Gene Expression **2026** vol. 25(2) | e00086
DOI: 10.14218/GE.2025.00086

Review Article

NF-κB Signaling Pathway: A Central Hub in the Pathogenesis and Therapeutic Targeting of Immunological Diseases

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Received: November 02, 2025 | **Revised:** March 28, 2026 | **Accepted:** April 02, 2026 | **Published online:** April 20, 2026

Abstract

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) family regulates fundamental processes in both innate and adaptive immunity. Aberrant NF-κB activation, whether through canonical or non-canonical signaling pathways, contributes to chronic inflammation, autoimmunity, allergy, and primary immunodeficiency/autoinflammatory syndromes, while also influencing host defense and tissue repair mechanisms. The present review aims to synthesize molecular architecture, upstream triggers, ubiquitin-centered relay systems, and the dynamic regulation of NF-κB activity. The major findings on the NF-κB signaling pathway encompass its dual molecular mechanisms (canonical and non-canonical), its central roles in immune and inflammatory responses, cell survival, and development, as well as its complex regulatory networks. We interpret NF-κB as a master integrator of diverse signals, essential for both acute and long-term physiological processes. Dysregulation of NF-κB underlies many diseases, and while it is a promising therapeutic target, its ubiquitous functions demand precise modulation to avoid adverse effects. In conclusion, the proper function of the NF-κB signaling pathway is essential for maintaining cellular homeostasis and immune defense; its dysregulation is linked to chronic inflammatory diseases, autoimmune disorders, and cancer, which underscores the pathway's significance as a therapeutic target. Although it elucidates molecular processes and treatment options, experimental validation of emerging therapeutic concepts such as ubiquitin code editing and spatial immunology remains limited.

Introduction

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a master transcription factor orchestrating the expression of a diverse range of genes implicated in both the initiation and resolution of inflammation. Upon stimulation by factors such as cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β), microbial products (LPS), or cellular stress, NF-κB translocates to the nucleus and activates the transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, and enzymes including iNOS and COX-2. This leads to the recruitment and activation of immune cells at infection or damage sites, facilitating pathogen elimination and tissue restoration. Nonetheless, prolonged stimulation leads to chronic inflammation, which contributes to conditions such as rheumatoid arthritis, inflammatory bowel disease (IBD), and atherosclerosis.[1,2]

NF-κB enhances cell viability by increasing the expression of anti-apoptotic genes (e.g., Bcl-2, Bcl-XL, c-IAP1/2, c-FLIP) and genes implicated in cell cycle progression (e.g., Cyclin D1). This is crucial for immune cell expansion during immune responses and for protecting cells from programmed cell death during tissue injury. Aberrant activation, however, can support the survival and

Keywords: NF-κB; Ubiquitin; Canonical pathway; Noncanonical pathway; Autoimmunity; Inflammation; Therapeutic target.

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How to cite this article: Sharma Y, Shrivastava A, Gupta JK, Mishra R, Dwivedi A, Chaturvedi P, *et al*. NF-κB Signaling Pathway: A Central Hub in the Pathogenesis and Therapeutic Targeting of Immunological Diseases. *Gene Expr* 2026;25(2):e00086. doi: 10.14218/GE.2025.00086.

proliferation of malignant cells, contributing to cancer development and therapy resistance.[2]

NF-κB is indispensable for the development, differentiation, and function of both innate and adaptive immune cells. It governs hematopoiesis, lymphoid organogenesis, T and B cell activation, and the maturation of regulatory T cells, which are crucial for immunological tolerance. Defects in NF-κB signaling can result in immunodeficiency or autoimmunity, while hyperactivation can drive pathological immune activation and tissue damage.[3]

NF-κB is activated by triggers such as proinflammatory cytokines (TNF-α, IL-1β), pathogen-associated molecular patterns, antigen receptors, and cellular stress, which is known as the canonical or classical pathway of NF-κB activation. The activation of the IκB kinase (IKK) complex results in the phosphorylation and degradation of IκB proteins, therefore liberating NF-κB dimers (predominantly p65/p50) to migrate to the nucleus and initiate target gene transcription. Negative feedback via induction of IκBα and A20 restricts the length and intensity of NF-κB activation.[4] The another pathway, known as the noncanonical or alternative pathway, involves specific triggers such as TNF receptor superfamily members (e.g., CD40, BAFF-R). This involves the stabilization of NF-κB inducing kinase (NIK), which results in the activation of IKKα and the conversion of p100 to p52 and nuclear translocation of RelB/p52 dimers, regulating genes implicated in the development of lymphoid organs and immune cell differentiation.[5] However, some atypical pathways are also implicated in NF-κB activation, such as UV light and oxidative stress, and the process involves IKK-independent mechanisms, such as CK2-mediated phosphorylation or calpain-dependent IκB degradation.[6] The activity of NF-κB is also regulated by phosphorylation, ubiquitination, acetylation, and methylation, as well as crosstalk with other signaling pathways (e.g., PI3K/AKT, MAPK, JAK-STAT), providing multiple regulatory nodes and therapeutic targets. NF-κB dysregulation is involved in a wide range of disorders, each with distinct clinical features such as rheumatoid arthritis, IBD, multiple sclerosis, systemic lupus erythematosus (SLE), atherosclerosis, asthma/COPD, immunodeficiency (NEMO mutations), lymphoma (e.g., DLBCL), neurodegeneration (AD), etc.[7]

Here, it is worth mentioning certain therapeutic approaches targeting the NF-κB pathway, which are categorized as established as well as emerging strategies. Among established therapies, there are proteasome inhibitors like bortezomib, which are approved for multiple myeloma and mantle cell lymphoma. They work by inhibiting the proteasomal degradation of IκB, thus blocking NF-κB activation. It has demonstrated significant improvements in response rates and survival in hematological malignancies. Another approach is using monoclonal antibodies like anti-TNF agents (e.g., infliximab, adalimumab), which are widely used in rheumatoid arthritis, IBD, and psoriasis, indirectly inhibiting NF-κB by blocking upstream cytokines.[8]

Among emerging strategies, there are IKK inhibitors, which directly target the IKK complex to block NF-κB activation. Despite promising preclinical data, toxicity and lack of specificity have limited clinical translation. While small molecules and peptides target various points in the NF-κB pathway, such as nuclear translocation and DNA binding, most are currently in early-phase trials. Tyrosine kinase inhibitors, such as ibrutinib, target BTK upstream of NF-κB in B-cell malignancies. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are being explored to modulate NF-κB signaling with high specificity. Engineered immune cells and gene-editing approaches are being developed to modulate NF-κB activity for cancer immunotherapy and autoimmunity.[9]

