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Regulation of pyroptosis by NF-κB signaling

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Pyroptosis is a form of proinflammatory cell death characterized by inflammasome activation, pore formation, and the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18 upon cell rupture. Nuclear factor-κB (NF-κB), a prototypical pro-inflammatory transcription factor, plays a critical role in immune system regulation. Recent research highlights the multifaceted roles of NF-κB signaling in pyroptosis. Various immunologically relevant ligands and their receptors can activate the NF-κB pathway to promote pyroptosis, with Toll-like receptors (TLRs), IL-1 receptors (IL-1Rs), and TNF receptors (TNFRs) being the most prominent. NF-κB regulates the transcription of key components of inflammasomes involved in pyroptosis, particularly the NLRP3 inflammasome. Recent studies also indicate that NF-κB modulates the activation of NLRC4 and AIM2 inflammasomes through distinct pathways in diverse inflammatory conditions, such as acute lung injury and neuroinflammation. Additionally, the NF-κB pathway mediates the production of inflammatory cytokines, including IL-1β, IL-33, and TNF-α, which further regulate pyroptosis. This review examines recent advances in understanding the role of the NF-κB signaling pathway in regulating pyroptosis during infection and inflammation.

KEYWORDS

pyroptosis, NF-κB, inflammasome, infection, inflammation

1 Introduction

Programmed cell death (PCD) refers to strictly regulated cell death, including apoptosis, necroptosis, autophagy, pyroptosis, ferroptosis, and recently characterized cuproptosis (Bedoui et al., 2020; Tsvetkov et al., 2022). Pyroptosis is a pro-inflammatory PCD characterized by the formation of plasma membrane pores, initiated by the cleavage of Gasdermins (GSDMs) between their N- and C-terminal domains by activated Caspases (Shao, 2021). Initially, pyroptosis was reported as a result of Caspase-1 dependent cleavage of GSDMD, constituting the canonical pathway. Later, Caspase-4/-5/-11 activation by cytosolic LPS, and subsequent cleavage of GSDMD represents a non-canonical pathway (Wei Y. et al., 2022). Recent studies have uncovered additional pathways of pyroptosis, including the Caspases-8 mediated cleavage of GSDMD, Caspase-3-mediated cleavage of GSDME, as well as granzyme A-mediated cleavage of GSDMB (Shen et al., 2021; Zhang X. et al., 2020; Shi et al., 2015; Orning et al., 2018; Sarhan et al., 2018; Zhou et al., 2020; Kayagaki et al., 2015; Wang et al., 2017). The inflammatory caspases are normally activated through the assembly of inflammasome in response to stimulation such as the invaded bacteria and viruses (Fattinger et al., 2023; Zhao and Zhao, 2020; Miao et al., 2010; Rathinam and Fitzgerald, 2016; Pandeya et al., 2023). The assembly of inflammasome is

initiated by the recognition of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) through the corresponding pattern recognition receptors (PRRs), also known as inflammasome sensors. This recognition leads to the recruitment of adaptor molecule ASC (apoptosis-associated speck-like protein containing a CARD) and pro-caspases (Rathinam and Fitzgerald, 2016). Release of inflammatory mediators is a crucial characteristic of pyroptosis.

The NF-κB transcription factors (p50/p105, p52/p100, RelA, c-Rel, RelB) and the pathways that control NF-κB activation are known to be involved in the regulation of immune responses and inflammation (Liu T. et al., 2017). Activation of NF-κB involves two major signaling pathways. The primary mechanism of canonical NF-κB activation is through the degradation of IκBα, which is triggered by its site-specific phosphorylation by a multi-subunit IκB kinase (IKK) complex. This complex becomes activated in response to injury, infection, inflammation and other stress conditions (Liu T. et al., 2017; Vallabhapurapu and Karin, 2009; Barnabei et al., 2021). The degradation of IκBα results in rapid and transient nuclear translocation of canonical NF-κB members, predominantly the p50/RelA and p50/c-Rel dimers (Liu T. et al., 2017; Hayden and Ghosh, 2008; Karin and Delhase, 2000). A second, non-canonical pathway, which is activated by a more limited set of stimuli, does not involve IκBα degradation. Instead, it relies on the processing of the NF-κB2 precursor protein p100 (Xiao et al., 2001a). A central signaling component of the non-canonical pathway is NF-κB-inducing kinase (NIK), which integrates signals and activates downstream IKKα. Activated IKKα triggers the processing of p100 into NF-κB2 p52, leading to the subsequent nuclear translocation of the noncanonical NF-κB complex p52/RelB (Sun, 2011).

Currently, much of our understanding of NF-κB signaling in pyroptosis has been acquired through the investigation of members of Toll-like receptors (TLRs), interleukin-1 receptors (IL-1Rs), and TNF receptors (TNFRs). These receptors play pivotal roles in sensing external stimuli and initiating downstream signaling cascades that ultimately regulate pyroptosis (Liu T. et al., 2017; Barnabei et al., 2021). Over the past decade, the DNA-sensing receptor cyclic GMP-AMP synthase (cGAS) and its downstream adaptor STING (stimulator of interferon genes) have been identified as central regulators of type I interferon (IFN) and NF-κB responses (Decout et al., 2021; Skopelja-Gardner et al., 2022; Domizio et al., 2022). cGAS detects cytosolic DNA from pathogens, DNA damage, or mitochondrial stress, activating STING to trigger immune responses. This pathway plays a pivotal role in cellular defense, mediating IFN production and NF-κB activation to combat infections and maintain homeostasis.

The NF-κB transcription factors have emerged as major regulators of PCD including apoptosis or necrosis (Dondelinger et al., 2015; Kucharczak et al., 2003; Karin and Lin, 2002). Recent evidence highlights the role of NF-κB signaling in regulating inflammasome activation, particularly the NLRP3, NLRC4, AIM2 (He Y. et al., 2016; Bezbradica et al., 2017; Wang J. et al., 2020; Chebly et al., 2022; Bombaci et al., 2022). Furthermore, NF-κB signaling exerts a bidirectional influence on inflammation mediated by inflammasomes (Kinoshita et al., 2015a). While inflammasome activation can trigger NF-κB activation and downstream proinflammatory responses, NF-κB signaling, in turn, regulates the assembly and activation of inflammasomes. Unsurprisingly, numerous studies have implicated NF-κB regulation as a key factor in the progression of diseases associated with pyroptosis (Wang et al., 2019; Chen X. et al., 2019; Cai et al., 2021; Xu et al., 2023; Chen et al., 2023). Therefore, a deeper understanding of the interplay between NF-κB activation and pyroptosis is crucial for developing therapeutic strategies for pyroptosis-related diseases.

2 Molecular mechanism of pyroptosis

Pyroptosis is a form of pro-inflammatory PCD, lacking characteristic features of apoptosis such as cell shrinkage, chromatin condensation, phospholipid externalization and exposure of phosphatidylserine on the outer surface of the cell, and Caspase-3/7 dependence. Cells undergoing pyroptosis appear flattened and swollen under the microscope, resembling deflated balloons. Other distinguishing features include cell membrane rupture and the release of large amounts of inflammatory cytokines and cellular contents. Inflammasome activation could lead to pyroptosis (Figure 1). The inflammasome is a protein complex that forms in response to different stimuli signals, including PAMPs from pathogens such as bacteria or viruses, and intrinsic signals DAMPs. Under certain conditions, the formation of the inflammasome requires assistance from NF-κB signaling, often referred to as “priming”. Priming triggers cells to adopt a heightened state of alertness, with increased expression of inflammasome-related proteins, preparing them for prompt response. Assembly of the inflammasomes leads to the activation of caspases, processing of pro-IL-1β and pro-IL-18 into their mature forms, and cleavage of gasdermins that lead to poration on the cell membrane (Yu P. et al., 2021; Martinon et al., 2002; Shi et al., 2017; Wei X. et al., 2022). Later studies revealed mechanisms of pyroptosis independent of inflammasomes. For example, Caspase-11, Caspase-3, Caspase-8, granzyme B, and granzyme A can directly cleave gasdermins, bypassing the inflammasome assembly (Zhou et al., 2020; Wang et al., 2017; Zhang Z. et al., 2020; Rathinam et al., 2019). Therefore, pyroptosis has been redefined as a type of the necrotic cell death mediated by gasdermin family proteins (Shi et al., 2017), including GSDMA, GSDMB, GSDMC, GSDMD, GSDME (DFNA5) and DFNB59. Recent findings reveal that GSDMD pore formation alone is insufficient to drive plasma membrane rupture (PMR), a crucial step in lytic cell death and the full release of DAMPs such as HMGB1 and the PMR marker lactate dehydrogenase (LDH). Emerging evidence identified the plasma membrane protein Ninjurin-1 (NINJ1) as a key regulator of PMR (Kayagaki et al., 2021; Degen et al., 2023; Han et al., 2024). Acting downstream of GSDMD activation, NINJ1 orchestrates the final steps of membrane disintegration during pyroptosis and other forms of lytic cell death. Structural and imaging studies have demonstrated that NINJ1 forms hydrophilic interfaces that encircle and detach membrane patches, promoting their fragmentation and ultimate loss (David et al., 2024). This mechanism is essential for complete PMR, enabling the release of LDH and other intracellular contents, thereby amplifying the inflammatory response.

All gasdermins, except for DFNB59, share a similar structure characterized by two distinct and conserved domains connected

