to form cytosolic complex II. At this checkpoint, active caspase-8 cleaves and inactivates RIPK1 and RIPK3, thereby directing the cell toward apoptosis. In contrast, when caspase-8 activity is inhibited or insufficient, RIPK1 and RIPK3 assemble the necrosome, leading to RIPK3 autophosphorylation and subsequent phosphorylation of mixed lineage kinase domain-like protein (MLKL). Phosphorylated MLKL oligomerizes and translocates to cellular membranes, ultimately executing necroptotic cell death[63]. During influenza A virus infection, viral replication generates Z-RNAs that activate nuclear ZBP1, triggering RIPK3-mediated MLKL activation and subsequent epithelial necroptosis[71]. Similarly, RSV infection induces RIPK1/RIPK3/MLKL-mediated necroptotic death of airway epithelial cells with HMGB1 release, driving epithelial injury[72]. Beyond viral infections, bacterial pathogens and chronic environmental insults also engage epithelial necroptosis. Pseudomonas aeruginosa induces cytochrome P450 (CYP450)-dependent necroptosis of airway club cells, driving type 17-skewed inflammation and epithelial damage[73]. In chronic obstructive pulmonary disease (COPD), RIPK1 is upregulated in airway epithelial cells and drives cigarette smoke-induced necroptotic cell death[74]. Consistently, RIPK3-MLKL-mediated necroptosis is significantly increased in cigarette smoke-exposed models, where it contributes to airway inflammation[75].

Although apoptosis, necroptosis, and pyroptosis were traditionally viewed as distinct death pathways, they can be coordinately activated under certain conditions in a unified process termed PANoptosis. PANoptosis is orchestrated by multiprotein PANoptosome complexes, including ZBP1-PANoptosome with NLRP3 inflammsome (ZBP1, RIPK-1/-3, ASC, Caspase1/6/8, NLRP3)[36,76], ZBP1-PANoptosome without NLRP3 inflammsome (ZBP1, RIPK3, ASC, Caspase6/8)[77], Absent in melanoma 2 (AIM2)-PANoptosome (AIM2, pyrin, ZBP1 together with ASC, caspase-1/-8, RIPK-1/-3, and FADD)[78], NLRP12-NLRC5-PANoptosome (NLRP12, NLRC5, RIPK3, NLRP3, ASC, Caspase1/8)[79,80], cytokine-induced PANoptosome (RIPK-1/-3, Caspase 8), and RIPK1-PANoptosome (RIPK-1/-3, Caspase 8, NLRP3, ASC, Caspase1)[81] (Fig. 3). Furthermore, in the respiratory epithelium, activation of the cGAS-STING pathway represents a potent trigger of