A primary hurdle in the development of NF-κB-targeted treatments is attaining selective inhibition. NF-κB is a pivotal regulator of immunological responses and cellular survival, serving critical functions in both normal physiology and pathology. Systemic or global inhibition of NF-κB can lead to immunosuppression and toxicity, as it disrupts not only pathological but also protective and homeostatic functions of the immune system. NF-κB inhibitors are being combined with chemotherapy, immunotherapy, and targeted agents to enhance efficacy and overcome resistance. Determining which patients are most likely to benefit from NF-κB-targeted therapy is an active area of research.[10]

The core objective of this review is to investigate the mechanisms, biological functions, and regulatory processes of the NF-κB signaling pathway, with a focus on its canonical and non-canonical branches. This review seeks to elucidate how this pathway integrates diverse signals to regulate immune responses, inflammation, cell survival, and development, while also examining the consequences of its dysregulation in diseases such as cancer, autoimmune disorders, and chronic inflammatory conditions. By providing a comprehensive analysis, the review aims to highlight the pathway's significance as a therapeutic target and the challenges associated with its precise modulation.

Figure 1 illustrates the NF-κB signaling pathway, showing how cytokines, microbial products, and cellular stress activate NF-κB. Transcription triggers immune cell activation with both positive (immunity) and negative (chronic inflammation) consequences.

NF-κB family: Structure and DNA binding

The NF-κB family consists of five structurally similar transcription factors: RelA (p65), c-Rel, RelB, p50 (NF-κB1), and p52 (NF-κB2). All have a conserved Rel homology region that enables DNA binding, dimerization, nuclear localization, and interaction with inhibitory IκB proteins. Certain components (RelA, c-Rel, RelB) have a transactivation domain, which facilitates gene transcription activation, but p50 and p52 lack transactivation domains and may function as transcriptional repressors when forming homodimers.[11,12]

NF-κB proteins generate diverse homo- and heterodimers, allowing for combinatorial diversity in gene regulation. The predominant dimer is p50:RelA, which is central to inflammatory and immune responses.

NF-κB pathway: Structure, regulation, functions, and therapeutic targeting

Regulation by IκB proteins and cytoplasmic sequestration

Under resting conditions, NF-κB dimers are sequestered in the cytoplasm by IκB proteins (IκBα, IκBβ, IκBε). These inhibitors attach to the Rel homology region of NF-κB, obscuring its nuclear localization signal and obstructing nuclear entry and DNA binding. Classical IκBs (IκBα, IκBβ, IκBε) retain NF-κB in the cytoplasm. Atypical IκBs (BCL-3, IκBζ, IκBNS, IκBη) can localize in the nucleus and regulate NF-κB activity at the genomic level. This tight regulation prevents inappropriate or excessive NF-κB activation, which may result in chronic inflammation or cancer.[11,12]

Signal-dependent activation: IKK complex, phosphorylation, and ubiquitination

Pro-inflammatory cytokines (e.g., TNF-α, IL-1), microbial compounds, or stress initiate a signaling cascade. The IKK complex,

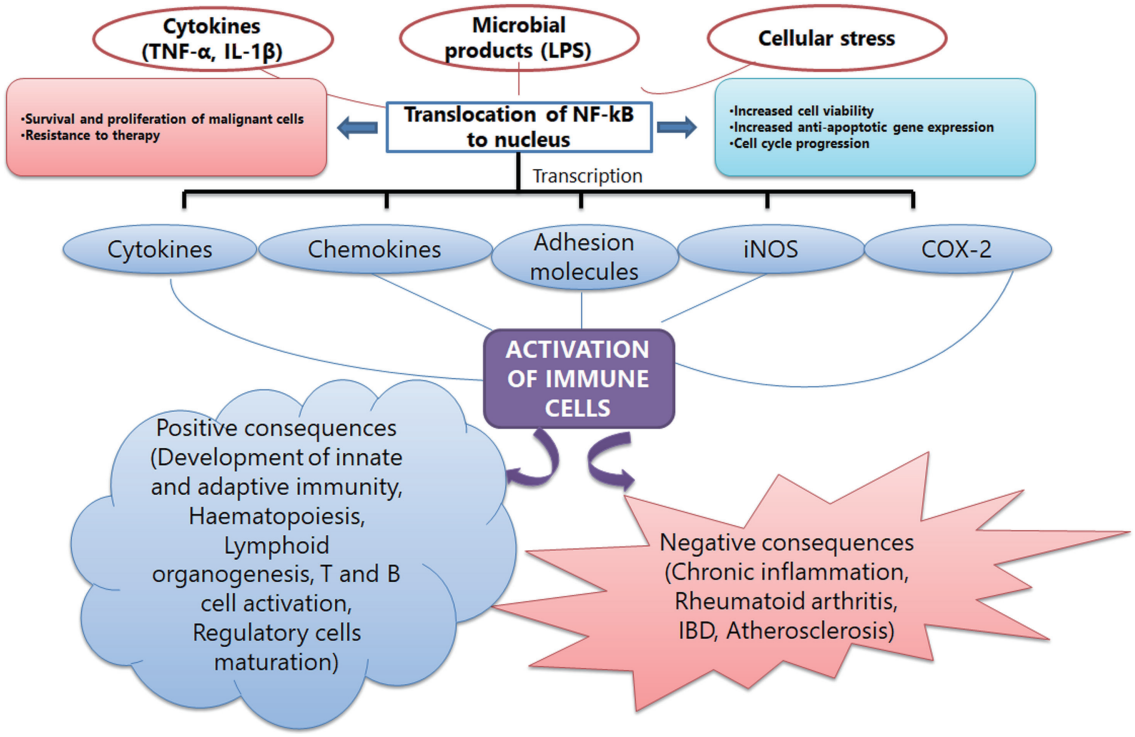

Fig. 1. NF-κB signaling pathway: Activation of immune cells and its consequences. COX-2, cyclooxygenase-2; IBD, inflammatory bowel disease; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharides; TNF-α, tumor necrosis factor-α.