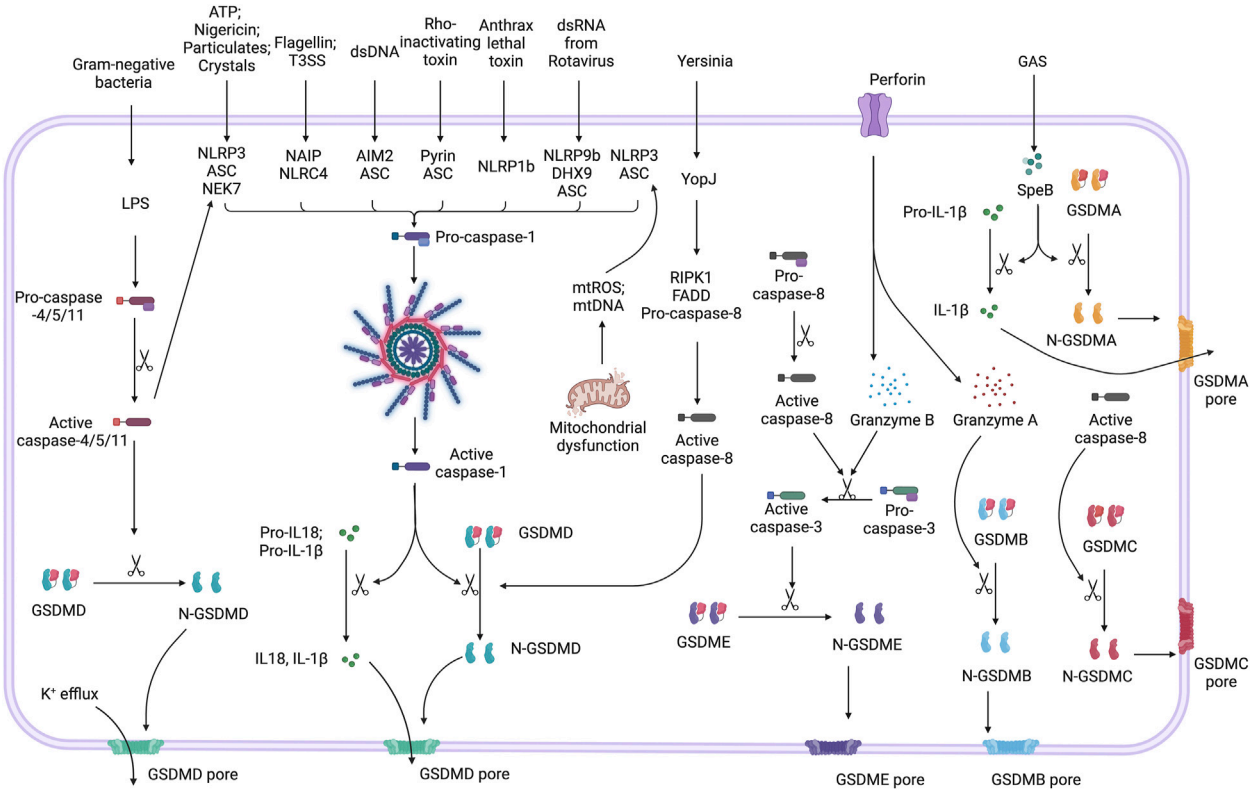

FIGURE 1
Mechanisms of pyroptosis pathways. Inflammasomes, such as NLRP3, NLRC4, AIM2, Pyrin, NLRP1b, and NLRP9b, are activated by stimuli including ATP, bacterial flagellin, dsDNA, Rho-inactivating toxins, anthrax lethal toxin, and viral dsRNA, respectively. Upon activation, these inflammasomes recruit and activate Caspase-1, a process known as canonical inflammasome activation. Active caspase-1 processes GSDMD into its active N-terminal form (N-GSDMD), which forms membrane pores. These pores lead to K^+ efflux, cell lysis, and the release of inflammatory cytokines such as IL-1β and IL-18. Caspase-4, -5, and -11 directly activate GSDMD in response to LPS, and can indirectly amplify canonical inflammasome activation by triggering NLRP3 inflammasome pathway. Caspase-8, which is activated in response to *Yersinia* (via YopJ), also cleaves GSDMD. Caspase-3 activated by caspase-8 via apoptotic signaling or granzyme B delivered by perforin triggers the cleavage of GSDME, resulting in pore formation and pyroptotic-like cell death. Granzyme A directly cleaves GSDMB to form pores. Additionally, Group A *Streptococcus* (GAS) activates GSDMA as well as IL-1β through bacterial protease SpeB. The activation of GSDMC is associated with caspase-8 activity.

through a hydrophobic linker. The N-terminal domain is capable of forming pores in membranes, while the hydrophobic linker facilitates interactions with lipid membranes. The C-terminal domain prevents oligomerization and pore-formation by the N-terminal domain. For gasdermins to become active, the C-terminal domain must be cleaved. Upon activation, the N-terminal gasdermin domains translocate to the plasma membrane, bind to phosphoinositides, and oligomerize to form membrane pores. These pores disrupt osmotic balance, leading to cell swelling and membrane rupture, ultimately causing the release of inflammatory cytokines and cell lysis. Notably, the pore-forming ability of gasdermin proteins has been demonstrated on artificial membranes *in vitro* (Ding et al., 2016). In contrast, DFNB59 has a highly truncated C-terminal domain, rendering it incapable of inhibiting the N-terminal domain. DFNB59 is associated with auditory function and stress-induced damage, mechanisms unrelated to pyroptosis (Zhang and Lieberman, 2020). Pyroptosis serves as a protective mechanism to eliminate harmful pathogens and alert neighboring cells. However, the release of cytokines during pyroptosis can amplify inflammatory responses, potentially leading to a cytokine storm and subsequent tissue damage (Wei Y. et al., 2022).

2.1 GSDMD-mediated pyroptosis

GSDMD is the first gasdermin to be associated with pyroptosis (He et al., 2015; Broz et al., 2020). Activated Caspase-1/4/5/11 cleaves GSDMD at the $_{272}$FLTD$_{275}$ site (equivalent to $_{273}$LLSD$_{276}$ in mouse GSDMD), inducing pyroptosis (Wang K. et al., 2020). In the canonical pathway, DAMPs and PAMPs trigger the activation of pattern recognition receptors (PRRs) such as the NOD-like receptors (NLRs) and the absent in melanoma 2 (AIM2)-like receptors (ALRs). Recognition of the agonists by their receptors normally lead to the assembly of inflammasome, which recruits and activates the corresponding caspases, leading to the processing of pro-cytokines and gasdermins, followed by pore formation on the cell membrane and lytic cell death.

The NLRP3 inflammasome is the most extensively studied pathway that function through GSDMD and have been extensively reviewed (Xu and Nunez, 2023; Li LR. et al., 2024). The NLRC4 inflammasome activation is triggered by selected PAMPs such as bacterial flagellin and the type 3 secretion system proteins, through its function partner NAIPs (Andrade and Zamboni, 2020). Cytosolic dsDNA, regardless of its sequence and

origin (from foreign bacteria, fungi, viruses, or damaged cells), triggers AIM2 activation and formation of the inflammasome complex, which lead to Caspase-1 activation and the initiation of pyroptosis (Sharma et al., 2019). Activation of the pyrin inflammasome, as a result of reduced pyrin phosphorylation, leads to the recruitment and activation of Caspase-1 (Aubert et al., 2016; Ng et al., 2010; Kamanova et al., 2008; Xu et al., 2014). *Bacillus anthracis* activates NLRP1b inflammasome through anthrax lethal toxins, which facilitate ubiquitination and degradation of the N-terminal domain of NLRP1b. The remaining C-termini of NLRP1b recruit and activate Caspase-1 (Sandstrom et al., 2019; Chavarría-Smith and Vance, 2013). Rotavirus infection activates NLRP9b inflammasome *via* double-stranded RNA (dsRNA) in intestinal epithelial cells. The dsRNA interacts with DEAH-box helicase 9 (DHX9), which then binds to NLRP9b. Subsequently, NLRP9b forms inflammasome complexes with the adaptor protein ASC and activates Caspase-1 (Liu and Gack, 2020; Zhu et al., 2017).

In the non-canonical pyroptosis pathway, cytosolic LPS binds directly to pro-Caspase-4/5 in humans and pro-Caspase-11 in mice, resulting in autophosphorylation and activation (Yu P. et al., 2021). The active forms of Caspase-4/5 and Caspase-11 then trigger cleavage of GSDMD, ultimately leading to pyroptosis. LPS-induced pyroptosis allows potassium (K^+) efflux through pores formed by GSDMD. This K^+ efflux subsequently stimulates the activation of NLRP3 inflammasomes, leading to canonical pyroptosis mediated by Caspase-1. This connection suggests a coordination between Caspase-1-mediated canonical pyroptosis and Caspase-11-mediated non-canonical pyroptosis through the involvement of NLRP3 inflammasomes.

The involvement of Caspase-8 in the cleavage of GSDMD and initiation of pyroptosis was discovered more recently (Gram et al., 2019; Chen and Brodsky, 2023). Mouse GSDMD was cleaved by active caspase-8 at two sites, D276 and D88, and the cleavage at D276 generated the active P30 fragment as in the case of caspase-1 cleavage (Orning et al., 2018; Sarhan et al., 2018; Chen KW. et al., 2019). Activation of caspase-8 was RIPK1-dependent, mediated through its interaction with FAS Associated Death Domain Protein (FADD). Interestingly, GSDMD cleavage and pyroptosis occur upstream of NLRP3 activation, triggered caspase-1 activation and additional cleavage of GSDMD similarly as in the case of non-cononical activation (Chen and Brodsky, 2023).

2.2 GSDME-involved pyroptosis

GSDME can be cleaved by Caspase-3 and Caspase-8 downstream of the NLRP3 inflammasome (Wang C. et al., 2021). Caspase-3 was reported to cleave human GSDME at ^{267}DMPD^{270}, mouse GSDME at ^{267}DMLD^{270}, and zebrafish GSDME1 at ^{253}SEVD^{256} (Wang et al., 2017). Previous studies revealed that Caspase-1 and/or Caspase-8 are critical for activating Caspase-3/GSDME-dependent cell death in the absence of GSDMD expression (Wei et al., 2023). In mice with the gain-of-function mutations in NLRP3, deficiency of GSDMD alone could not prevent secretion of IL-1β and IL-18 from macrophages in response to LPS or TNF-α stimulation (Wang C. et al., 2021). Sustained NLRP3 inflammasome activation induced Caspase-8/3 activation, GSDME cleavage, and IL-1β maturation in *Gsdmd*$^{-/-}$ macrophages. Aizawa *et al.* reported that Caspase-8 induced GSDME-dependent pyroptosis in Caspase-1/11-deficient macrophages (Aizawa et al., 2020). NLRP3 inflammasome activation recruited ACS, and subsequently Caspase-8. Activated Caspase-8 cleaved GSDME. Recently, Caspase-3/GSDME-mediated pyroptosis has been reported in human lung epithelial cells infected by SARS-CoV-2 (Planès et al., 2022). Interestingly, multiple SARS-CoV-2 3CL-(3C-like) proteases cleaved human NLRP1 at the Q333 site, triggering inflammasome assembly and cell death. At the same time, 3CL proteases also inactivate GSDMD, and alternatively, cells died *via* Caspase-3/GSDME mediated pyroptosis. The 3C protease from the EV71 enterovirus has been shown to cleave and inactivate GSDMD at the Q193 site (Lei et al., 2017).

The mechanisms of GSDME-mediated pyroptosis in tumor cells have been well studied (Hu et al., 2023). A variety of chemotherapeutic drugs kill tumor cells through both apoptosis and GSDME-mediated pyroptosis via Caspase-3 or Caspase-8 activation. For example, Zhang et al. reported doxorubicin (DOX)-induced pyroptosis via the Caspase-3/GSDME pathway in two breast cancer cell lines (MDA-MB-231 and T47D) (Zhang Z. et al., 2021). The GSDME-dependent pyroptosis is activated by the ROS/JNK signaling pathway. DOX treatment induced ROS production, which promoted the phosphorylation of JNK into p-JNK that initiated Caspase-3 activation. In parallel, Caspase-8 was also activated by ROS, which promoted the cleavage/activation of Caspase-3. Similarly, Shen et al. reported that DOX-induced pyroptosis occured through the ROS-JNK-Caspase 3-GSDME signaling in human tubular epithelial cells (Shen et al., 2021).

2.3 Other GSDMs involved in pyroptosis

Other gasdermins, including GSDMA, GSDMB and GSDMC are previously considered lacking the inflammatory Caspase (Caspase-1 and Caspase-4/5/11) cleavage site (Shi et al., 2017). However, recent study reveals that GSDMA in many bird, amphibians, and reptiles species contain caspase-1 cleavage sites such as YVAD or FASD in the linker and were cleaved by activated caspase-1 (Billman et al., 2024). Another protease that cleaves GSDMA is *Streptococcal pyrogenic* exotoxin B (SpeB), the virulence factor of group A *Streptococcus* (GAS), which directly cleaves GSDMA after Gln246 in keratinocytes (Deng et al., 2022; LaRock et al., 2022). In addition, recent studies have unveiled a correlation between the degradation of GSDMA and cisplatin resistance in tumor cells, suggesting that platinum-based drugs may induce GSDMA-mediated cell death in tumors through some unknown mechanism (Wang H. et al., 2024).