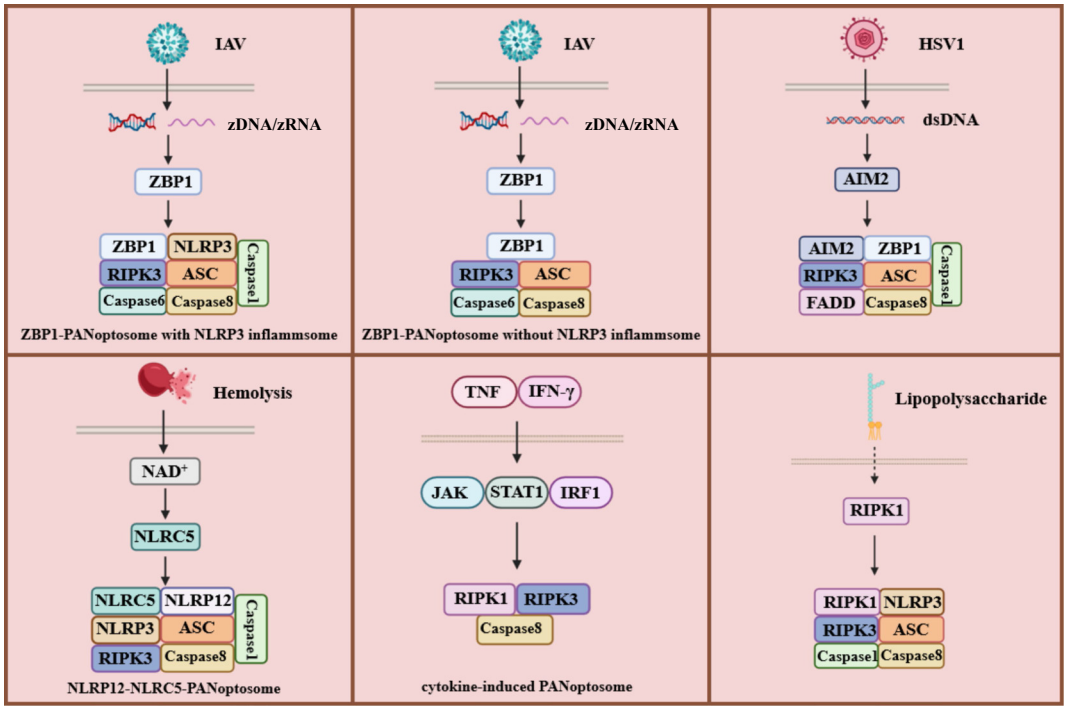


Figure 3 Diverse stimuli activate PANoptosis through distinct PANoptosome signaling pathways. Various pathogens and inflammatory stimuli trigger PANoptosis through distinct PANoptosome complexes. Influenza A virus (IAV)-derived Z-RNA/Z-DNA is sensed by ZBP1, promoting formation of the ZBP1-PANoptosome containing RIPK3, NLRP3, ASC, caspase-1, caspase-6 and caspase-8 or ZBP1-PANoptosome without NLRP3 inflammasome. HSV-1 infection activates AIM2-PANoptosome signaling via AIM2, ZBP1, RIPK3, ASC, FADD, Caspase1 and Caspase8. Hemolysis-induced NAD^+ depletion activates the NLRC5-NLRP12 PANoptosome, while cytokines such as TNF and IFN-γ induce PANoptosis through a RIPK1-RIPK3-caspase-8 complex. In addition, lipopolysaccharide (LPS) can trigger a RIPK1-PANoptosome involving RIPK1, RIPK3, NLRP3, ASC, Caspase1 and Caspase8. These pathways illustrate how diverse infectious and inflammatory signals converge on PANoptosome assembly to drive PANoptotic cell death.

PANoptosis. STING activation during house dust mite (HDM)-induced asthma drives airway epithelial PANoptosis, barrier disruption, thereby exacerbating airway hyperresponsiveness[82]. Similarly, airway activation of STING by the agonist diABZI induces epithelial PANoptosis and barrier damage-driven neutrophilic lung inflammation in acute respiratory distress syndrome (ARDS) pathology[83].

Beyond above PCD, alterations in neutrophil death programs also critically shape airway pathology. In COPD, airway dysbiosis-particularly Staphylococcus aureus colonization-drives accelerated lung function decline by promoting a neutrophil apoptosis-to-NETosis shift via the homocysteine-AKT serine/threonine kinase 1 (AKT1)- S100 calcium-binding protein A8/A9 (S100A8/A9) axis, linking microbiota alterations to NETosis-mediated disease progression[84]. Moreover, in COPD, cigarette smoke or E-cigarette induced NETosis releases oxidatively damaged NET-derived DNA that activates cGAS/Toll-like receptor 9 (TLR9) signaling in airway epithelial, leading to persistent airway inflammation, mucus remodeling and disease severity[84,85]. Thus, inhibition of NET formation or Deoxyribonuclease (DNase) treatment attenuates immunopathology and disease severity of COPD[86,87]. Similarly, NETosis plays central pathogenic roles in neutrophilic asthma. In neutrophilic asthma, interleukin-23 (IL-23) suppresses a $CD39^+CD9^+$ interstitial macrophage subset that normally inhibits NETosis by depleting perineutrophil ATP, thereby amplifying Th17-driven neutrophilic inflammation[88]. Consistently, allergen and endotoxin exposure induce NETosis and neutrophil cytoplast formation, which promote Th17-driven, non-type 2 airway inflammation and correlate with IL-17-associated disease severity[85].

3.2 Activation of programmed cell death in gastrointestinal epithelia

The gastrointestinal epithelium is a rapidly renewing barrier whose tightly regulated PCD maintains epithelial integrity, immune surveillance, and microbial tolerance, whereas excessive or dysregulated PCD disrupts barrier function and promotes inflammation. Ferroptosis has emerged as a critical mechanism in gastrointestinal pathology due to the intestine's unique exposure to dietary iron, lipid substrates, microbiota-derived metabolites, and oxidative stress. Mechanically, Transferrin receptor (TFRC) and lactotransferrin (LTF) facilitate iron uptake, increasing intracellular Fe^{2+} levels, whereas ferritin and the iron exporter SLC40A1 (ferroportin) normally limit iron availability through storage and efflux. NCOA4-mediated ferritinophagy enhances ferroptosis susceptibility by degrading ferritin and expanding the labile iron pool. Excess Fe^{2+} catalyzes ROS production via the Fenton reaction, generating hydroxyl radicals that initiate lipid oxidation. Meanwhile, lipid remodeling provides the necessary substrates for ferroptotic damage. Enzymes such as acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), sterol O-acyltransferase 1 (SOAT1), and transmembrane protein 164 (TMEM164) promote incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids, while arachidonate lipoxygenase (ALOX) facilitates enzymatic lipid peroxidation. Accumulation of phospholipid hydroperoxides ultimately destabilizes cellular membranes and drives cell death. To counteract oxidative stress, cells rely on antioxidant defense systems, primarily the solute