consisting of IKKα, IKKβ, and NEMO (IKKγ), is activated by upstream kinases such as TAK1. IKKβ phosphorylates IκBα at serine residues (Ser32 and Ser36), establishing a recognition motif for ubiquitination. The phosphorylated IκB is identified by the $SCF^{\beta\text{-}TrCP}$ E3 ubiquitin ligase complex, which polyubiquitinates IκB, marking it for destruction by the 26S proteasome.[6,13] The breakdown of IκB protein reveals the nuclear localization signal of NF-κB, promoting its relocation to the nucleus.[11] This process is rapid and reversible, enabling cells to respond quickly to external stimuli.[14]

Nuclear translocation and gene regulation

Upon entering the nucleus, NF-κB interacts with particular κB sites inside the promoters and enhancers of target genes, recruiting coactivators and transcriptional machinery. This leads to the expression of a broad spectrum of genes implicated in inflammation (e.g., TNF-α, IL-1β, IL-6, COX-2), immune responses (e.g., cytokines, chemokines, adhesion molecules), cell survival and proliferation (e.g., Bcl-2, cyclin D1), anti-apoptotic proteins (e.g., IAPs), and cell cycle regulators. A negative feedback loop is formed as NF-κB stimulates the production of IκBα, which re-enters the nucleus, dislocates NF-κB from DNA, and translocates it to the cytoplasm, therefore concluding the reaction.[4]

NF-κB functions as a principal regulator of immunological and inflammatory responses, as well as cell survival and proliferation. The activity is rigorously regulated by IκB proteins and the IKK complex, ensuring rapid but transient responses to stimuli. Dysregulation of NF-κB is central to the pathogenesis of cancer, chronic inflammation, and autoimmune diseases. Therapeutic targeting of this pathway is a primary emphasis of contemporary research, with multiple strategies in development or clinical use, aiming to achieve effective disease control while minimizing adverse effects.[15] Figure 2 illustrates the NF-κB signaling pathway, showing TNF activation, ubiquitination processes, and regulatory proteins like OTULIN and A20. It highlights therapeutic targets, including anti-TNF, proteasome, BTK, and IKK/NIK/MALT1 inhibitors, to manage pathway-related diseases.

Canonical versus noncanonical pathways

Canonical pathway (classical): Activated by TNF-α, IL-1, TLRs, antigen receptors (TCR/B cell receptor (BCR)), and stressors. Signals converge on the trimeric IKK complex—IKKα, IKKβ, and the regulatory subunit NEMO/IKKγ—which lead to the phosphorylation of IκBα, targeting it for ubiquitin-proteasome degradation. Predominant transcriptional outputs are RelA:p50 or c-Rel:p50 dimers; responses are rapid and often oscillatory. NF-κB proteins are rapid-acting, primary transcription factors that modulate genes linked to immunological and inflammatory responses (e.g., chemokines, cytokines), cellular survival, and anti-apoptotic mechanisms (e.g., Bcl family, IAPs), cell proliferation (e.g., cyclins), stress responses, and development. In quiescent cells, NF-κB dimers are confined to the cytoplasm by IκB proteins, which obscure their nuclear localization signals. Following activation, IκBs undergo degradation, allowing NF-κB to translocate to the nucleus and commence gene transcription.[16] Diseases associated with this pathway are chronic inflammatory diseases (rheumatoid arthritis, IBD, COPD, asthma), autoimmune diseases (SLE, Sjögren's syndrome), cancer (colorectal, hepatocellular, lymphoid malignancies), atherosclerosis, neurodegenerative diseases, and genetic immunodeficiencies.[17]

Noncanonical pathway (alternative): Activated by a spe-

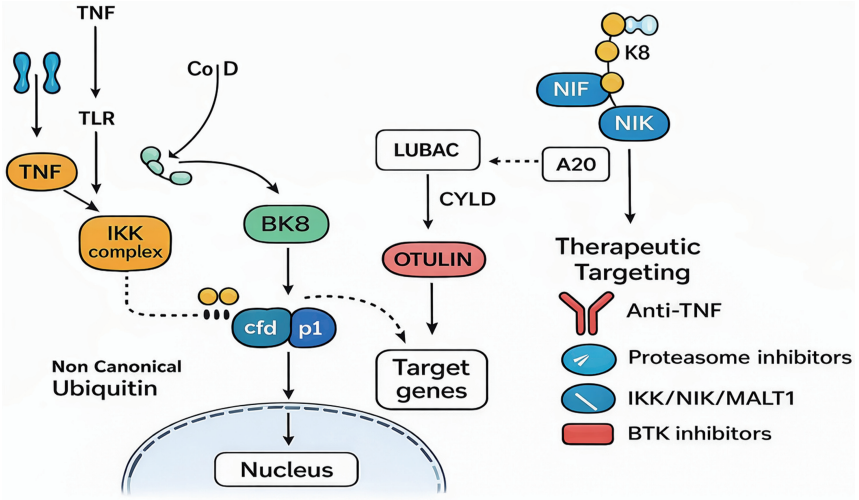

Fig. 2. NF-κB signaling pathway and therapeutic targets. A20, tumor necrosis factor alpha-induced protein; BTK, Bruton's tyrosine kinase; CYLD, cylindromatosis lysine 63 deubiquitinase; IKK, inhibitor of kappa B kinase; LUBAC, linear ubiquitin chain assembly complex; MALT1, mucosa-associated lymphoid tissue lymphoma translocation gene-1; NIK, NF-κB inducing kinase; OTULIN, ovarian tumor domain deubiquitinase with linear linkage specificity; TLR, Toll-like receptor; TNF, tumor necrosis factor.

cific subset of TNFR superfamily members (e.g., BAFF-R, CD40, LTβR). Physiologically restrained NIK accumulates upon TRAF2/3–cIAP1/2 complex inactivation, enabling IKKα homodimers to process p100→p52 and activate RelB:p52 dimers. Responses are slower, sustained, and critical for B cell maturation, lymphoid organogenesis, and immune tolerance. Diseases associated with this pathway are autoimmune diseases (SLE, rheumatoid arthritis, multiple sclerosis), chronic inflammatory diseases (IBD, liver diseases), lymphoid and hematological malignancies (lymphoma, multiple myeloma), autoinflammatory diseases, and metabolic disorders (hyperglycemia).[17] The main differences between canonical and noncanonical pathways are summarized in Table 1.

Ubiquitin-centric signal relays and negative control

The NF-κB signaling pathway is a central regulator for immunological and inflammatory responses, with its regulation heavily reliant on ubiquitin-mediated signaling relays. These relays involve the assembly and disassembly of specific ubiquitin chains, orchestrated by E3 ligases, deubiquitinases (DUBs), and regulatory proteins, including negative NLRs. Dysregulation at any layer can result in profound immune dysfunction, manifesting as combined immunodeficiency and autoinflammation.