In airway epithelial cells, GSDMB has been shown to be cleaved by activated Caspase-1 after D236, releasing N-terminal fragments capable of inducing pyroptosis (Panganiban et al., 2018). Pyrotosis mediated by Granzyme A (GZMA)/GSDMB has been reported in tumor cells. GZMA released from cytotoxic lymphocytes and natural killer (NK) cells enter tumor cells *via* perforin. GSDMB is cleaved by cytosolic GZMA at Lys244 to release the N-terminal domain, which perforates the plasma membrane and leads to pyroptosis (Zhou et al., 2020). Research on granzymes has spanned over 30 years, and granzymes are involved in the

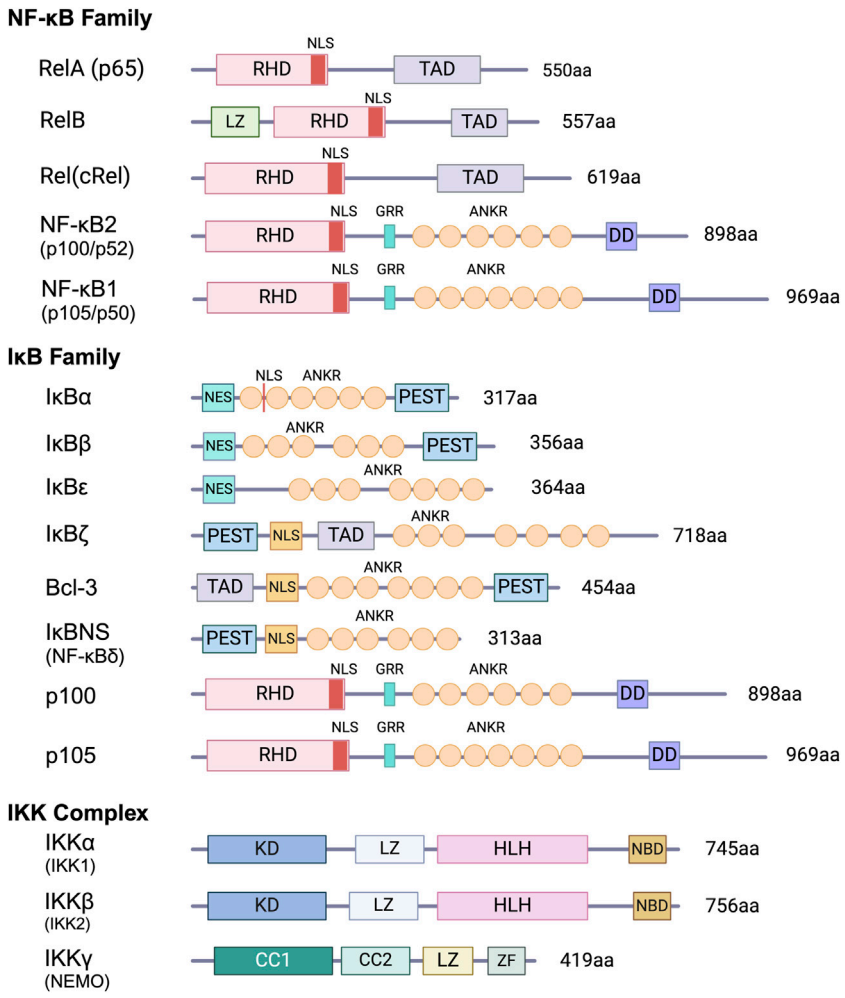

FIGURE 2
Schematic representation of NF-κB, IκB and IKK proteins. Key features of members of the NF-κB and IκB protein families and components of the IKK complex are shown. RHR, Rel homology region; NLS, nuclear localization sequence; ANKR, ankyrin repeats; DD, death domain; TAD, transactivation domain; PEST, region rich in proline, glutamate, serine. and threonine; LZ, leucine zipper; Kinase, kinase domain; HLH, helix-loop-helix region; NBD, NEMO-binding domain; CC, coiled-coil domain; ZF, zinc-finger.

elimination of virus-infected cells by immune cells. The discovery of GSDMB cleavage by GZMA offered a new mechanism for GZMA-mediated cell death. Interestingly, full-length GSDMB can promote oligomerization of Caspase-4 by a direct binding to its CARD domain, thereby facilitating cleavage of GSDMD and triggering non-canonical pyroptosis (Chen Q. et al., 2019).

GSDMC is expressed in multiple tissues, including the trachea, small intestine, colon, esophagus, skin, spleen, and vagina (Zhu et al., 2024). Both artificially truncated GSDMC-NT and the GSDMC-NT fragment that intracellularly cleaved by Caspase-8 have been demonstrated to provoke pyroptosis (Zhang JY. et al., 2021). A recent study by Hou et al. demonstrated that PD-L1 nuclear translocation in hypoxic tumor cells increases the production of GSDMC, which converted apoptosis to pyroptosis (Hou J. et al., 2020). In a hypoxic environment, phosphorylated STAT3 (Signal transducer and activator of transcription 3) interacts with PD-L1, leading to its nuclear translocation and subsequent upregulation of GSDMC transcription. As GSDMC levels increase, TNF promotes the cleavage of GSDMC by Caspase-8, producing the GSDMC-N-terminal fragment that drives pyroptosis. Additionally, the cellular metabolite α-ketoglutarate (α-KG) facilitates the assembly of the DR6 receptosome in tumor cells, forming a molecular platform that enables the efficient proteolysis of GSDMC by activated Caspase-8, thereby inducing pyroptosis.

3 NF-κB signalling pathway

3.1 NF-κB family members and regulators

NF-κB, IκB, and IKK are the main signaling nexus/hubs of the NF-κB signaling pathway. The NF-κB family consists of five main members: p65 (RelA), RelB, c-Rel, p105/p50 (NF-κB1) and p100/p52 (NF-κB2) (Figure 2). They share a conserved Rel Homology Domain (RHD) of over 300 amino acids at the N-terminus, which endows the ability of dimerization, nuclear translocation, and binding to specific sequences on DNA (Dorrington and Fraser, 2019; Yu et al., 2020; Zinatizadeh et al., 2021). Based on their

structural characteristics at the C-terminus, the NF-κB family can be divided into NF-κB subfamily and Rel subfamily. NF-κB subfamily members, p105 and p100, possess long repetitive sequences, ankyrin repeats, at their C-terminus. While the Rel subfamily members, p65, RelB, and c-Rel, have a transcription-activation domain (TAD) at their C-terminus. The TAD is considered essential for the nuclear translocation of NF-κB, hence NF-κB subfamily homodimers are regarded as inhibitory regulators due to the lack of TAD. NF-κB subfamily could only activate gene transcription when forming heterodimers with the Rel subfamily members (Yu H. et al., 2021). In recent years, a sixth member of the NF-κB family has been discovered: RelAp43, a new splicing variant of RelA, lacking the TAD at its C-terminus. It is primarily activated by the rabies virus matrix protein, although its ability to interact with other NF-κB family members has been demonstrated *in vitro*, this perspective has not been widely accepted (Struzik and Szulc-Dąbrowska, 2019; Ben Khalifa et al., 2016; Luco et al., 2012).

Inhibitor of κB (IκB) serves as a key regulator in the NF-κB signaling pathway, as its name suggests, by inhibiting NF-κB. Its members include IκBα, IκBβ, IκBε, IκBγ, IκBz, Bcl-3, as well as the precursors of NF-κB subfamily, p105, and p100 (Zhang J. et al., 2023). Within 2 years of discovering NF-κB, Baltimore proposed the concept of IκB and identified IκBα, which remains the most extensively studied IκB to date (Baeuerle and Baltimore, 1988). IκB sequesters NF-κB in the cytoplasm, forming an inactive complex. Phosphorylation and degradation of IκB, which is typically mediated by the ubiquitin-proteasome system, are required for activating NF-κB, after that the free NF-κB, with the assistance of the nuclear transport receptor importin α/β, translocate through the nuclear pore and activates transcription (Hinz et al., 2012; Wang X. et al., 2020). The classical IκB proteins, including IκBα, IκBβ, and IκBε, are typically distributed in the cytoplasm. They contain six ankyrin repeats and are capable of binding to and covering the Rel Homology Domain (RHD), thereby exerting inhibitory effects. Non-classical IκB primarily resides in the nucleus (aka nuclear IκB) and is induced to increase as a target gene of NF-κB, which contains more than six ankyrin repeats (Wang X. et al., 2020).

IκB kinase (IKK) is primarily responsible for the phosphorylation of IκB, which was discovered nearly a decade after NF-κB. The IKK complex consists of active IKKα and IKKβ, and two molecules of the non-active IKKγ (NEMO) to form a tetramer (DiDonato et al., 1997; Rothwarf et al., 1998), while whether other components are involved is still under considerable controversy. IKKα and IKKβ are highly similar in sequence and structure, their N-terminal kinase domains need to be activated to phosphorylate IκB (Zhang J. et al., 2023). This activation mechanism may arise from autophosphorylation or upstream signals from kinases such as TAK1, MEKK3, and others (Wang et al., 2001; Mulero et al., 2019). *In vitro* recombination experiments have shown that IKKγ can only directly bind to IKKβ, while the binding of IKKγ to IKKα depends on IKKβ. Therefore, it is inferred that the non-enzymatic IKKγ plays a scaffold and regulatory role (Zandi and Karin, 2023). Although IKK possesses two enzymatically active subunits (α and β), studies showed that in specific pathways, the enzymatic activity of only one subunit is required (Israël, 2010). Other proteins that may participate in the IKK complex include NIK, MEKK1, IKAP (Cohen et al., 1998). It is worth noting that IKK does not always act as a positive regulator of NF-κB: in immune cells (T and B lymphocytes), IKK phosphorylates Bcl10, leading to inhibition of the NF-κB pathway (Abd-Ellah et al., 2018; Zhou et al., 2004).

3.2 Activation of NF-κB signaling pathway

During infection and oxidative stress, NF-κB regulates the transcription of inflammation-related genes (Capece et al., 2022; Xu G. et al., 2024). During the resting state, NF-κB is sequestered in the cytoplasm by IκB, preventing excessive gene transcription activity. Upon receiving specific stimuli, such as inflammatory cytokines or cellular stress, IKK phosphorylates and cleaves IκB, releasing NF-κB to enable nucleus translocation that initiates transcription of target genes (Anilkumar and Wright-Jin, 2024).

The NF-κB activation may proceed through the canonical and non-canonical pathways. Initially signaling mediated by IKKβ/NEMO/RelA was regarded as the canonical pathway. However, with the discovery that IKKβ can be partially replaced by IKKα and the involvement of RelA in the non-canonical pathway, this viewpoint has been challenged. It has been suggested that NEMO dependency to be used to define the canonical pathway (Liu T. et al., 2017). Despite this, research on the canonical pathway primarily focuses on IKKβ. Similarly, studies of RelA predominantly focused on the canonical pathway (Shih et al., 2011). Upon stimulation, ligand-loaded receptors recruit adaptor proteins such as TRADD, TRAF2, and RIK1 to activate IKKβ (Ma et al., 2024). The IκB proteins are then phosphorylated by IKK followed by ubiquitination and degradation, releasing the NF-κB dimer for translocation into the nucleus. The dimers corresponding to the classical pathway mainly consist of four types: RelA:RelA, RelA:p50, cRel:cRel, and cRel:p50.