carrier family 3 member 2 (SLC3A2)- solute carrier family 7 member 11 (SLC7A11)- glutathione (GSH)- glutathione peroxidase 4 (GPX4) axis, Fas apoptosis inhibitory molecule 2 (FAIM2)-related superfamily protein 1- coenzyme Q (FSP1-CoQ), and dihydroorotate dehydrogenase-coenzyme Q (DHODH-CoQ) systems[89]. In intestinal epithelial cells, diverse upstream stress signals converge on ferroptosis. Microbiota-dependent farnesoid X receptor (FXR) signaling, radiation-induced signal transducer and activator of transcription 1 (STAT1)- interferon regulatory factor 1 (IRF1) activation, and 15-lipoxygenase (15-LOX)-mediated lipid remodeling collectively enhance acyl-CoA synthetase long-chain family member 4 (ACSL4)-driven arachidonic acid peroxidation, indicating polyunsaturated fatty acid (PUFA) enrichment as a central execution axis[90-93]. Beyond lipid substrate, disruption of antioxidant process further lowers the threshold for ferroptotic membrane damage. Loss of neural precursor cell expressed developmentally downregulated gene 4-like (NEDD4L) destabilizes solute carrier family 3 member 2 (SLC3A2), compromising the SLC7A11-GPX4 dependent axis and sensitizing intestinal epithelial cells to lipid peroxidation[94]. Of note, impaired GPX4 activity in small intestinal epithelial cells permits arachidonic acid-driven lipid peroxidation and ferroptosis, mechanistically linking Western diet-enriched PUFA composition to granulomatous enteritis and Crohn's disease-like pathology[95]. However, the functional consequences of GPX4 activity are highly context dependent. In gastric cancer cells, overexpressed GPX4 suppresses ROS accumulation to stabilize the epithelial–mesenchymal transition (EMT)-associated oncogene regulator of chromosome condensation 2 (RCC2), whereas GPX4 inhibition induces ROS-driven phosphorylation and ubiquitination of RCC2, thereby preventing gastric cancer (GC) progression and metastasis (Fig. 4)[96].

In addition to ferroptosis, multiple other forms of programmed cell death, such as apoptosis, pyroptosis, and necroptosis, have been identified in gastrointestinal epithelial tissues. In people with human immunodeficiency virus (HIV), colon-resident $CD8^+$ T cells, characterized by impaired lipid metabolism, drives intestinal epithelial apoptosis and barrier disruption, contributing to persistent tissue damage[97]. Similarly, excessive TNF induces epithelial apoptosis, further aggravating mucosal damage[98]. Beyond epithelial cells, caspase recruitment domain-containing protein 9 (CARD9) deficiency promotes oxidative neutrophil apoptosis in gastrointestinal epithelia, amplifying inflammation[99]. Moreover, caspase-3/7-dependent apoptosis of gastrointestinal epithelial cells releases metabolites that fuel *Enterobacteriaceae* expansion, creating a death-driven dysbiosis axis that delays intestinal recovery[100,101]. In contrast to apoptosis-driven barrier collapse, inflammasome-mediated pyroptosis exerts context-dependent effects on mucosal homeostasis. Intestinal epithelial NLRP10-dependent ASC/caspase-1 activation promotes IL-1b/IL-18 release together with GSDMD-mediated pyroptotic death or caspase-1/11-driven cell extrusion, collectively limiting pathogen expansion and reinforcing mucosal immunity[102-104]. However, dysregulated pyroptotic signaling-such as type III interferon-induced ZBP1-caspase-8-GSDMC activation or Shiga toxin-triggered caspase-8/3-GSDME pathways-drives inflammatory epithelial injury and delays tissue repair[105,106]. Similarly, intestinal epithelial cell fate is governed by necroptosis and RIPK3-dependent death signaling. Disruption of X-box binding protein 1 (XBP1)-driven endoplasmic reticulum (ER) stress signaling, suppression of FADD or caspase-8, or loss of the histone methyltransferase su(var)3–9, enhancer-of-zeste, trithorax domain bifurcated histone lysine methyltransferase 1 (SETDB1) converges on activation of RIPK3-dependent necroptotic signaling, leading to mucus barrier breakdown and colitis[107-109]. Notably, prostaglandin prostaglandin E2 (E2)- E-prostanoid receptor 4 (EP4) signaling suppresses TNF-induced RIPK1/MLKL-mediated necroptosis, thereby promoting epithelial barrier preservation and resolution of colitis in inflammatory bowel disease[109].