K63-linked ubiquitin chains

K63-linked chains are established by linking the C-terminal glycine of one ubiquitin to lysine 63 of the subsequent ubiquitin. These chains adopt an open, extended conformation and do not direct proteins towards breakdown. Instead, they serve as dynamic scaffolds for the assembly of signaling complexes. K63 chains are rapidly assembled in response to receptor stimulation (e.g., TNFR, TLRs, IL-1R, TCR/BCR). They recruit and activate kinases such as TAK1 (via TAB2/3) and the IKK complex, resulting in the activation of NF-κB and MAPK signaling pathways.[18]

M1-linked (linear) ubiquitin chains

The C-terminal glycine of one ubiquitin links to the N-terminal methionine (M1) of another, resulting in a linear, head-to-tail structure of the M1-linked chains. M1 chains are essential for the canonical NF-κB pathway. They are particularly recognized by the NEMO (IKKγ) subunit of the IKK complex, promoting its oligomerization and activation. M1 chains can also induce phase

Table 1. Key differences between canonical and noncanonical pathways

Feature	Canonical NF-κB pathway	Noncanonical NF-κB pathway
Activation triggers	Broad (cytokines, TLRs, antigens, etc.)	Restricted (BAFFR, CD40, LTβR, RANK)
Key mediators	IKK complex (IKKα, IKKβ, NEMO/IKKγ)	NIK, IKKα
Inhibitor	IκBα (degraded)	p100 (processed to p52)
NF-κB dimers	p50/RelA, p50/c-Rel	p52/RelB
Response kinetics	Rapid, transient	Slow, sustained
Main functions	Inflammation, immunity, and cell survival	Lymphoid organogenesis, B cell function
Dysregulation	Chronic inflammation, cancer	Immunodeficiency, autoimmunity, lymphoma

BAFER, B-cell activating factor receptor; CD40, cluster of differentiation 40; c-Rel, cellular Rel proto-oncogene; IKK, inhibitor of B kinase; LTβR, lymphotoxin β receptor; NEMO, nuclear factor-kappa B essential modulator; NIK, nuclear factor-kappa B-inducing kinase; p50, p52, p100, proteins function as transcription factors; RANK, receptor activator of nuclear factor-β; TLRs, toll-like receptors.

separation of NEMO, forming biomolecular condensates that enhance signaling efficiency.[19]

E3 ligases: Assembly of ubiquitin scaffolds

Upon activation by upstream signals (e.g., TLRs, IL-1R), TRAF6 interacts with the E2 enzyme Ubc13/Uev1A to catalyze K63-linked chain formation. These chains function as docking sites for downstream effectors, including TAB2/3 and TAK1. cIAP1/2 E3 ligases, often working with TRAF2, also catalyze K63-linked ubiquitination, especially in TNFR signaling. They function redundantly with TRAF6 to ensure robust K63 chain formation and pathway activation. The K63 chains assembled by TRAF6 and cIAP1/2 induce the TAK1/TABs complex, which then activates the IKK complex, culminating in the activation of NF-κB.[20]

LUBAC (HOIP, HOIL-1L, SHARPIN)

LUBAC is the sole identified E3 ligase complex that constructs M1-linked (linear) ubiquitin chains. LUBAC consists of HOIP (catalytic core), HOIL-1L (regulatory, with additional catalytic activity), and SHARPIN (structural stabilizer). HOIP catalyzes the formation of linear chains, with HOIL-1L and SHARPIN stabilizing the complex and relieving autoinhibition. NEMO binding: M1 chains generated by LUBAC are specifically recognized by the UBAN domain of NEMO, facilitating IKK complex activation and efficient NF-κB signaling.[21,22]

Ubiquitin-centric signal relays, orchestrated by the interplay of K63- and M1-linked ubiquitin chains, E3 ligases (TRAF6, cIAP1/2, LUBAC), DUBs (A20, CYLD, OTULIN), and negative NLRs, are fundamental to the regulation of NF-κB signaling. These mechanisms ensure that immune responses are robust yet self-limiting. Dysregulation at any point—whether by genetic mutation or acquired defect—can tip the balance toward combined immunodeficiency and autoinflammation, underscoring the clinical importance of these pathways in human health and disease.[2]

Important and rapidly developing areas

NF-κB–driven metabolic reprogramming

NF-κB–driven metabolic reprogramming is a central process by which the NF-κB transcription factor orchestrates profound changes in cellular metabolism, supporting immune activation, cancer progression, and chronic inflammation. This reprogramming involves direct regulation of metabolic genes, coordination with other signaling pathways, and has both beneficial and detrimental consequences for health and disease.

NF-κB directly binds to promoters of genes involved in major metabolic pathways. For example, NF-κB upregulates HIF-1α, a master regulator of glycolytic genes, amplifying the glycolytic switch, especially under hypoxic or inflammatory conditions. GLUT1 and PFKFB3 genes enhance glucose uptake and glycolytic flux, supporting rapid ATP production. Co-regulated with STAT3, GOT2 is crucial for amino acid metabolism and biosynthesis in proliferating cells. COX-2 and iNOS enzymes link inflammation to lipid mediator production and mitochondrial function. SCO2 promotes mitochondrial oxidative phosphorylation, balancing energy production.

NF-κB also coordinates with other pathways like PI3K–AKT–mTOR signaling pathways, integrating survival, proliferation, and metabolic adaptation signals. As stated earlier, it has both physiological and pathological roles. Physiologically, NF-κB drives a switch to glycolysis, fueling the energy and biosynthetic needs for cytokine production and proliferation. Metabolic reprogramming supports cell migration, survival, and angiogenesis during tissue repair (wound healing). Pathologically, NF-κB promotes the Warburg effect, supporting tumor proliferation, survival under hypoxia, and resistance to apoptosis. Persistent NF-κB activation leads to chronic inflammatory states and metabolic dysfunction, contributing to diseases like rheumatoid arthritis, atherosclerosis, obesity, and type 2 diabetes.[23]

Cellular stress responses and NF-κB

NF-κB is a pivotal transcription factor that senses and responds to a wide array of cellular stressors, including oxidative stress, ER stress, DNA damage, hypoxia, and metabolic disturbances. Upon activation, NF-κB regulates genes involved in inflammation, cell survival, immune responses, and tissue repair. As discussed earlier, the pathway's activation is highly context-dependent, involving canonical, noncanonical, and atypical mechanisms.