The non-canonical pathway is mediated by IKKα and the NF-κB-inducing kinase (NIK) (Rodriguez et al., 2024). NIK (also known as MAP3K14) is the first identified component in the non-canonical pathway. Currently identified inducers of the non-canonical NF-κB pathway all converge at NIK. Therefore, the activation of NIK is defined as a key event in the non-canonical pathway, which normally lead to the RelB:p52 dimer. Under resting conditions, NIK remains at relatively low levels due to its degradation by TRAF3. Degradation of TRAF3 triggered by the stimulation signals results in the accumulation of NIK within the cell. However, since NIK requires *de novo* synthesis, it takes some time to reach the threshold required to trigger the non-canonical pathway, this may explain why the signaling response of this pathway is relatively slow. In the steady state, p52 primarily exists in the form of its precursor, p100. Both p100 and IκBα are phosphorylated by NIK (Xiao et al., 2001b). Subsequently, p100 is processed into p52, forming the RelB:p52 dimer. Phosphorylation of IKKα activates it. While p100 has been proposed to be a substrate for IKKα, IKKα did not induce the direct processing of p100. A potential explanation is the binding between IKKα and p100 requiring NIK (Yu et al., 2020; García-García et al., 2024). Although the role of IKKα has not been directly demonstrated, studies on transgenic mice have shown that mice with IKKα deficiency and NIK knockout have similar phenotypes, indicating the critical role of IKKα in the non-canonical NF-κB pathway. On the other hand, IKKα also

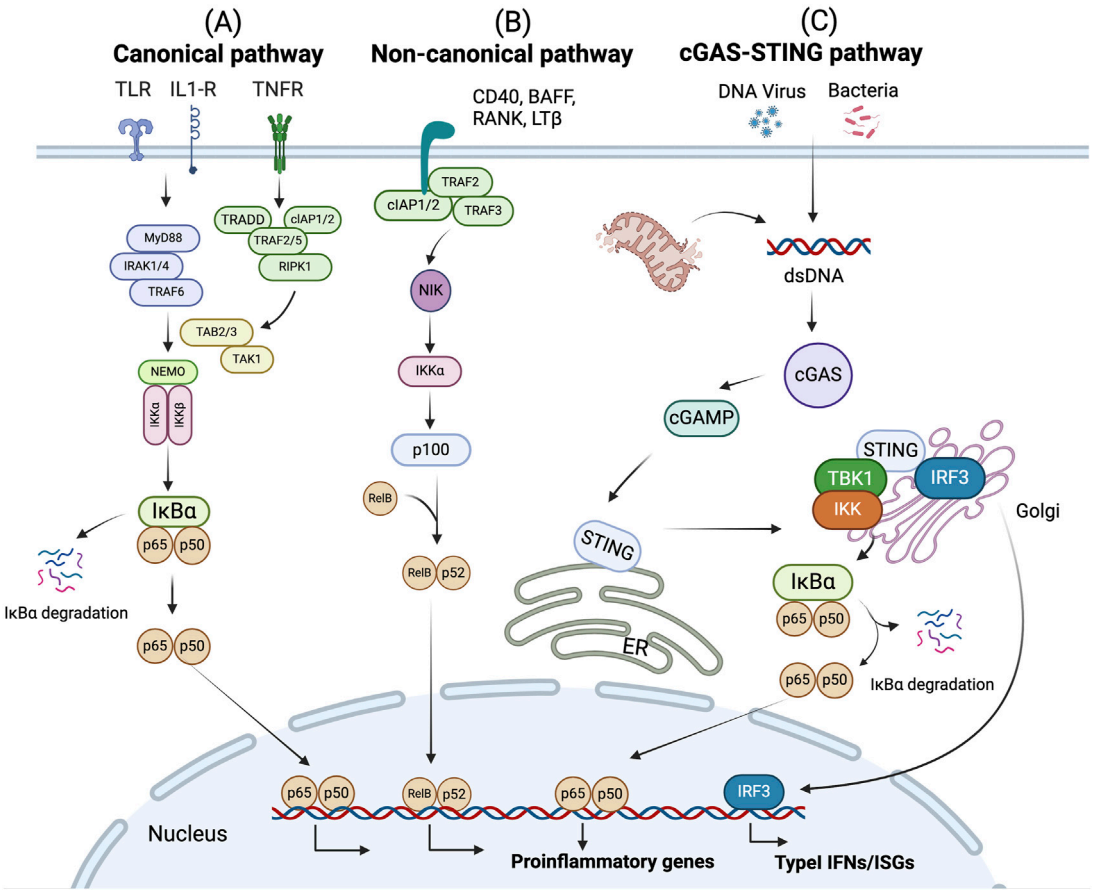

FIGURE 3
NF-κB signaling pathway. **(A)** The canonical pathway is induced by TLRs, TNFRs, and IL-1R. Activation of this cascade leads to the phosphorylation and degradation of inhibitory protein IκB. NF-κB p65 and p50 are activated by releasing from the IκB-containing complex, then translocating into nucleus. **(B)** The non-canonical pathway is dependent on the activation of p100 through BAFFR, CD40, RANK or LTβ. This cascade induces phosphorylation of NIK, which subsequently phosphorylates IKKα. Activated p100 releases p52. Then RelB/p52 heterodimer is activated and translocate to the nucleus. The activation of NF-κB signaling leads to the expression of proinflammatory genes. **(C)** cGAS recognizes dsDNA fragments from bacteria, viruses, mitochondria, etc., and catalytically generates 2′3′-cGAMP. STING proteins located in the ER are activated upon recognition of cGAMP. STING then translocates from the ER to Golgi. During this process, STING oligomers recruit TBK1, triggering TBK1 autophosphorylation. In turn, STING is phosphorylated by TBK1. Activated STING then recruits IRF3, facilitating the phosphorylation of IRF3 by TBK1. Activated IRF3 dimers then translocate to the nucleus to activate the transcription of type I IFNs, which in turn leads to the production of diverse IFN-stimulated genes (ISGs). Besides, STING induces NF-κB activity *via* TBK1-dependent and independent manners, resulting in the IκBα phosphorylation and subsequently translocation of p65/p50 to the nucleus, leading to the production of proinflammatory genes.

functions as a negatively feedback regulator of non-canonical NF-κB activity by phosphorylating and degrading NIK, these contradictory results may be related to signal crosstalk (Razani et al., 2010; Gray et al., 2014). Other regulatory mechanisms mainly involve modulating the levels of NIK, such as TNAP, Zfp91, TBK1, and NLRP12 (Sun, 2011; Jin et al., 2012), but the specific regulatory mechanisms are not yet fully understood. OTUD1b has been reported to deubiquitinate TRAF3 to prevent its degradation, thus being regarded as a negative regulatory factor (Hu et al., 2013).

It is almost impossible to have completely independent signaling pathways in complex cells. Crosstalk within the NF-κB signaling pathways has been nicely-reviewed (Oeckinghaus et al., 2011). Here, we summarize the reports of NF-κB signaling pathway activation in inflammation over the past decade. The activation of NF-κB is thought to be part of a stress response as it is activated through the recognition of a variety of stimuli by receptors. These include, but are not limited to, the pattern recognition receptors like TLRs, cytokine receptors such as TNFR and IL-1R, and antigen receptors TCR (T cell receptor) and BCR (B cell Receptor) (Barnabei et al., 2021). Additionally, the cGAS-STING pathway has been identified as a central regulator of type I interferon (IFN) and NF-κB. In this review, we will focus on NF-κB signaling pathways mediated by TLRs, IL-1R,TNFR and cGAS-STING (Figure 3).

3.2.1 TLR-mediated NF-κB signalling

TLRs are pattern recognition receptors that recognize prototypical structures of microbes, including microbial surface components such as acylated lipopeptides, peptidoglycans, lipopolysaccharides and flagellin, and microbial nucleic acids such as dsRNA, ssRNA, or unmethylated DNA (Beutler et al., 2003). TLRs are transmembrane proteins characterized by the extracellular domains containing variable numbers of leucine-rich-repeat (LRR) motifs responsible for ligand recognition and a cytoplasmic Toll/interleukin 1 (IL-1) receptor (TIR) homology

domain responsible for initiating intracellular signaling (Moresco et al., 2011). To date, 11 human TLRs and 13 mouse TLRs have been identified (Kawai and Akira, 2007a). The ligands of each TLR have previously been reviewed (Moresco et al., 2011; Fan Y. et al., 2023; Chen et al., 2021; Kawai and Akira, 2007b). There are two groups of TLRs. The group on cell surface (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11) mainly recognizes microbial envelope components, such as lipids and lipoproteins. The other group is intracellular TLRs (TLR3, TLR7, TLR8, and TLR9) that sense the nucleic acids derived from bacteria or viruses. TLRs are widely expressed in various immune cells (e.g., monocytes, macrophages, dendritic cells (DCs), B cells, T cells and neutrophils) as well as non immune-cells (e.g., fibroblast cells, epithelial cells and endothelial cells), and usually acts as the first responders to initiate pyroptosis, which play a crucial role in defending against pathogenic microbial infection through the induction of inflammatory cytokines (Kumar et al., 2009).

TLR signaling pathways lead to the activation of NF-κB and IRF3 to induce the expression of various genes encoding inflammatory cytokines, the inactive pro-forms of inflammatory cytokines such as IL-1β and IL-18, and type I interferons and chemokines (Liu T. et al., 2017). Upon binding by specific ligands, TLRs recruit a set of adaptor proteins with TIR domains by homophilic interaction of their TIR domains. TLR signaling depends critically on a total of four adaptor proteins—myeloid differentiation primary response protein 88 (MyD88), TIR-associated protein (TIRAP, also known as MyD88-adaptor like protein, MAL), Toll-receptor-associated activator of interferon (TRIF), and Toll-receptor-associated molecule (TRAM), which directly bind to activated TLRs and recruit downstream signaling components (Moresco et al., 2011). Ligand binding leads to dimerization of TLR, and the dimerized cytosolic TIR domains (Latz et al., 2007) recruit MyD88 and TRIF (some TLRs require adaptor TIRAP or TRAM), respectively, to stimulate the assembly of a large supramolecular complex called Myddosome or Triffosome (O'Neill and Bowie, 2007; Fitzgerald and Kagan, 2020). Depending on the components of those large oligomeric signaling complexes, TLR signaling pathways can be mainly classified as either MyD88-dependent pathways, which leads to the activation of NF-κB, IFN-responsive factors (IRFs), and the mitogen-activated protein kinases (MAPK) pathways, inducing the expression of pro-inflammatory cytokines (E.g., TNF, IL-1β, IL-8, IL-18, IL-6, IL-12 and IL-8 et al.); or TRIF-dependent pathways, which mainly activate IRFs to mediate the expression of type I IFNs (IFNa or IFNβ) (Duan et al., 2022; Balka and De Nardo, 2019). All TLRs, except TLR3, utilize a MyD88-dependent pathway resulting in the production of cytokines through NF-κB, and also trigger MAPK cascades that lead to activation of AP-1 (activator protein 1) and cAMP (cyclic AMP) response element-binding protein (CREB) (Moresco et al., 2011). TLR3 and TLR4 utilize the TRIF-dependent pathway to activate NF-κB and additionally activate IRF3 to induce type I IFNs (Hu et al., 2015).