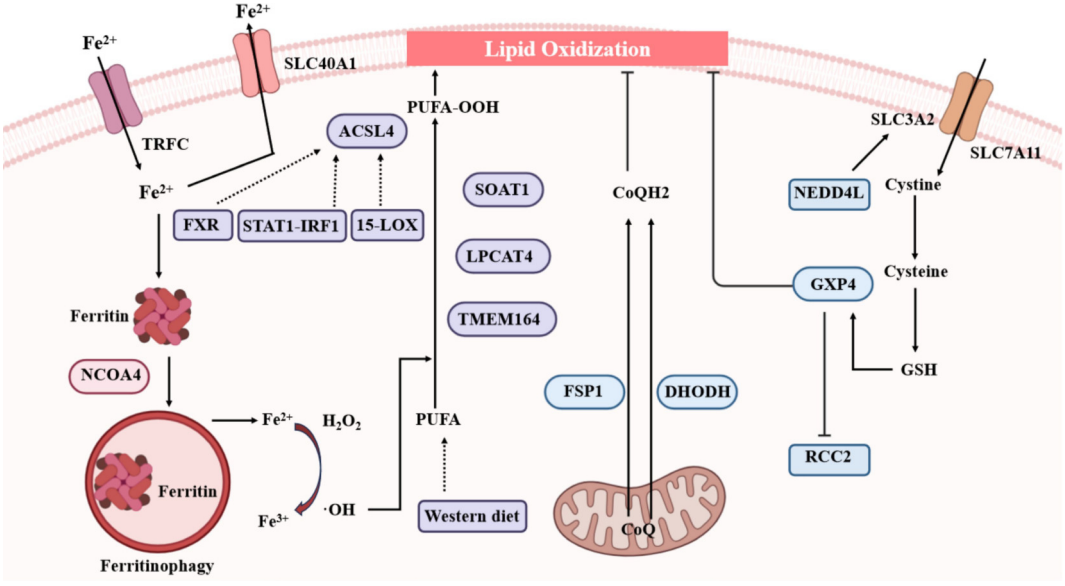


Figure 4 Molecular pathways regulating lipid peroxidation and ferroptosis in gastrointestinal epithelia. Iron uptake through TFRC together with ferritin degradation mediated by NCOA4-dependent ferritinophagy, increases intracellular Fe^{2+} levels and promotes ROS generation. PUFAs are incorporated into membrane phospholipids by ACSL4, LPCAT4, and TMEM164, facilitating lipid peroxidation. Cellular antioxidant systems counteract lipid peroxidation via the SLC7A11-GSH-GPX4 axis, while alternative defense pathways include FSP1-CoQH2 and DHODH-mediated mitochondrial CoQ reduction. Additional regulators, including NEDD4L, RCC2, and metabolic inputs such as cystine transport and dietary factors, further modulate ferroptotic sensitivity.

3.3 Activation of programmed cell death in oral epithelia

Similar to other mucosal surfaces, the oral epithelium constitutes a highly specialized stratified squamous barrier that is constantly challenged by mechanical stress, environmental stimuli, and pathogen infection. Precise regulation of PCD, including apoptosis, pyroptosis and necroptosis, plays a pivotal role in maintaining epithelial integrity and regulating immune homeostasis. In oral lichen planus, NF-κB-mediated upregulation of parkinsonism associated deglycase 7 (PARK7) protects oral keratinocytes by interacting with BCL2-associated X protein (BAX) and p65, thereby attenuating apoptosis and preserving epithelial integrity[110]. Similarly, Smad7 confers resistance to radiation-induced oral mucositis by suppressing TGF-β and NF-κB signaling, reducing inflammation, growth inhibition, and apoptosis[111]. While protective mechanisms restrain excessive apoptosis to preserve epithelial integrity, dysregulated inflammasome activation represents a pathogenic escalation of PCD within the oral mucosa. *P. gingivalis*, an important periodontal pathogen resident in the oral cavity, is capable of activating the NLRP3 inflammasome, thereby driving myeloid cell recruitment and proinflammatory remodeling[112]. In parallel, necroptotic pathways further exacerbate oral mucosal injury under stress conditions. RIPK3/MLKL-mediated necroptosis promotes keratinocyte death and inflammatory cytokine release in radiation-induced oral mucositis, and pharmacologic inhibition of this pathway mitigates tissue damage[113]. Consistently, 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol (PLAG) treatment attenuates ulceration, systemic inflammation, and weight loss by suppressing necroptosis-associated pathways[114].