Immune checkpoint inhibitor (ICI) resistance

ICIs, such as anti-PD-1/PD-L1 and anti-CTLA-4 therapies, have revolutionized cancer immunotherapy by reinvigorating T-cell-mediated anti-tumor immunity. However, ICI resistance remains a major limitation, preventing durable responses in many patients. Resistance can be categorized into primary resistance, where patients fail to respond initially, and acquired resistance, where patients relapse after an initial response. The mechanisms underlying this resistance are multifaceted and involve tumor-intrinsic factors, the immunosuppressive tumor microenvironment (TME), and systemic influences, such as the gut microbiome.[24]

Mechanisms of ICI resistance

1. Tumor-intrinsic mechanisms
   - Defects in antigen presentation: Tumors evade immune detection by mutating or downregulating key components of the antigen presentation machinery, such as MHC class I molecules or β2-microglobulin. This impairs recognition of tumor cells by cytotoxic T lymphocytes.[25]
   - Loss of immunogenic neoantigens: Tumors with low mutational burden or those that eliminate immunogenic neoantigens via immune pressure are less likely to trigger effective immune responses.[26]
   - Mutations in interferon pathways: Mutations in interferon-γ signaling components (e.g., JAK1/2) render tumor cells unresponsive to immune-mediated signaling, shutting down anti-tumor immune responses.[27]
   - Upregulation of alternative checkpoints: Tumors can express other inhibitory molecules, such as TIM-3, LAG-3, or TIGIT, which suppress T-cell activation and bypass PD-1/PD-L1 blockade.[28]
2. TME: The TME plays a critical role in ICI resistance through the recruitment and activity of immunosuppressive cells.
   - Myeloid-derived suppressor cells and regulatory T cells suppress effector T-cell activity via cytokine secretion (e.g., IL-10, TGF-β) and checkpoint upregulation.[29]
   - Immunosuppressive cytokines: Tumor-secreted TGF-β and VEGF promote immune evasion by impairing T-cell infiltration and promoting angiogenesis.[30]
   - T-cell exhaustion: Chronic antigen exposure in the TME leads to T-cell exhaustion, characterized by increased expression of inhibitory receptors (e.g., PD-1, TIM-3) and reduced effector function.[31]
   - Immune exclusion: Dense stromal barriers, extracellular ma-

trix remodeling, and abnormal vasculature hinder immune cell infiltration into the tumor core.

3. Systemic influences: Microbiome dysbiosis — The gut microbiota shapes systemic immune responses, and an unfavorable microbiome composition can contribute to ICI resistance. Specific bacterial species (e.g., *Bacteroides fragilis*) have been linked to enhanced ICI responses, while dysbiosis correlates with resistance.[32]

Interference with alternative signaling pathways

NF-κB does not operate in isolation. Its activity and outcomes are profoundly shaped by crosstalk with other major signaling pathways, including the JAK–STAT pathway. NF-κB can induce cytokines (e.g., IL-6) that activate JAK–STAT signaling. STAT3 activation can, in turn, modulate NF-κB activity, creating feedback loops. This crosstalk is critical in cancer and inflammation, where dual pathway activation sustains survival and inflammatory gene expression.[33] The MAPK pathway shares upstream activators (e.g., TAK1, TRAF6) and can simultaneously activate both NF-κB and MAPK. MAPK and NF-κB co-regulate many inflammatory and survival genes, amplifying responses. Feedback and compensatory mechanisms between these pathways can drive resistance to single-pathway inhibitors.[34] PI3K–AKT–mTOR pathway can activate NF-κB via IKK phosphorylation. NF-κB can transcriptionally regulate PI3K–AKT–mTOR components, creating positive feedback. Crosstalk contributes to cancer cell survival, drug resistance, and metabolic adaptation.[23] Wnt/β-catenin pathway has bidirectional regulation: β-catenin can inhibit or enhance NF-κB activity, and vice versa. Direct protein-protein interactions and competition for co-activators (e.g., CBP/p300) modulate gene expression. Context-dependent effects: In some cancers, Wnt/β-catenin suppresses inflammation; in others, it synergizes with NF-κB to promote tumorigenesis.[35] Notch and interferon signaling also intersect with NF-κB, influencing immune cell differentiation, antiviral responses, and inflammation. These interactions further diversify the possible outcomes of NF-κB activation.[36]

NF-κB in immunological diseases

Autoimmune diseases

Rheumatoid arthritis

NF-κB functions as a crucial regulator of inflammation and immunological responses in rheumatoid arthritis. Its activation in synovial tissues and fibroblasts from rheumatoid arthritis patients leads to the upregulation of proinflammatory cytokines, chemokines, and matrix metalloproteinases. These mediators drive synovial inflammation, pannus formation, and ultimately joint destruction. Experimental models demonstrate that NF-κB activity often precedes the onset of disease, and pharmacological inhibition of this pathway can significantly reduce disease severity. Furthermore, NF-κB is essential for osteoclast differentiation through RANKL signaling, contributing to bone erosion. Genetic studies have also identified risk alleles in genes that encode elements of the NF-κB signaling pathway, including TNFAIP3, TRAF1, and c-REL, that are linked to heightened vulnerability to rheumatoid arthritis.[37]

IBD

In IBD, sustained activation of NF-κB is a characteristic trait, resulting in chronic intestinal inflammation. This prolonged activation triggers the production of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6, as well as chemokines that facilitate the recruitment of immune cells to the gut mucosa. Both the conventional and non-canonical NF-κB pathways are implicated in the development of IBD, as demonstrated by research in animal models and human tissues. NF-κB activation in intestinal epithelial and immunological cells sustains the chronic inflammatory milieu typical of IBD.[2]

SLE

The aberrant activation of NF-κB greatly contributes to the buildup and evolution of SLE. In SLE, dysregulated NF-κB signaling increases the survival, activation, and differentiation of autoreactive lymphocytes, resulting in the generation of harmful autoantibodies. This pathway also enhances the resistance of self-reactive T cells to regulatory mechanisms, thereby sustaining autoimmunity. Chronic activation of NF-κB is closely linked to the ongoing buildup of autoantibodies and the maintenance of systemic inflammation in SLE.[38]

Psoriasis

NF-κB is a pivotal modulator of inflammatory signaling in psoriasis, modulating the synthesis of cytokines such as TNF-α, IL-23, and IL-17. These cytokines are essential for keratinocyte activation and immune cell recruitment, leading to the persistent skin inflammation characteristic of psoriasis. The TNF/IL-23/IL-17 axis, essential to psoriasis pathogenesis, is meticulously controlled by NF-κB signaling. Activation of this pathway in both keratinocytes and immune cells drives the persistent inflammatory response and epidermal hyperplasia observed in psoriatic lesions.[39]