3.2.2 IL-1R family-mediated NF-κB signaling

IL-1R family members are receptors for endogenous alarm mediators sensing the integrity of barriers or the fitness of cells. The first biochemical characterization of an IL-1 receptor (IL-1R) was reported in 1985 (Dower et al., 1985). The IL-1R family now consists of 10 members that are receptors or co-receptors for presently 11 ligands of the IL-1 family of cytokines (Boraschi et al., 2018). All members of the IL-1R family are characterized by an intracellular TIR domain (except for IL-1R2 which lacks the TIR domain) that are homologous to other members of the IL-1R and TLR families, and three extracellular immunoglobulin domains that bind specific IL-1 related cytokines (Boraschi et al., 2018). Among those IL-1R families, only IL-1R1, IL-1R4, IL-1R5 and IL-1R6 have the capability to bind cytokines of the IL-1 family and initiate signaling, while IL-1R3 and IL-1R7 are essential in forming the signaling receptor complexes (Zarezadeh Mehrabadi et al., 2022) (Li et al., 2021). Upon ligand binding, the accessory co-receptor (IL-1R3 or IL-1R7) is recruited, which leads to the recruitment of MyD88 to the receptor complex through TIR:TIR domain interactions, forming myddosome. IL-1Rs interact directly with MyD88 and the signaling of all IL-1Rs is MyD88 dependent. The formation of myddosome leads to the recruitment of IL-1R-associated kinases (IRAKs). The IRAK family contains four members, IRAK-1, IRAK-2, IRAK-3 (also known as IRAK-M), and IRAK-4, and the different roles of them in the signaling of TLRs and IL-Rs have been reviewed (Flannery and Bowie, 2010). Next, effector TRAF6 is recruited to the C-terminal domains of either oligomeric IRAK-1 or IRAK-2 and activated via K63 autoubiquitination. TRAF6 subsequently ubiquitinates and activates TGFβ-associated kinase (TAK1), which is responsible for phosphorylating/activating IKK-β. TRAF6 and TAK1 both facilitate the degradation of IKKγ. This allows the release of the NF-κB dimer and its translocation to the nucleus (Liu T. et al., 2017).

3.2.3 TNFR family-mediated NF-κB signaling

TNFα is expressed by multiple cells of the innate and adaptive immune systems, including macrophages, monocytes, B lymphocytes and T lymphocytes, and by nonimmune cells, such as endothelial cells and fibroblasts (MacEwan, 2002). As an inflammatory factor, it plays a prominent role in the interconnection of different types of programmed cell death, including apoptosis, necrosis and pyroptosis (Frank and Vince, 2019). There are two forms of TNF, membrane-bound TNF (mTNF, 26 KDa) and soluble TNF (sTNF, 17 KDa) which lacks the transmembrane domain (Richter et al., 2012; Grell et al., 1995). TNF signaling is initiated by the interaction between TNFα and its membrane receptors TNFR1 or TNFR2 (Jang et al., 2021). TNFR1 is expressed at low level across all human tissues and can respond to both mTNFa and sTNFa, whereas expression of TNFR2 is restricted to particular cells, including oligodendrocytes, astrocytes, T cells, myocytes, thymocytes, endothelial cells and in human mesenchymal stem cells, and TNFR2 binds only with mTNFα (Grell et al., 1995; Cabal-Hierro and Lazo, 2012). TNFR1 and TNFR2 have similar extracellular structures where TNFα binds, but distinct intracellular structures for binding of adaptor proteins (Tartaglia et al., 1991). Both TNFR1 and 2 signaling pathways lead to the activation of NF-κB (Ting and Bertrand, 2016). TNFR1 contains an intracellular death domain (DD) to recruit the DD-containing proteins, enabling strong activation of proinflammatory pathways and cytotoxic signaling. TNFR2 does not have a DD. It recruits the TNFR associated factor 1 (TRAF1) and 2 (TRAF2) with the help of a short peptide motif and activates the alternative NF-κB pathway (Hsu et al., 1995; Rothe et al., 1995; Medler and Wajant, 2019).

TNFR1 mediated signaling pathways have been well characterized. Binding of TNFα to TNFR1 leads to the formation of two different TNF signaling complexes, referred to as complexes I and complex II (including IIa, IIb, and IIc), which result in distinct cellular responses (Brenner et al., 2015). The functional outcome of complex I signaling is the induction of inflammation, cell survival and proliferation, and the immune defense against pathogens (Brenner et al., 2015). During the formation of complex I, activated TNFR1 undergoes conformational change in the DD, followed by the recruitment of TRADD, and subsequently receptor-interacting serine/threonine-protein kinase 1 (RIPK1), TNFR-associated factor 2 or 5 (TRAF2/5), cellular inhibitor of apoptosis protein 1 or 2 (cIAP1/2), and the linear ubiquitin chain assembly complex (LUBAC) (Jang et al., 2021). Formation of the Complex I triggers the activation of NF-κB or AP-1 family transcription factors, which control the expression of antiapoptotic proteins that prevent the initiation of the cell death processes (Haas et al., 2009). The NF-κB pathway activated by the formation of TNF Complex I relies on the ubiquitination of RIPK1. The ubiquitinated RIPK1 recruits the transforming growth factor-beta (TGF-β)-activated kinase 1 (TAK1) complex, consisting of TAK-binding protein 1 (TAB1), 2 (TAB2) and 3 (TAB3), and the IKK complex constituted of NEMO, IKKα, and IKKβ(144). The IKK complex is essential for the phosphorylation of IκBα, which lead to its degradation and release of NF-κB to translocate to the nucleus to initiate transcription. NF-κB can induce the transcription of anti-apoptotic genes such as cIAP-1, cIAP-2, cFLIP, TRAF1 and TRAF2 (Micheau and Tschopp, 2003), which are also components of TNF Complexes.

While the assembly of complex I occurs on the plasma membrane, complex II is assembled in the cytoplasm. Formation of the Complex II (also known as death-inducing signaling complex, DISC) triggers cell death processes (apoptosis, necroptosis or pyroptosis) after the internalization of the receptor (Micheau and Tschopp, 2003). Based on their components, they can be further sub-grouped into complex IIa, IIb and IIc (Holbrook et al., 2019). Complex IIa consists of TRADD, RIPK1, TRAF2, cIAP1/2, pro-Caspase-8, and Fas-associated protein with death domain (FADD). Complex IIb contains all components in complex IIa plus RIPK3 (Wang et al., 2008). Both Complex IIa and IIb (known as apoptosome) activate Caspase-8 and downstream Caspase-3 to trigger apoptosis or induce GSDME-mediated pyroptosis (Micheau and Tschopp, 2003; Zhai et al., 2022). Complex IIc (also known as necrosome) is composed of RIPK1 and RIPK3, which induces necroptosis through a Caspase-8/RIPK3/MLKL (mixed lineage kinase domain-like protein) pathway (Gough and Myles, 2020; Vandenabeele et al., 2010).

TNFR2 can activate both canonical and non-canonical NF-κB signaling, leading to numerous changes in gene expression that drive inflammation, cell proliferation and cell survival (Borghi et al., 2016). Binding of TNF to TNFR2 triggers the recruitment of TRAF2 along with TRAF1, TRAF3, cIAP1, and cIAP2 to activate the canonical NF-κB pathway (Jang et al., 2021; Rodríguez et al., 2011). TRAF2 also acts as a negative regulator of TNFR2-induced non-canonical NF-κB signaling. Degradation of TRAF2 is a fundamental step in TNFR2-induced activation of the non-canonical NF-κB pathway (Borghi et al., 2016; Ruspi et al., 2014; Vallabhapurapu et al., 2008). The cIAP1/2–TRAF2–TRAF3 signaling complex normally targets NIK for degradation and keeps it at a low level under unstimulated conditions. In the absence of TRAF2, NIK accumulates and phosphorylates IKKa, which in turn phosphorylates the NF-κB p100 subunit (Sun, 2017). Phosphorylates NF-κB p100 is also ubiquitinated by the SCF-beta-TRCP ubiquitin ligase complex at K48 and is subsequently processed by the proteasome to NF-κB p52. Then p52, together with another transcriptionally competent NF-κB subunit RelB, translocate into the nucleus, and initiates gene transcription (Borghi et al., 2016; Ruspi et al., 2014).

3.2.4 cGAS-STING mediated NF-κB signaling

Over the past decade, significant progress has been made in understanding how nucleic acid recognition is coupled to immune gene expression, particularly through the DNA-sensing receptor cGAS and its downstream effector, STING (Motwani et al., 2019; Du et al., 2023). The detection of mislocalized DNA in the cytosolic by cGAS has been recognized as a pivotal mechanism in cellular responses to pathogen invasion, DNA damage, and mitochondrial stress (Decout et al., 2021; Skopelja-Gardner et al., 2022; Domizio et al., 2022). cGAS-mediated STING activation drives IFN responses and also activates NF-κB signaling pathway.

Activation of the cGAS-STING pathway begins with the recognition of double-stranded DNA (dsDNA), either of foreign or mislocalized self-origin, by cGAS (Decout et al., 2021; Chen et al., 2016). Upon binding dsDNA, cGAS is activated to catalyze the synthesis of the second messenger 2′3′-cyclic GMP-AMP (cGAMP). The cGAMP binds to the endoplasmic-reticulum (ER)-membrane located adaptor protein STING, inducing a conformational change that activates STING. Once activated, STING traffics from the ER to the ER-Golgi intermediate compartment and the Golgi apparatus. During this process, STING recruits and activates TANK-binding kinase 1 (TBK1), which phosphorylates both IRF3 and IKKε. The phosphorylation of IRF3 results in its dimerization and nuclear translocation, where it drives the expression of type I IFNs. Concurrently, activated IKKε phosphorylates IκB, which is subsequently ubiquitinated and degraded *via* the proteasome, releasing NF-κB to enable nuclear localization (Zhang L. et al., 2023). This dual activation of IRF3 and NF-κB amplifies the immune response, enabling robust inflammatory and antiviral signaling.

The critical role of cGAS-STING-mediated NF-κB activation in promoting inflammation and immune regulation is well established (Zhang L. et al., 2023; Balka et al., 2020). Studies have demonstrated that AIM2-deficient cells, which bypass rapid pyroptotic elimination, rely on the cGAS-STING-TBK1-IRF3/NF-κB axis to produce pro-inflammatory cytokines such as C-X-C motif chemokine 10 (CXCL10), TNF-α, and IFN-β (Baatarjav et al., 2022). In a cerebral venous sinus thrombosis model, cGAS–STING was found to activate the NF-kB cascade and downstream NLRP3 inflammasome (Ding et al., 2022). Function of cGAS-STING in pyroptosis has been reviewed recently (Liu et al., 2024).