3.4 Activation of programmed cell death in genitourinary epithelia

Distinct from other mucosal surfaces, the uterine, cervical, and urinary epithelia undergo hormone-driven cyclical remodeling, in which PCD regulation is essential for epithelial shedding, regeneration, and decidual reprogramming. Apoptosis serves as a central determinant of tissue remodeling and pathology across genitourinary epithelia. In the kidney, Twist1 expression in distal tubular epithelial cells drives apoptosis-associated tubular injury and profibrotic signaling, thereby amplifying inflammation and fibrosis in toxin-induced chronic kidney disease[115], while loss of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (ErbB4) disrupts the balance between proliferation and apoptosis in cyst-lining epithelia, accelerating cyst expansion and renal functional decline in polycystic kidney tissue[116]. In the uterus, physiological apoptosis restores endometrial integrity after tissue shedding, where estrogen-mediated suppression of Notch signaling activates Nestin$^+$ perivascular progenitors to restore endometrial integrity[117]. Conversely, protective regulators such as transcriptional coactivator with PDZ-binding motif (TAZ) safeguard decidual tissue from oxidative stress-induced apoptosis by enhancing mitochondrial function and activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/ antioxidant response element (ARE)/ forkhead box O1 (Foxo1) antioxidant axis, thereby sustaining stromal proliferation and differentiation during decidualization[118]. Beyond apoptosis, inflammasome-mediated pyroptosis further shapes tissue integrity and inflammatory remodeling in these organs. In diabetic kidney disease, an interferon-stimulated gene 15 (ISG15)- mitochondrial DNA (mtDNA)-STING signaling hub amplifies NLRP3-dependent pyroptosis in renal tubular epithelial cells, linking intrarenal inflammatory cell death to fibrosis progression[119]. At the maternal–fetal interface, tightly regulated epithelial pyroptosis supports embryo implantation and decidualization through interleukin-18 (IL-18)- a disintegrin and metalloproteinase 12 (ADAM12)-epiregulin signaling, whereas excessive activation disrupts endometrial homeostasis and results in implantation failure[120]. Similarly, in early pregnancy loss, activated CD11c$^+$CD8$^+$cytotoxic T cells accumulate within placental tissue and trigger NLRP3-caspase-1-GSDMD-mediated pyroptotic death of trophoblasts, impairing placental invasion and leading to embryo resorption[121]. In parallel, ferroptosis has emerged as a convergent mechanism of tissue injury across genitourinary organs. Environmental cadmium exposure induces ferroptotic death of ovarian granulosa cells, contributing to intrafollicular cell loss and diminished ovarian reserve[122]. In diabetic kidney disease, autophagy deficiency and 5' AMP-activated protein kinase (AMPK) inactivation heighten ferroptotic susceptibility in proximal tubular epithelial cells, predisposing renal tissue to acute injury[123]. In early-onset pre-eclampsia, excessive apolipoprotein D (APOD) secretion drives phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (Akt)-dependent placental ferroptosis, impairing trophoblast function and placentation[124]. Similarly, ROS-driven ferroptosis promotes fibrosis and glandular loss in intrauterine adhesion[125], and GPX4 deficiency-induced ferroptosis in endometrial epithelium accelerates transforming growth factor-beta 1 (TGF-β 1)/SMAD family member 2/3 (Smad2/3)-mediated fibrosis and decidualization failure in polycystic ovary syndrome (PCOS)[126]. In addition, necroptosis represents another stress-responsive death pathway contributing to reproductive tissue injury. Stress granule-mediated recruitment of ZBP1 and RIPK3 activates necroptosis within the testicular microenvironment, coupling cellular stress sensing to regulated germline cell death and reproductive aging[127]. Together, these findings reveal that genitourinary tissue homeostasis depends on a precise regulation among apoptotic, pyroptotic, ferroptotic, and necroptotic cell death.

4 Regulation of programmed cell death in mucosal system

PCD in mucosal tissues is not merely triggered by infection or injury but is tightly regulated by multilayered regulatory networks, including epigenetic and transcriptional regulation, translational regulation and post-translational modifications (PTMs). Epigenetic and transcriptional networks set the intrinsic threshold for PCD responsiveness, translational control dynamically modulates the availability of core death effectors under stress, and post-translational modifications dictate the activation, stability, and assembly of death complexes, including inflammasomes, necrosomes, and ferroptotic machinery[128,129].