Allergy and asthma

Airway epithelial NF-κB is a master integrator of TLR, IL-1, and TSLP signals, driving the expression of chemokines, mucus genes, and remodeling factors that underlie the pathophysiology of asthma and allergic airway disease. Persistent NF-κB activation, in cooperation with TH2 cytokines and oxidative stress, establishes a network of positive feedback loops that perpetuate chronic inflammation, airway remodeling, and disease severity. Disrupting these circuits, particularly the NF-κB axis, represents a promising therapeutic strategy for controlling chronic allergic airway diseases.[40]

Primary immunodeficiencies & autoinflammatory syndromes

NEMO/IKBKG deficiency (X-linked anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)) and incontinentia pigmenti

NEMO (IKKγ), encoded by IKBKG, serves as the regulatory component of the IKK complex, crucial for canonical NF-κB activation. Following immunological activation, the IKK complex phosphorylates IκB proteins, resulting in their breakdown and permitting NF-κB to translocate to the nucleus to activate target genes essential for immune responses and ectodermal development. NEMO functions as a scaffold, uniting the catalytic subunits (IKKα, IKKβ) and promoting their activation. Hypomorphic mutations in IKBKG diminish, but do not completely eliminate, NF-κB signaling. This results in EDA-ID, distinguished by ectodermal dysplasia (abnormalities in skin, hair, teeth, and sweat glands) and immunodeficiency (recurrent infections). Amorphic mutations (complete loss-of-function) lead to incontinentia pigmenti, an X-linked dominant disorder characterized by skin abnormalities (blistering, hyperpigmentation, atrophy), as well as

dental, hair, and occasionally neurological or ocular involvement, which is lethal in males unless they are mosaic or have Klinefelter syndrome.[41,42]

LUBAC defects (HOIL-1/RBCK1, HOIP/RNF31, SHARPIN)

LUBAC (linear ubiquitin chain assembly complex) is the only E3 ligase complex responsible for the formation of linear (M1-linked) ubiquitin chains, consisting of HOIL-1 (RBCK1), HOIP (RNF31), and SHARPIN. Linear ubiquitination by LUBAC is crucial for the complete activation of the IKK complex and classical NF-κB signaling. LUBAC-mediated ubiquitination stabilizes signaling complexes downstream of TNFR, TLRs, and antigen receptors. HOIP is the catalytic core, while HOIL-1 and SHARPIN stabilize the complex and regulate its activity. Impaired linear ubiquitination disrupts IKK activation, resulting in combined immunodeficiency (recurrent infections, poor lymphocyte function) and autoinflammation (recurrent fevers, dermatitis, enteropathy). HOIL-1 deficiency is directly connected to glycogen storage disease because HOIL-1, as part of the LUBAC complex, is essential for the ubiquitylation and removal of unbranched glucosaccharides. When HOIL-1 is deficient, this process fails, resulting in the accumulation of polyglucosan bodies (abnormally structured glycogen) in tissues. This pathological storage mimics glycogen storage disease, particularly affecting the heart, skeletal muscle, and brain, leading to progressive myopathy, cardiomyopathy, and, in some cases, neurological symptoms, and is clinically and histologically similar to other polyglucosan body diseases such as adult polyglucosan body disease and GSD IV.[43,44]

A20/TNFAIP3 haploinsufficiency (HA20)

A20, encoded by TNFAIP3, is a key negative regulator of NF-κB signaling. It acts as a ubiquitin-editing enzyme, removing K63- and linear ubiquitin chains from signaling intermediates (e.g., TRAF6, RIP1), thereby terminating NF-κB activation. A20 is activated by NF-κB and operates within a negative feedback mechanism to restrain inflammation. Haploinsufficiency (HA20) arises from heterozygous loss-of-function mutations, resulting in early-onset autoinflammation (recurrent fevers, mucosal ulcers, arthritis), Behçet-like features (oral/genital ulcers, skin rashes), and variable autoimmunity (gastrointestinal inflammation, increased risk of other autoimmune diseases).[45–47]

Therapeutic landscape: What works and what's next

Indirect pathway suppression (approved)

Anti-cytokine therapies upstream of NF-κB

These medicines focus on pro-inflammatory cytokines (TNF-α, IL-1, IL-6), which are principal activators of the NF-κB pathway. By neutralizing these cytokines, they diminish NF-κB activation and subsequent inflammatory gene expression across several cell types. Anti-TNF agents (e.g., infliximab, adalimumab, etanercept) are widely used in diseases with TNF-driven pathology, including some monogenic autoinflammatory syndromes (e.g., TRAPS, Blau syndrome) and secondary immunodeficiencies with inflammatory complications. Anti-IL-1 agents (anakinra, canakinumab, rilonacept) are particularly effective in monogenic autoinflammatory syndromes such as cryopyrin-associated periodic syndromes, familial Mediterranean fever, and systemic juvenile idiopathic arthritis. They are also used in some PIDs with excessive IL-1 signaling. Anti-IL-6 agents (tocilizumab, sarilumab) are approved for systemic juvenile idiopathic arthritis and have been used off-label in other autoinflammatory conditions with IL-6-driven features.[48–50]

These agents have broad efficacy in diseases where a single cytokine is a dominant driver of inflammation. They are less effective in conditions with redundant or multiple cytokine drivers or where the underlying defect is downstream of cytokine signaling (e.g., intrinsic NF-κB pathway mutations). Risks include infections (due to immunosuppression), paradoxical inflammation, and, rarely, malignancy.

BCR axis inhibitors (e.g., BTK inhibitors)

BTK inhibitors block BCR-mediated activation of NF-κB in B cells, reducing B cell activation, autoantibody production, and pro-inflammatory cytokine release. While primarily developed for B-cell malignancies, BTK inhibitors are being explored in autoimmune cytopenias, autoimmune lymphoproliferative syndromes, and monogenic PIDs with B-cell hyperactivity or dysregulation (e.g., activated PI3Kδ syndrome, some CVID subtypes). They may also modulate myeloid cell function, relevant in autoinflammatory syndromes with myeloid-driven inflammation.