4 Regulation of inflammasome through NF-κB

4.1 NLRP3

NLRP3 inflammasome activation normally occurs in two stages, involving a priming signal (signal I) and an activation signal (signal

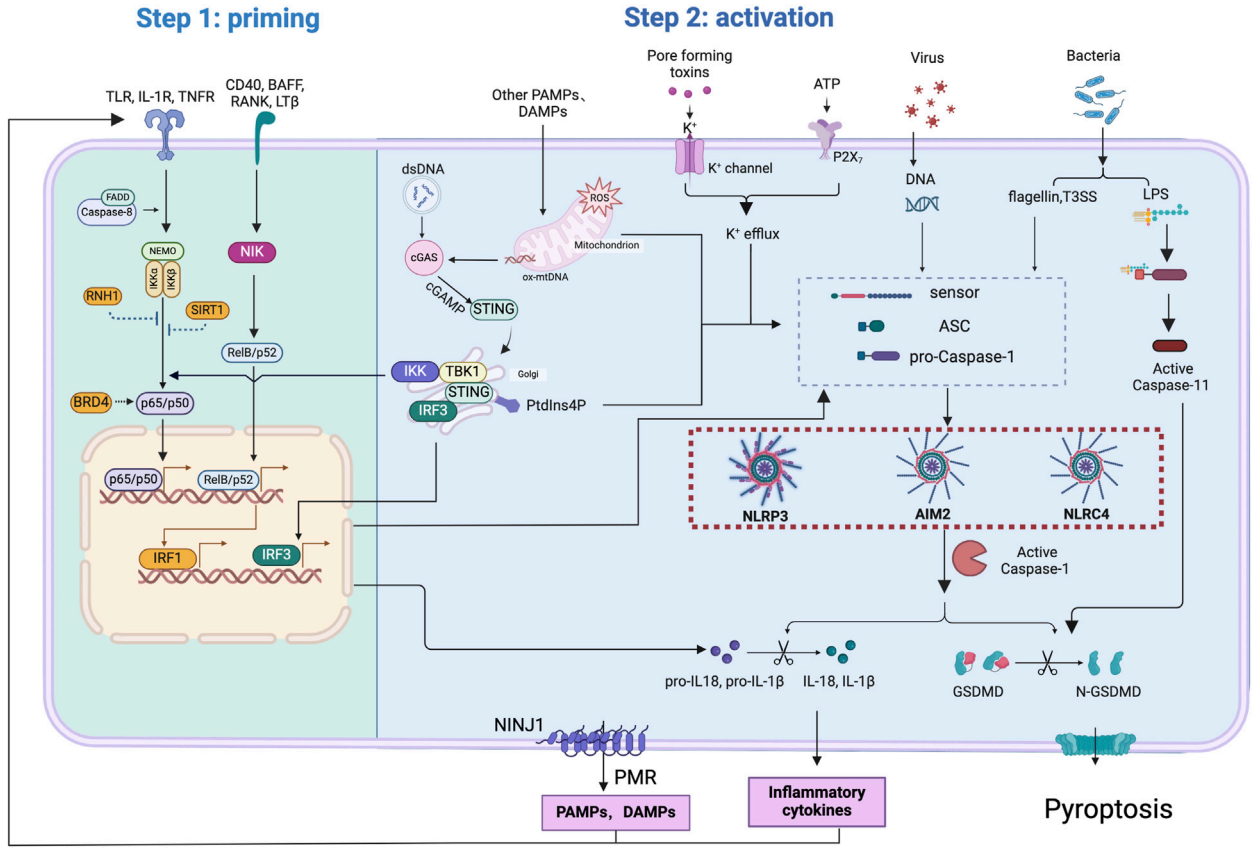

FIGURE 4
Mechanisms involved in the regulation of inflammasome activation and pyroptosis through NF-κB signaling. NF-κB signaling primes inflammasome activation by canonical NF-κB pathway (through receptors such as TLR,TNFR, and IL-1R), non-canonical pathway (through receptors such as CD40, BAFF, RANK, LTβ) or cGAS-STING pathway. FADD and caspase-8 contribute to canonical NF-κB activation. Binding of transcription factor, including p65/p50,RelB/p52, IRF1 and IRF3,on nuclear DNA drives the expression of inflammasome components, including NLRP3, NLRC4, AIM2, CASPASE11, GSDMD, pro-IL-1β, and pro-IL-18. Inhibitors like RNH1 and SIRT1 negatively regulate canonical NF-κB activation. PAMPs and DAMPs, released through plasma membrane rupture caused by activation of NINJ1 or GSDMD pores, act as priming signals activating NF-κB pathway.

II) (Figure 4). In most cell types, including macrophages, minimal levels of NLRP3 were observed before inflammasome activation, and pro-IL-1β was not constitutively expressed (He Y. et al., 2016). Signal I upregulated the transcription of NLRP3 and pro-IL-1 (Garlanda et al., 2013; McKee and Coll, 2020). NLRP3 is regulated at the transcriptional level, by TLR and cytokine stimulation through activating the NF-κB pathway (Bauernfeind et al., 2009). It has been reported that NF-κB regulates NLRP3 transcription by binding directly to the NLRP3 promoter region (Qiao et al., 2012). Recent research has added Sphingosine 1-phosphate (S1P)/S1P Receptor (S1PR) signaling as an additional inducer for NLRP3 priming (Hou L. et al., 2020). While the precise mechanism behind S1P/S1PR signaling mediated NLRP3 inflammasome priming remains unclear, S1PR has been shown to activate the NF-κB pathway under acute pancreatitis conditions (Yang et al., 2022).

Several other factors regulate NLRP3 activation through modulating the NF-κB pathway. Leucine rich repeat protein ribonuclease inhibitor (RNH1) plays a role in attenuating NLRP3 inflammasome activation and is involved in reducing the priming signal. RNH1 knockout cells exhibited reduced levels of IκBα and increased levels of phospho-IκBα, indicating enhanced NF-κB activation (Bombaci et al., 2022). Inhibition of bromodomain-containing protein 4 (BRD4), which reduces NF-κB signaling through the suppression of IκBα phosphorylation and degradation, results in the upregulation of NLRP3 at the transcriptional level by enhancing the activity of the NLRP3 promoter (Tan et al., 2020). NEK7 has been identified as a mediator of increased expression of Caspase-1, NLRP3, and GSDMD in inflammatory bowel disease (IBD). In NEK7 knockdown intestinal epithelial cells, ATP/LPS-induced activation of the NLRP3 inflammasome was abolished. NEK7 itself is regulated by the NF-κB signaling pathway, with p65 promoting the transcription of NEK7 through binding to its corresponding binding site within the NEK7 promoter, while p65 inhibition blocks this effect (Chen X. et al., 2019).

FAS-associated death domain protein (FADD) and Caspase-8 were found to contribute to NLRP3 inflammasome priming (Lemmers et al., 2007). Caspase-8 was recruited to the complex containing IKKαβ in response to TLR4 stimulation (Lemmers et al., 2007), This interaction is pivotal for the initiation of NF-κB signaling. Macrophages derived from mice deficient in Caspase-8 exhibited reduced pro-IL-β and TNF levels upon priming and decreased NLRP3 activation (Allam et al., 2014). FADD has been

identified as an upstream regulator of Caspase-8, as supported by the observation that FADD-depleted macrophages exhibit significantly reduced processing of mature Caspase-8 when subjected to canonical NLRP3 inflammasome stimuli. Accordingly, FADD deficiency impaired NLRP3 activation by LPS or *C. rodential* infection (Gurung et al., 2014). Both FADD and Caspase-8 were required for the transcriptional upregulation of NLRP3 and pro-IL-1β in an NF-κB dependent manner. Moreover, deletion of both Caspase-8 and NEMO, the NF-κB essential modulator, resulted in the transcriptional downregulation of NLRP3, TNF-α and IL-1β expression after LPS treatment in hepatocytes (Boaru et al., 2015).

The role of IKKβ in inflammasome activation is controversial. Firstly, Nanda and co-workers have reported a pivotal role for IKKβ in the transcriptional upregulation of inflammasome components (Nanda et al., 2021). Inhibition of IKKβ resulted in decreased inflammasome activation, which is consistent with other studies (Bauernfeind et al., 2009; Boaru et al., 2015; Unterreiner et al., 2021; Schroder and Tschopp, 2010). Intriguingly, their research also unveiled the involvement of IKKβ in the assembly of the NLRP3 inflammasome through recruiting the NLRP3 inflammasome to the trans-Golgi network, where the assembly occurs. Furthermore, IKKβ directly binds to NLRP3, facilitating NLRP3 binding to phosphatidylinositol-4-phosphate (PI4P) on the trans-Golgi network, thereby promoting oligomerization and inflammasome assembly (Asare et al., 2022; Schmacke et al., 2022). Contrary to the observations mentioned above, Greten et al. reported that inhibition of IKKβ, either pharmacologically or genetically, enhanced Caspase-1 dependent IL-1β production in macrophages and related inflammation upon LPS challenge (Greten et al., 2007). Despite a decrease in pro-IL-1β mRNA synthesis under these conditions, efficient pro-IL-1β processing by casaspe-1 leads to even higher IL-1β secretion. It is speculated that during LPS challenge, NF-κB contributed to the upregulation of transcriptions of several genes encoding inhibitors of Caspase-1 activity, thus reducing IL-1β processing. The use of prolonged LPS treatment alone in the latter study, in contrast to the combined use of LPS and NLRP3 stimuli to rapidly activate the NLRP3 inflammasome, might explain the contradictory observation mentioned above.

Additionally, inhibitors targeting TBK1/IKKε have been found to amplify NLRP3 inflammasome responses, including IL-1β and IL-18 secretion, Caspase-1 cleavage, and ASC speck formation. Interestingly, the inhibition of TBK1/IKKε on NLRP3 inflammasome responses does not seem to rely on transcriptional mechanisms but rather through posttranslational regulation, mediated by the phosphorylation of the serine 3 (S5 in humans) on NLRP3 (Fischer et al., 2021). Conversely, a more recent study highlightes an alternative role for TBK1, demonstrating that TBK1 activation enhances NF-κB signling, as evidenced by increased phosphorylation of NF-κB p65. This activation is associated with elevated protein levels of key NLRP3 inflammasome components (NLRP3, ASC, and caspase-1) and increased production of cleaved IL-1β in microglia (Liao et al., 2024).

Moreover, previous research has demonstrated that IKK/NF-κB pathway plays a role in promoting autophagy by upregulating the expression of the autophagy receptor p62, which enhanced the clearance of damaged mitochondria through mitophagy via a Parkin-ubiquitin-dependent mechanism (Zhong et al., 2016). Deletion of p62 specifically in myeloid cells lead to the abnormal accumulation of damaged mitochondria and excessive production of IL-1β, resulting in increased sensitivity to endotoxin-induced shock. A truncating variant of p50 ($NFKB1^{R157*/R157*}$) has been identified in patients with necrotizing fasciitis or severe soft tissue inflammations (Nurmi et al., 2024). Autophagy was impaired in patients' cells, causing increased release of mtROS and mtDNA from damaged mitochondria, which enhances NLRP3 inflammasome activation. These findings collectively suggest that while NF-κB may mediate the priming signal of NLRP3 inflammasome activation, the induction of mitophagy or autophage by NF-κB may function as an autoregulatory mechanism to restrain the pro-inflammatory function.

Recent studies have increasingly highlighted the activation of the NF-κB/NLRP3 pathway in various disease models. Molecules and chemicals that modulate this pathway are being investigated for their therapeutic potential (Li Y. et al., 2024; Xiong et al., 2025; Zhao P. et al., 2024; Hao et al., 2024; Alad et al., 2024; Wei et al., 2024). One notable study examined the role of acetyl-CoA synthetase 2 (ACSS2) in the pathogenesis of acute kidney injury (AKI). Mice deficient in ACSS2 showed reduced NLRP3 inflammasome activation in renal tubular epithelial cells. These effects are regulated by the transcription factor KLF5, which mediates NF-κB activation (Lu et al., 2024). In cardiovascular diseases, the NF-κB/NLRP3 pathway is frequently implicated, especially upon activation by oxidative stress or ROS (Xu Z. et al., 2024; Antar et al., 2024). However, the detailed mechanisms remain poorly understood. In a cadmium (Cd) induced chronic kidney injury model, ROS was found to promote NLRP3 inflammasome activation by inhibiting SIRT1 expression and deacetylase activity. This led to decreased SIRT1–p65 interactions, increased acetylated p65 levels, and subsequent NF-κB activation (Dong et al., 2024a). A similar regulatory role of SIRT1 has been observed in shortwave blue light (SWBL)-induced cataracts. SWBL irradiation suppressed SIRT1 expression, promoted nuclear translocation of NF-κB and activation of the NLRP3 inflammasome, leading to lens epithelial cells pyroptosis and cataract formation (Ji et al., 2024). Furthermore, under hypoxic conditions, NF-κB signaling is regulated by HIF-1α, which acts as a positive regulator of NLRP3 inflammasome actuvation and ASC oligomerization in human dental pulp fibroblasts (Wang D. et al., 2024).