4.1 Regulation of programmed cell death at mRNA level in mucosal system

PCD in mucosal tissues is tightly regulated at the mRNA level through epigenetic transcriptional control, RNA modifications, and noncoding RNA-mediated regulatory networks. These mechanisms determine the transcription, stability, and translation efficiency of genes involved in apoptosis, pyroptosis, ferroptosis, and necroptosis, thereby shaping epithelial cell fate during inflammation, infection, and tumorigenesis.

DNA methylation and histone modifications represent major epigenetic mechanisms that control transcription of PCD regulators in mucosal tissues. In cigarette smoke-induced COPD, reduced ten-eleven translocation 2 (TET2) expression in lung epithelial cells promotes ferroptosis by altering methylation status at the GPX4 promoter, thereby suppressing antioxidant defense and exacerbating epithelial injury[130]. Similarly, in renal tubular cells, the isocitrate dehydrogenase 1 (IDH1)-R132H mutation induces promoter hypermethylation-mediated repression of NADH:ubiquinone oxidoreductase subunit A1 (NDUFA1), resulting in mitochondrial lipid peroxidation and ferroptosis during cisplatin-induced acute kidney injury[131]. Histone modifications also critically influence epithelial cell death pathways. For example, the histone demethylase jumonji domain-containing protein 3/lysine demethylase 6B (JMJD3 (KDM6B)) promotes transcriptional activation of arachidonate 5-lipoxygenase (ALOX5) through removal of the repressive histone H3 lysine 27 trimethylation (H3K27me3) mark in gastric cancer cells, linking epigenetic reprogramming to chemoresistance and ferroptotic vulnerability[132].

Epitranscriptomic regulation, particularly N6-methyladenosine (m^6A) RNA modification, has emerged as a key regulator of mucosal PCD. In airway and alveolar epithelial cells, m^6A-modified circular RNA SAV1 (circSAV1) promotes ferroptosis through the YTH N6-methyladenosine RNA binding protein 1 (YTHDF1)-iron-responsive element-binding protein 2 (IREB2)-mediated iron overload pathway, contributing to airway remodeling and emphysema in COPD[133]. Similarly, in oral mucosal tissue, methyltransferase-like 3 (METTL3)-mediated m^6A methylation promotes NLRP3 inflammasome-dependent pyroptosis during periodontitis, thereby exacerbating inflammatory tissue destruction[134]. In colonic tissue, radical S-adenosyl methionine domain containing 2 (RSAD2)-driven m6A-dependent mitochondrial dysfunction in smooth muscle cells promotes epithelial ferroptotic cell death, thereby driving inflammatory injury in ulcerative colitis[135].

In addition to epigenetic transcriptional control and RNA modifications, noncoding RNAs, including circular RNAs (circRNAs), long noncoding RNAs (lncRNAs), microRNAs, and PIWI-interacting RNAs (piRNAs) form extensive regulatory networks that control transcriptional and post-transcriptional gene expression involved in epithelial PCD. For instance, circular RNA alpha-aminoadipic semialdehyde synthase (circAASS) deficiency impairs mitochondrial biogenesis and mitophagy in renal tubular epithelial cells, leading to apoptosis and inflammation during acute kidney injury[136]. Conversely, the lncRNA RSDR epigenetically upregulates dihydroorotate dehydrogenase (DHODH) through heterogeneous nuclear ribonucleoprotein K, thereby suppressing ferroptosis and protecting tubular epithelial cells from injury[137]. In bronchial epithelial cells exposed to particulate matter, lncRNA taurine-upregulated gene 1 (TUG1) acts as a competing endogenous RNA (ceRNA) that sequesters miR-222-3p, activating CUGBP Elav-like family member 1 (CELF1)-p53 signaling and promoting apoptosis associated with airway hyperreactivity[138]. Similarly, p53-induced lncRNA NEAT1_2 promotes miR-129-5p-dependent derepression of the fas-associated death domain protein (FADD)- caspase-8 (CASP8)- caspase-3 (CASP3) apoptotic cascade, accelerating the progression from acute kidney injury to chronic renal fibrosis[139]. Moreover, in lung epithelial tumor tissue, auramine stabilizes G-quadruplex structures to enhance mutant p53-dependent lincRNA-p21 transcription, thereby promoting apoptosis and increasing chemosensitivity in tumor protein p53 (TP53)-mutant non-small cell lung cancer[140]. In lung epithelial cells exposed to PM2.5, the oncogenic piRNA PMLCPIR binds nucleolin to activate PI3K/AKT signaling, thereby suppressing apoptosis and promoting malignant transformation[141]. Collectively, mRNA-level regulation, including epigenetic transcriptional control, RNA modifications, and noncoding RNA-mediated networks, plays a fundamental role in orchestrating PCD in mucosal tissues. Dysregulation of these multi-layered mechanisms alters barrier integrity, thereby contributing to mucosal inflammatory diseases, infections, and malignancies.