However, they have some limitations—not all PIDs or autoinflammatory syndromes are B-cell-driven. Off-target effects and infection risk are concerns, especially in immunodeficient patients.[50]

Proteasome inhibitors (e.g., bortezomib)

Proteasome inhibitors prevent degradation of IκB, thereby blocking activation of NF-κB in both canonical and noncanonical pathways. They also induce apoptosis in highly secretory or proliferative cells (e.g., plasma cells in multiple myeloma). They are approved for multiple myeloma and mantle cell lymphoma and are used off-label in refractory autoimmune cytopenias (e.g., autoimmune hemolytic anemia, immune thrombocytopenia) and antibody-mediated transplant rejection. In PIDs, bortezomib has been used in select cases of autoimmune complications or lymphoproliferation.

Broad inhibition of protein degradation leads to significant off-target effects: neuropathy, cytopenias, GI toxicity, and increased infection risk. They are not suitable for chronic use in most PIDs or autoinflammatory syndromes due to toxicity.[51,52]

Direct and next-generation strategies (in development)

IKKβ and NEMO targeting

Direct inhibition of IKKβ or NEMO blocks the core kinase complex required for canonical activation of NF-κB. Ubiquitous expression and essential roles in tissue homeostasis and immunity lead to severe adverse effects (immunosuppression, tissue degeneration). Despite potent preclinical inhibitors, none have reached clinical approval due to toxicity. Tissue-targeted delivery (e.g., nanoparticles, local administration) and inducible inhibitors are being explored to limit systemic exposure and improve safety.[53] Direct inhibitors of the NF-κB/IKK pathway targeting IKKβ, IKKα, or the IKK complex demonstrate robust anti-inflammatory and anti-tumor effects *in vitro* and in animal models. Compounds such as BMS-345541, IMD-0354, IKK-16, and BAY 11-7082 effectively suppress NF-κB–dependent gene expression, reduce cytokine production, and inhibit disease phenotypes in models of arthritis, colitis, and cancer. These agents block the phosphorylation and degradation of IκBα, preventing NF-κB nuclear translocation and transcriptional activity, resulting in potent suppression of inflammation and cell proliferation. NF-κB and IKK proteins are ubiquitously expressed and indispensable for immune responses, cell survival, and tissue homeostasis. Systemic inhibition disrupts both

Table 2. Therapeutic strategies that modulate NF-κB signaling

Strategy/Class	Mechanism/Target	Clinical status	Relevance to PIDs/autoinflammatory syndromes
Anti-cytokines (TNF, IL-1, IL-6)	Block upstream cytokine activation of NF-κB	Approved (various)	Mainstay for many autoinflammatory syndromes
BTK inhibitors	Inhibit BCR-driven NF-κB in B cells	Emerging/approved (malignancy)	Used in B-cell-driven PIDs, autoimmune cytopenias
Proteasome inhibitors	Block IκB degradation, inhibit NF-κB	Approved (hematologic)	Used in refractory autoimmunity, lymphoproliferation
IKKβ/NEMO inhibitors	Direct block of canonical NF-κB	Preclinical	Toxicity limits use; tissue-targeted approaches in development
NIK inhibitors	Block noncanonical NF-κB	Preclinical	Potential in B cell/ lymphoproliferative PIDs
MALT1 inhibitors	Block CBM complex, lymphocyte activation	Preclinical/early clinical	For CBM complex-driven PIDs, lymphomas
DUB modulators (A20, CYLD, OTULIN)	Restore negative regulation of NF-κB	Preclinical	For monogenic autoinflammatory syndromes
Nanoparticles, PROTACs, degraders	Targeted delivery, protein degradation	Preclinical	Reduce toxicity, enable cell/tissue specificity
HDAC inhibitors	Epigenetic suppression of NF-κB	Approved (malignancy), in trials	Potential for synergy, broad immunomodulation
miRNA/lncRNA therapeutics	Post-transcriptional/ epigenetic regulation	Preclinical	Fine-tuning of NF-κB in specific cell types

pathological and protective functions, leading to severe, mechanism-based adverse effects. NF-κB also acts as a tumor suppressor in certain tissues. Its inhibition can increase the risk of malignancies, particularly in the liver and skin, due to impaired immune surveillance.[54] Direct inhibition impairs both innate and adaptive immunity, increasing susceptibility to infections and impairing host defense. Clinical and preclinical studies consistently report immunodeficiencies and increased infection risk. NF-κB is critical for hepatocyte survival and tissue repair. Inhibition of IKKβ or NEMO leads to liver dysfunction, hepatocyte apoptosis, and tissue degeneration. These toxicities are observed in both animal models and clinical trials.[9] The major therapeutic strategies targeting NF-κB signaling, along with their mechanisms and clinical relevance, are summarized in Table 2. Paradoxically, IKKβ inhibition can enhance IL-1β secretion and caspase-1 activity, resulting in systemic inflammation and increased lethality in animal models. Such effects have been dose-limiting in early-phase clinical trials.[55]

NIK inhibitors (noncanonical pathway)

NIK is crucial for the noncanonical NF-κB pathway, which plays a significant role in the maturation of B cells, lymphoid organogenesis, and some autoinflammatory processes. Inhibitors block p100 processing to p52, reducing noncanonical activity of NF-κB. Potential targets include B cell-driven PIDs, lymphoproliferative disorders, and autoinflammatory syndromes with aberrant noncanonical pathway activation. Preclinical data are promising, but clinical trials are pending.[56]

MALT1 paracaspase inhibitors (CBM complex)

MALT1 is a key protease in the CBM complex, required for antigen receptor-induced activation of NF-κB in lymphocytes. Inhibitors block both scaffolding and proteolytic functions, suppressing lymphocyte activation. Targeted for MALT lymphoma, DLBCL, and potentially for autoimmune/autoinflammatory diseases with CBM complex mutations (e.g., CARD11, BCL10, MALT1 gain-of-function PIDs). Early clinical and preclinical data show selective efficacy in lymphocyte-driven diseases.[57]

DUB modulators (A20, CYLD, OTULIN)

DUBs such as A20, CYLD, and OTULIN are negative NF-κB regulators, removing ubiquitin chains from signaling intermediates. Mutations in these genes cause autoinflammatory syndromes (e.g., A20 haploinsufficiency, OTULIN-related autoinflammation). Modulating DUB activity could restore balance in patients with loss-of-function mutations or excessive NF-κB activation. Small-molecule DUB modulators are in early development.[58]

Pathway-aware delivery technologies

Nanoparticles

Enable targeted delivery of NF-κB inhibitors (small molecules, RNA, proteins) to inflamed tissues or specific cell types, reducing systemic toxicity. Preclinical studies show improved efficacy and safety in models of inflammation and autoimmunity.[59]