4.2 NLRC4

Much less is known about the role of NF-κB in the activation of the NLRC4 inflammasome. In intestinal epithelial cells, the activation of the NLRC4 inflammasome and subsequent pyroptosis induced by flagellin from the gram-positive bacterium *Clostridioides difficile* is mediated by the NF-κB pathway (Chebly et al., 2022; Keestra-Gounder and Nagao, 2023). Unlike in macrophages, inhibition of IKKα in intestinal epithelial cells leads to decreased expression of pro-casapase-1 and interleukin genes, suggesting a role of NF-κB in NLRC4 activation in this context (Chebly et al., 2022). Further evidence supporting a role of the NF-κB pathway in NLRC4 inflammasome activation is provided by findings that TLR4 inhibition in HK-2 cells (an

immortalized proximal tubule epithelial cell line) reduced NLRC4 inflammasome activation, as indicated by decreased protein levels of NLRC4, Caspase-1, ASC, and IL-1β (Dong et al., 2024b). Moreover, NF-κB signaling has been demonstrated to negatively regulate NLRC4-induced cell death. Pretreatment of macrophages with NF-κB activators blocks the NLRC4/Caspase-8-dependent cell death, likely through the initiation of transcriptional anti-apoptotic responses (Lee et al., 2018). *Anaplasma Phagocytophilum* has been reported to activate the NLRC4 inflammasome in macrophages, mediated by RIPK2 through activating NF-κB signaling upon infection, which promoted COX2 expression. COX2 contributed to the production of PGE2, which activated the NLRC4 inflammasome. (Wang et al., 2016). However, we found the evidence provided by the authors on the involvement of NLRC4 activation is not convincing. Experiments using cells deficient in NLRC4 should be included as controls.

4.3 AIM2

A few studies reported a role of the NF-κB pathway in regulating the AIM2 inflammasome activity, however, the exact mechanism was not clearly defined. A correlation, rather thatn causation, was normally reported. In human papilloma virus (HPV)-infected cervical cancer cells, Sirtuin 1 (SIRT1) enabled HPV-infected cervical cancer cells to continue growing by nullifying AIM2 inflammasome-mediated immunity. Mechanistically, SIRT1 repressed the NF-κB-driven transcription of the AIM2 gene by destabilizing the RELB mRNA (So et al., 2018). In an LPS induced acute lung injury model, HMGB1 functioned through the TLR2/TLR4 dependent NF-κB signaling pathways to regulate AIM2 inflammasome activation (Wang J. et al., 2020). The mRNA levels of AIM2, ASC and Caspase-1 are upregulated upon administration of recombinant HMGB1. Additionally, ozanimod, a sphingosine 1-phosphate (S1P) receptor modulator, has been shown to suppress intracerebral hemorrhage (ICH) and neuroinflammation by inhibiting the SIRT3/NF-κB/AIM2 pathway. This inhibition is evidenced by the downregulation of AIM2 expression level, less cleaved Caspase-1, and reduced levels of NF-κB signaling pathways, as indicated by decreased p65 levels (Li et al., 2023). Similarly, Nicorandil, an ATP-sensitive potassium channel opener, was reported to protect against neuroinflammation in ischemic stroke by suppressing the NF-κB/AIM2/GSDMD pathway (Zhao C. et al., 2024). Treatment with channel moculators was found to affect inflammatory cytokine secretion and pyroptosis-related protein expression, including AIM2, while at the same time lead to changes of the level of p-NF-κB p65, NF-κB p65, and p-IκBα. But a direct regulation of NF-kB on AIM2 is lacking. Moreover, Pseudorabies virus (PRV) infection enhances mRNA levels and protein expression of pro-IL-1β by targeting the TLR-NF-κB axis. The AIM2 inflammasome, activated by PRV genomic DNA, is essential for mature IL-1β secretion both *in vivo* and *in vitro*. AIM2-deficient mice displayed heightened susceptibility to PRV infection, indicating a critical role of AIM2-mediated inflammatory responses in host defense against PRV infection. Notably, multiple TLR receptors (including TLR2,3,4 and 5), participate in pro-IL-1β upregulation, all capable of activating NF-κB upon PRV infection (Zhou et al., 2023). While a direct role of NF-κB on AIM2 was not reported, the two pathways are clearly integrated function collaboratively to fend off virus infection.

5 Regulation of pyroptosis through NF-κB

Many studies have highlighted the connection between NF-κB signaling and pyroptosis in the pathogenesis of various diseases, including IBD, diabetic kidney disease (DKD), osteoarthritis (OA), myocardial infarction, rheumatoid arthritis, and neurodegenerative diseases (Yu H. et al., 2021; Yang et al., 2021; Xu et al., 2020; Lei et al., 2018; Erdem et al., 2024), making NF-κB inhibitors potential therapeutic agents for relevant diseases. Recent research has shed light on mechanisms by which NF-κB signaling regulates pyroptosis in different cell types/context.

The role of NF-κB in tumorigenesis involves both inhibition and promotion of gasdermin-mediated pyroptosis. On one hand, NF-κB activation may facilitate pyroptosis and demonstrate anti-tumor effects. For instance, increased NF-κB expression, induced by metformin-triggered AMPK/SIRT1 signaling, activated Bax and promoted cytochrome c release, subsequently initiated Caspase-3 activation and GSDME cleavage, resulting in pyroptosis in various cancer cells (Zheng et al., 2020). Additionally, polyphyllin VI (PPVI), a primary saponin derived from traditional Chinese medicine, exhibited potent anti-tumor effects through the stimulation of cytosolic ROS production, which activated the NF-κB/NLRP3/GSDMD pathway and led to pyroptosis in non-small cell lung cancer (NSCLC) (Teng et al., 2020). GALNT6 knockdown inhibited pancreatic ductal adenocarcinoma (PDAC) cell growth through promoting NF-κB phosphorylation and subsequently stimulating the expression of NLRP3, GSDMD and GSDME to augment pyroptosis (Ding et al., 2023). On the other hand, inhibition of NF-κB signaling has also been found to promote tumor cell pyroptosis and impede tumor development. For instance, the piperlongumine analogue L50377 suppressed cell growth and promoted pyroptosis, through ROS-mediated NF-κB inhibition in NSCLC (Li et al., 2019). Tanshinone II A also prevented NF-κB activation and enhanced the miR-145/Caspase-3/GSDMD pathway mediated pyroptosis in Hela cells, thereby repressing cervical cancer progression (Tong et al., 2020). Moreover, the tumor suppressor DRD2 restricts NF-κB signaling, triggering GSDME mediated pyroptosis and exerting anti-tumor effects in breast cancer (Tan et al., 2021). The seemingly controversial conclusions could reflect the complexity of NF-κB signaling in different contexts.

In adipose tissue from LPS treated or obese mice, the transcription of multiple inflammasome components, including GSDMD, was significantly enhanced. The GSDMD promoter contains two NF-κB binding sites, and the transcription of GSDMD was blocked when either one of the two binding sites was mutated. Inhibition of NF-κB using melatonin was found to inhibit inflammasome activation and GSDMD induced pyroptosis (Liu Z. et al., 2017). Interferon regulatory factor 1 (IRF1) has been found to play a compensatory role with IRF2 in regulating GSDMD gene expression and pyroptosis in EA. hy926 endothelial cells

(Kayagaki et al., 2019). Recent findings further elucidate that IRF1 was crucial in upregulating the transcription of GSDMD through binding at the −526/-515 site in GSDMD promotor. IRF1 is transcriptionally regulated by the p52/RelB heterodimer, which is activated by the non-canonical NF-κB signaling pathways mediated by NIK. Downregulation of GSDMD expression was observed in IRF1-mutant or NIK siRNA transfected endothelial cells. Silencing NIK or knockdown of p100/p52 impeded pyroptosis mediated by NLRP3 signals, underscoring the significance of the noncanonical NF-κB signaling in NLRP3 inflammasome-mediated pyroptosis in endothelial cells (Fan X. et al., 2023). Overall, the regulation of GSDMD expression through NF-κB signaling appears to occur at the transcription level in specific cells, likely attributable to the low basal levels of GSDMD in those cells.

In macrophages, TLR-mediated priming signals redirect cell death from apoptosis towards pyroptosis during wild-type *Yersinia pseudotuberculosis* infection, and this process depends upon an intact *Yesinia* T3SS (Bergsbaken and Cookson, 2007). Bergsbaken and Cookson found that activation of TLR-mediated signaling prior to infection simultaneously rendered macrophages susceptible to killing by YopJ deficient *Yersinia* and induced Caspase-1 dependent pyroptosis in macrophages. Inhibition of the TLR/NF-κB pathway has been proven to suppress pyroptosis (Bergsbaken and Cookson, 2007). Wang et al. showed that TLR4/NF-κB signaling induces GSDMD-mediated pyroptosis in tubular epithelial cells and contributed to the progression of diabetic kidney disease. *In vivo*, treatment of db/db mice (mice under diabetic conditions) with TLR4 inhibitor decreased the cleavage of Caspase-1 and GSDMD in renal cortex tissue, protected tubular cell injury by suppressing pyroptosis (Wang et al., 2019). *In vitro*, TLR4 or NF-κB inhibition led to a significant decrease of phosphorylated-p65, Caspase-1 p20 and GSDMD-NT in high glucose stimulated HK-2 cells, indicating that NF-κB was the downstream signal molecule of TLR4 under high glucose conditions and the activation of pyroptosis in HK-2 cells was markedly inhibited by TLR4/NF-κB signaling inhibition.

The inflammatory cytokines, like IL-1β, IL-33 and TNFα also play a role in regulating pyroptosis through NF-κB signaling pathway. The biological effects of IL-1β are mediated through IL-1R. In nucleus pulposus cells, IL-1β treatment induced NLRP3 inflammasome priming and activation, and formed a positive feedback loop through NLRP3 inflammasome activation *via* the IL-1β/IL-1R/NF-κB pathway (Chen et al., 2020). Similarly, Cai et al. found that cadmium induced NLRP3 inflammasome-dependent cerebral pyroptosis through the TRAF6/NF-κB pathway. And this NLRP3 inflammasome-dependent cerebral pyroptosis contributes to aggravating the inflammatory response through activating the IL-1β/IL-1R/IκBα/NF-κB/NLRP3 inflammasome feedback loop in the brain of swine (Cai et al., 2021). In alveolar macrophages, LPS-TLR4 signaling not only induced IL-1β maturation and release through NLRP3 activation, but also upregulated IL-1R1 expression on alveolar macrophage surface through MyD88 and NF-κB dependent pathway. At the same time, IL-1β was able to increase ASC speck formation and Caspase-1 activation in the alveolar macrophage in WT and Nlrp3$^{-/-}$ mice, but not in the alveolar macrophage from IL-1R1$^{-/-}$ mice. This indicates an important role of IL-1β/IL-1R1 signaling in mediating alveolar macrophage pyroptosis (He X. et al., 2016). IL-1β released from pyroptosis could lead to further activation of inflammasomes in neighboring cells, thereby promoting additional pyroptosis (Zhou et al., 2021). During pulmonary ischemia-reperfusion injury (IRI), monocytes trigger pyroptosis in human pulmonary microvascular endothelial cells (HPMECs) *via* IL- 1β secretion (Zhou et al., 2021). *In vivo*, monocyte depletion attenuated IRI-induced pulmonary edema, cytokine production and pyroptosis activation. *In vitro*, activation of monocytes (U937 cells) was detected under hypoxia-reoxygenation (H/R) conditions, as indicated by the increased levels of inflammatory factors (IL-1β, IL-6, IL-8, IL-18, and TNF-α) and NLRP3 protein. In a co-culture experiment of U937 cells and HPMECs In under H/R conditions, HPMEC pyroptosis was reduced when NLRP3 or IL-1β was inhibited in monocytes, or knockdown of IL-1R, and inhibition of the NF-κB pathway in HPMECs, suggesting that the IL-1R/NF-κB/NLRP3 pathway mediated HPMEC pyroptosis.