4.2 Regulation of programmed cell death at protein level in mucosal system

PCD in mucosal tissues is tightly regulated by diverse PTMs at the protein level that control the stability, localization, and activity of key signaling proteins. Among these mechanisms, ubiquitination, phosphorylation, methylation, acetylation, glycosylation, and lactylation represent major regulatory layers that dynamically shape epithelial cell fate during infection, inflammation, and tumorigenesis.

Ubiquitination is a critical mechanism controlling PCD in mucosal epithelia[142]. For instance, the E3 ubiquitin ligase (E3) ligase neural precursor cell expressed developmentally downregulated 4-like (NEDD4L) ubiquitinates gasdermin D (GSDMD) in alveolar epithelial cells, preventing its pathological accumulation and attenuating excessive pyroptosis and subsequent epithelial barrier damage[143]. Conversely, pathogen-derived factors can exploit ubiquitin pathways to induce epithelial injury. The Streptococcus suis serine/threonine protein kinase 1 (SKT1) promotes kelch-like ECH-associated protein 1 (Keap1)-dependent ubiquitination and degradation of Nrf2, leading to ferroptosis in airway epithelial cells and subsequent epithelial barrier disruption[144]. Similarly, ankyrin repeat domain 1 (ANKRD1) promotes tripartite motif-containing 25 (TRIM25)-mediated lysine 63 (K63)-linked ubiquitination of acyl‐CoA synthetase long‐chain family member 3 (ACSL3) to induce ferroptosis in renal ischaemia-reperfusion injury[145]. In mucosal cancers, ubiquitin signaling also contributes to PCD resistance. In oral squamous cell carcinoma, kinesin family member 20A (KIF20A) inhibits tripartite motif-containing protein 21 (TRIM21)-mediated lysine 48 (K48)-linked ubiquitination of DEAH-box helicase 9 (DHX9), thereby stabilizing DHX9 and promoting ferroptosis resistance[146]. In epithelial tumors, ubiquitin-specific protease 38 (USP38)-mediated deubiquitination stabilizes mouse double minute 2 homolog (MDM2), suppressing p53 signaling and inhibiting apoptosis and ferroptosis to enhance cancer cell survival and chemoresistance[147]. Similar regulatory mechanisms occur in gastrointestinal malignancies, where USP8 stabilizes GPX4 through deubiquitination in intestinal epithelial cells, suppressing lipid peroxidation-driven ferroptosis and influencing anti-tumor immune responses[148]. Likewise, ubiquitin-specific protease 29 (USP29) antagonizes SMAD ubiquitin regulatory factor 1 (SMURF1)-mediated ubiquitination of ferroptosis suppressor protein 1 (FSP1), suppressing ferroptosis and conferring chemoresistance in gastric cancer[149]. In contrast, protective deubiquitination pathways may limit epithelial injury under stress conditions. For example, OTU domain-containing protein 4 (OTUD4) stabilizes plasminogen activator inhibitor-1 (PAI-1) through deubiquitination, thereby preventing cigarette

smoke-induced apoptosis in airway epithelial cells and attenuating emphysematous lung injury[150]. Additionally, protein ubiquitination frequently cooperates with methylation to control epithelial cell fate. In diabetic renal ischemia-reperfusion injury, the histone methyltransferase histone-lysine N-methyltransferase G9A (G9a) methylates forkhead box O3a (FoxO3a), facilitating tripartite motif-containing protein 21 (TRIM21)-mediated K48-linked ubiquitination and degradation of FoxO3a. This methylation-dependent ubiquitination cascade enhances oxidative stress, activates the NLRP3 inflammasome, and promotes pyroptotic cell death[151].

Protein phosphorylation also plays an important role in modulating epithelial cell PCD. The metabolic signal mannose activates AMPK, which phosphorylates GSDME and prevents its caspase-3-mediated cleavage, thereby suppressing pyroptosis and protecting intestinal and renal tissues from chemotherapy-induced injury[152]. Similarly, α1-antitrypsin activates protein phosphatase 2A (PP2A), leading to reduced phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) and consequently limiting TNF-induced epithelial apoptosis and inflammatory responses in the lung[153]. In contrast, pathological phosphorylation events may exacerbate epithelial injury. For example, ataxia telangiectasia mutated (ATM)-dependent phosphorylation of folliculin (FLCN) enables F-box only protein 23 (FBXO23)-mediated ubiquitination and degradation of FLCN, increasing cigarette smoke-induced cytotoxicity in airway epithelial cells[154].

Emerging evidence highlights lactylation as an important link between metabolic reprogramming and PCD. In V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant cancers, metabolic rewiring drives glutamate-cysteine ligase modifier subunit (GCLM) lactylation, enhancing glutathione synthesis and suppressing ferroptosis[155]. Similarly, increased histone lactylation promotes ferroptosis resistance in ectopic endometrial stromal cells, supporting tissue survival in endometriosis[156]. In airway epithelial cells during asthma, lactate-driven lactylation of ATPase H^+ transporting V1 subunit B2 (ATP6V1B2) disrupts lysosomal function, leading to mitochondrial ROS accumulation and activation of the caspase-8/3-GSDME pyroptosis pathway, thereby linking immunometabolic remodeling to epithelial injury and airway inflammation[157].

In addition to ubiquitination, methylation, phosphorylation and lactylation, PTMs such as acetylation, and O-GlcNAcylation further regulate mucosal PCD. In renal epithelial cells, Sirtuin 2 (SIRT2)-mediated deacetylation of septin4 at lysine 174 (K174) suppresses caspase-3-dependent apoptosis, thereby protecting against hypertensive renal injury[158]. Conversely, excessive O-GlcNAcylation induced by Shiga toxin promotes ER stress-associated apoptosis in renal tissues, contributing to toxin-mediated organ damage[159]. Collectively, these findings illustrate that multiple protein-level modifications, such as ubiquitination, methylation, phosphorylation, acetylation, glycosylation, and lactylation, coordinate the activation or suppression of pyroptosis, apoptosis, and ferroptosis in mucosal tissues. Dysregulation of these PTM networks disrupts epithelial homeostasis and contributes to inflammatory diseases, infections, and mucosal cancers, highlighting PTM-targeted interventions as promising therapeutic strategies for mucosal pathology.

5 Discussion

Despite the expanding classification of PCD forms, it remains unclear whether these PCD represent truly discrete form or interconnected outcomes of shared regulatory networks. Increasing evidence suggests that diverse PCD forms are often triggered by overlapping upstream stress signals, including ROS accumulation, organelle damage, and changes in plasma membrane properties, such as membrane rigidity and lipid remodeling. At the molecular level, these signals frequently converge on common regulatory hubs, such as mitochondrial integrity, inflammasome activation, and metabolic dysregulation, leading to coordinated or context-dependent activation of multiple PCD. This has led to the emerging view that PCD should not be considered as a collection of strictly independent pathways, but rather as a dynamic and integrated network of cell fate programs. Furthermore, recent concepts such as PANoptosis highlight the coordinated engagement of pyroptotic, apoptotic, and necroptotic pathways, reinforcing the notion of extensive crosstalk and functional integration.

Importantly, beyond this network-based integration, the temporal dimension of PCD activation represents an additional layer of complexity that remains poorly understood. Emerging evidence suggests that distinct forms of PCD may occur in a context-dependent manner, rather than being activated simultaneously. For example, cells may initially engage apoptotic programs under moderate stress, while sustained or intensified insults can shift the balance toward more inflammatory forms of cell death, such as pyroptosis or necroptosis. This dynamic transition may be governed by the intensity, duration, and nature of the stress signals, as well as by the cellular metabolic state and micro-environmental stimulus. However, the precise mechanisms that dictate the timing, switching, and hierarchy of different PCD pathways remain largely unclear, particularly in complex mucosal tissues.

Moreover, it remains unknown whether other yet-to-be-characterized forms of PCD exist in mucosal systems. In addition, current therapeutic strategies targeting epithelial injury and inflammation in mucosal diseases remain limited. Therefore, identifying key regulatory mechanisms and molecular signatures governing PCD will be essential for advancing diagnostic approaches and developing effective therapeutic interventions.

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Data available statement

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Author contribution

T.L., Y.Z., R.C., and A.Z. conceived the study, established the conceptual framework, and supervised the project. Q.Z., D.C., and

Y.C. performed literature analysis. M.A. and F.S. contributed to manuscript editing and refinement.

Ethics approval and consent

N/A

Consent for publication

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Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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