Other members of the IL-1 family, most prominently IL-1α and IL-33, are constitutively produced by non-immune cells, frequently by barrier cells such as keratinocytes or endothelial cells (Martin, 2016). The precursor forms of IL-1α and IL-33 are already biologically active if released into the tissue. A recent research revealed that IL-33 can induce macrophage pyroptosis in septic mice via the NF-κB/p38 MAPK signaling pathway (Ke and Cai, 2021). In the sepsis model of IL-33$^{-/-}$ transgenic mice, there was significant reduction of the NF-κB/p38 MAPK signaling, mitigation of macrophage pyroptosis, and a reduction in the mortality rate of septic mice. IL-33 is considered crucial for human mucosal epithelial allergic responses. A recent study characterized the effects of Dermatophagoides pteronyssinus 1 (DerP1), one of the most common allergens from mites that causes ocular allergies, in mice and human corneal epithelial cells (HCECs). *In vivo*, DerP1 triggered the activation of the NLRP3 inflammasome, release of inflammatory cytokines and IL-33, in mouse corneas. *In vitro*, pyroptotic bodies were found in the HCECs after sensitization with DerP1. Deficiency of IL-33 attenuated DerP1 induce pyroptosis in HCECs, indicating that the IL-33 feedback signaling contributed to pyroptosis (Ran et al., 2023).

Recent investigations have uncovered the involvement of TNF/TNFR signaling in the regulation of pyroptotic cell death, which occurs in the absence of X-linked inhibitor of apoptosis (XIAP). XIAP is a member of the IAP (inhibitor of apoptosis proteins) family, initially identified for its ability to inhibit caspases that execute apoptosis. XIAP regulates cell death triggered by various stimuli and mediates inflammatory signaling (Witt et al., 2023; Knop et al., 2019; Shemin et al., 1989). It has been proved that XIAP is a strong stimulator of NF-κB (Hofer-Warbinek et al., 2000). In the absence of XIAP, pathogen ligands or TNFα stimulated the extrinsic apoptotic Caspase-8 activation in a TNF/TNFR signaling dependent manner in dendritic cells, macrophages and neutrophils (Lawlor et al., 2017; Lawlor et al., 2015; Vince et al., 2012; Yabal et al., 2014; Wicki et al., 2016). Activated Caspase-8 can process precursor IL-1β directly in addition to inducing NLRP3 inflammasome assembly, leading to Caspase-1 activation and subsequent processing of relevant substrates. Recently, Hughes et al. reported that two human patients with XIAP deficiency suffered from inflammatory bowel disease, exhibiting heightened Caspase-8-

activation and increased IL-1β and GSDMD processing in peripheral blood mononuclear cells (PBMCs) and inflamed colonic mucosae (Hughes et al., 2023). Using a XIAP deficient model, they demonstrated that extrinsic Caspase-8 activation led to the processing of multiple downstream apoptotic and pyroptotic effectors, which act redundantly to cause both excess cell death and inflammatory IL-1β release. Moreover, upon anti-TNF therapy with immune suppression for the patient, the levels of cleaved Caspase-8 and GSDMD detected in patient were substantially reduced (Hughes et al., 2023). Also in the absence of XIAP, TNFR2-specific activation (triggered by TNC-sc (mu)TNF80) led to a NF-κB driven transcriptional profile similar as TNFR1 activation with the exception of upregulation of NLRP3 and Caspase-11. Activation and upregulation of the canonical inflammasome upon loss of XIAP were mediated by RIPK1 kinase activity and ROS production (Knop et al., 2019).

Additionally, NF-κB signaling plays a key role in regulating noncanonical pyroptosis. The noncanonical pyroptosis pathway involves the direct activation of Caspase-11 by cytosolic LPS. Like NLRP3, the activation of Caspase-11 also requires an initial increase in the level of its inactive precursor, pro-Caspase-11. The mechanisms controlling the transcriptional priming for the Caspase-11 display diversity (Agnew et al., 2021; Downs et al., 2020). Caspase-11 expression is initially undetectable in resting macrophages but can be transcriptionally regulated *via* NF-κB pathways. Induction of pro-Caspase-11 expression by LPS or IFN-γ occurred through TLR4/TRIF signaling and subsequent binding of NF-κB and STAT to the Caspase-11 promoter (Schauvliege et al., 2002). Consistent with this conclusion, a reduction in pro-Caspase-11 levels has been observed when the NF-κB signaling pathway is inhibited through various methods in LPS-treated cells (Kobori et al., 2004; Hu et al., 2024; Appleton et al., 1987). Therefore, we speculate that various other molecules that are capable of activating the NF-κB signaling pathway may also upregulate Caspase-11 expression.

The crosstalk between the NF-κB pathway and PANoptosis (a combined mechanism of pyroptosis, apoptosis, and necroptosis) through the cGAS-STING pathway in the context of lung inflammation and acute respiratory distress syndrome (ARDS) has been reported (Messaoud-Nacer et al., 2022). Activation of STING by diABZI, a synthetic agonist, triggers NF-κB signaling and TBK1/IRF3 phosphorylation, leading to the production of pro-inflammatory cytokines (TNF-α, IL-6) and type I interferons. This initiates cell death through PANoptosis mechanisms, including necroptosis *via* MLKL phosphorylation, apoptosis through Caspase-3 activation, and pyroptosis mediated by Gasdermin D cleavage following inflammasome activation (NLRP3, AIM2). Cell death releases self-dsDNA, which is sensed by cGAS to produce 2′3′-cGAMP, resulting in STING hyperactivation and an amplified inflammatory response. This feedback loop, marked by increased DNA sensor expression (IFI204, DDX41) and inflammasome activity, sustains NF-κB-driven cytokine production and enhances PANoptosis. The interplay between STING signaling and PANoptosis underscores the potent inflammatory potential of this pathway, with implications for therapeutic strategies targeting STING in infection or cancer that must balance immune activation with the risk of excessive inflammation and ARDS.

6 Inflammasome modulates inflammation via NF-κB

NLPR3 activation has been shown to trigger NF-κB activation (Cai et al., 2024; Kinoshita et al., 2015b). Kinoshita and colleagues observed reduced NF-κB activation and cytokine production in response to *Staphylococcus aureus* infection in NLRP3 knocking down THP-1 cells. Notably, this effect is not affected by a Caspase-1 inhibitor. In addition, the NF-κB activation observed is not mediated through an autocrine mechanism in response to newly synthesized IL-1β. Although the precise mechanism by which NLRP3 regulates NF-κB activation is not elucidated, these findings highlight a role of NLRP3 in inducing inflammation in the innate immune system (Kinoshita et al., 2015a).

NLRC4, much like NLRP3, plays a crucial role in regulating various innate immune pathways, including the NF-κB pathway. NLRC4 was found to cooperate with ASC to activate NF-κB (Masumoto et al., 2003). Activation of NF-κB by cytosolic flagellin is evidenced by events including p65 phosphorylation, nuclear translocation and IκB-α degradation. Interestingly, Caspase-1 is shown dispensable for NF-κB activation in this condition, but crucial for robust NOS2 expression. This is achieved through cleavage of the chromatin regulator PARP1 and enhanced chromatin accessibility of the NF-κB binding sites on the Nos2 promoter (Buzzo et al., 2017).

Elevated glucose levels have been shown to upregulate NLRC4 expression and induces its phosphorylation on Ser533, both in diabetic mice and macrophages (Zhang et al., 2019). Furthermore, high glucose levels lead to increased NLRC4-dependent NF-κB activation, resulting in the induction of a senescence-associated secretory phenotype (Zhang et al., 2019; Chien et al., 2011; Salminen et al., 2012). In the context of septic shock, silencing NLRC4 has been found to decrease levels of TNF-α and IL-6, two key pro-inflammatory cytokines mediated by the NF-κB pathway (Wang SS. et al., 2021). However, the precise mechanisms behind NLRC4-dependent NF-κB activation remains unclear. Further investigation is needed to determine whether the release of IL-1β following NLRC4 inflammasome activation initiates a feedback loop that activates the NF-κB pathway (Bent et al., 2018; Dey et al., 2014).

The AIM2 inflammasome plays a protective role by reducing pro-inflammatory response in cardiomyocytes through regulating NF-κB activation. AIM2-deficient cells exhibit increased NF-κB activation, as evidenced by increased IκBα degradation, p65 phosphorylation and acetylation, following stimulation with IFN-γ and LPS (Furrer et al., 2016). Mechanistically, AIM2 indirectly restricts NF-κB p65-dependent pro-inflammatory cytokine transcription, primarily by blocking STAT1 phosphorylation. The inhibitory effect of AIM2 is attenuated in the absence of STAT1.

Many inflammasomes, including NLRP3, NLRC4, and AIM2 require the adaptor protein ASC for inflammasome assembly and activation. However, the role of ASC in NF-κB activity appears more complex. High doses of ASC transfection inhibit RIP2 and Caspase-1 induced NF-κB activity (Sarkar et al., 2006), while other studies suggest that ASC mediates NF-κB activation, which requires the catalytic activity of Caspase-8

(Hasegawa et al., 2005). This dual role of ASC in regulating NF-κB signaling may reflect a balance between the interaction of ASC with its many binding/functional partners.

7 Conclusion

The ever-expanding collection of studies has significantly advanced our understanding of pyroptosis regulation. Among the myriad of pathways influencing pyroptosis, the intricate interplay between pyroptosis and NF-κB signaling stands out as a critical axis in orchestrating inflammatory responses and governing cell death mechanisms. While much is known about NF-κB's role in driving the production of pro-inflammatory cytokines and inflammasome components, questions persist regarding the context-dependent activation of specific NF-κB subunits and their downstream targets in pyroptosis. Additionally, how NF-κB signaling interacts with other cellular pathways to fine-tune pyroptotic responses under varying physiological and pathological conditions remains incompletely elucidated.

Understanding these regulatory mechanisms holds profound implications for the development of targeted therapeutic strategies. Dysregulated pyroptosis and NF-κB activation contribute to the progression of numerous inflammatory and autoimmune disorders, as well as infectious and malignant diseases. Thus, a better understanding of NF-κB's multifaceted role in pyroptosis could unlock new avenues for mitigating excessive inflammatory responses, controlling tissue damage, and improving outcomes in inflammatory pathologies.

Future research should prioritize identifying the specific NF-κB components involved in pyroptosis regulation, delineating the spatiotemporal dynamics of NF-κB activation in different cellular contexts, and unraveling the feedback mechanisms that balance pyroptosis induction and resolution. Furthermore, integrating systems biology approaches with *in vivo* models of disease may offer holistic insights into the interplay between NF-κB signaling and pyroptosis. By bridging these knowledge gaps, we can advance not only our fundamental understanding of these pathways but also their translational potential in the development of innovative anti-inflammatory therapies.

Author contributions

LY: Writing–original draft, Writing–review and editing. YaZ: Writing–original draft, Writing–review and editing. ZC: Writing–original draft, Writing–review and editing. YuZ: Writing–original draft, Writing–review and editing. ZL: Conceptualization, Funding acquisition, Resources, Writing–original draft, Writing–review and editing. YW: Conceptualization, Funding acquisition, Resources, Supervision, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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