Proteolysis-targeting chimaeras (PROTACs) and degraders

PROTACs induce selective NF-κB pathway protein degradation (e.g., IKKβ, NEMO, RelA). They offer catalytic, reversible, and potentially tissue-selective inhibition, overcoming limitations of traditional inhibitors. They are still largely preclinical but represent a promising approach for "undruggable" targets.[60]

Epigenetic co-targeting (HDAC inhibitors)

HDAC inhibitors modulate chromatin structure and gene expres-

sion, including NF-κB target genes. They can also affect acetylation of NF-κB subunits, altering their activity and localization. They are approved for some hematologic malignancies and are under investigation for autoimmune and autoinflammatory diseases. They may synergize with other NF-κB inhibitors or RNA-based therapeutics.[61]

miRNA/lncRNA therapeutics

miRNAs and lncRNAs modulate NF-κB pathway components at the post-transcriptional and epigenetic levels. Therapeutic approaches encompass miRNA mimics (to reinstate suppressive miRNAs) or antagomirs (to obstruct pro-inflammatory miRNAs). Preclinical studies show that modulating specific miRNAs/lncRNAs can suppress NF-κB-driven inflammation in autoinflammatory and autoimmune models. Delivery and specificity remain challenges, but advances in nanoparticle and tissue-targeted delivery are promising.[62]

Biomarkers and translational readouts

Tissue assay techniques for NF-κB pathway analysis

Nuclear p65 (RelA) immunostaining identifies the translocation of the p65 subunit from the cytoplasm to the nucleus, indicative of conventional NF-κB activation. In resting cells, p65 is cytoplasmic; upon activation (e.g., by cytokines or stress), it moves to the nucleus to regulate gene expression. Immunohistochemistry or immunofluorescence is used to visualize this shift in tissue sections. Phosphorylation of IκB and IKK is an early event in NF-κB activation. Phospho-specific antibodies can detect these modifications, serving as markers of pathway activation. RelB/p52 localization is a marker of the noncanonical NF-κB pathway. Their nuclear localization is assessed similarly to p65, using specific antibodies.[63]

Molecular signature approaches

Molecular signatures are curated sets of genes or proteins whose expression patterns reflect NF-κB pathway activity. These are identified through gene expression profiling (e.g., RNA-seq, PCR arrays), proteomics, and bioinformatics. Signature refinement involves integrating transcriptomic, proteomic, and epigenetic data, often using machine learning or network analysis to improve specificity and predictive power. NF-κB signatures can distinguish between healthy and diseased tissues and between molecular subtypes of cancers (e.g., DLBCL subtypes). Certain NF-κB gene signatures predict patient outcomes and response to therapies, such as chemoradiotherapy in glioma or colorectal cancer. Signatures further assist in identifying patients who are likely to benefit from NF-κB-targeted therapy or immunomodulatory treatments.[64,65]

Functional dynamics techniques

NF-κB activation is not simply "on" or "off"; it exhibits complex temporal patterns (oscillatory, pulsatile, sustained) that encode information about the type and strength of stimuli.

Key techniques

- *Live-cell imaging:* Fluorescently labeled NF-κB subunits (e.g., p65-GFP) provide real-time monitoring of nuclear translocation and oscillations in single cells.
- *Quantitative image analysis:* Extracts features such as amplitude, duration, and frequency of NF-κB activation from time-lapse data.
- *Single-cell multi-omics:* scRNA-seq and ATAC-seq elucidate heterogeneity in NF-κB target gene expression and chromatin accessibility at the single-cell level.
- *Reporter assays:* Luciferase or GFP reporters under NF-κB-responsive promoters provide real-time readouts of pathway activity.
- *Microfluidics:* Enables precise temporal control of stimuli to dissect how cells decode dynamic environmental signals.
- *Mathematical modeling:* Simulates pathway dynamics and predicts gene expression outcomes based on dynamic features.[66–68]

Future directions

- *Dynamics-guided precision therapy:* Dynamics-guided precision therapy leverages real-time patient data, molecular profiling, and adaptive trial designs to optimize treatment strategies for individual patients. This approach provides real-time monitoring and temporal control to intervene only during pathological activation patterns, sparing physiological responses. Combination logic uses coordinated timing of multiple drugs to disrupt disease-specific signaling cascades without broadly suppressing immunity. This approach is especially prominent in oncology but is expanding into other disease areas.[69]
- *Ubiquitin code editing:* Ubiquitin code editing refers to the targeted manipulation of ubiquitin modifications—either by inhibiting or enhancing specific enzymes like ligases (LUBAC) or DUBs (A20, CYLD) in the ubiquitin pathway—to achieve therapeutic outcomes. Pathway-selective inhibitors focus on disease-relevant ubiquitin enzymes, sparing normal pathway function. The ubiquitin system is central to protein homeostasis and cell signaling.[70]
- *Spatial immunology:* Spatial immunology uses advanced imaging and molecular profiling to map the organization, interactions, and functional states of immune cells within their native tissue context. This approach is transforming diagnostics, prognostics, and therapeutic strategies, especially in oncology.[71]
- *Tissue-targeted delivery:* Nanoparticles and SLFPs deliver inhibitors directly to diseased tissues or cell types, reducing systemic exposure.
- *Genotype-to-therapy:* Genotype-to-therapy approaches use a patient's genetic information to guide the selection, dosing, and monitoring of therapies. This is central to precision medicine, moving beyond the "one-size-fits-all" model. Use of monogenic NF-κBopathies (e.g., NEMO, LUBAC, A20) as natural experiments helps guide interventions in complex disease.[72]
- *Combination logic:* Combination logic therapeutic strategies involve using two or more drugs or treatment modalities, often with different mechanisms of action, to address complex diseases. This approach is especially valuable in conditions like cancer, epilepsy, and chronic diseases, where biological complexity and redundancy in disease pathways often render single-target therapies insufficient. Rational co-targeting of upstream cytokines with BCR/TCR or metabolic nodes broaden efficacy while minimizing toxicity. These emerging concepts collectively outline the future landscape of NF-κB-targeted precision therapies (Figure 3).[73]

Scientific and clinical significance of the review

The NF-κB signaling pathway is crucial to immune control, regulating the equilibrium between defensive host reactions and detrimental chronic inflammation. Its complex architecture, involving canonical and noncanonical activation routes, ubiquitin-mediated

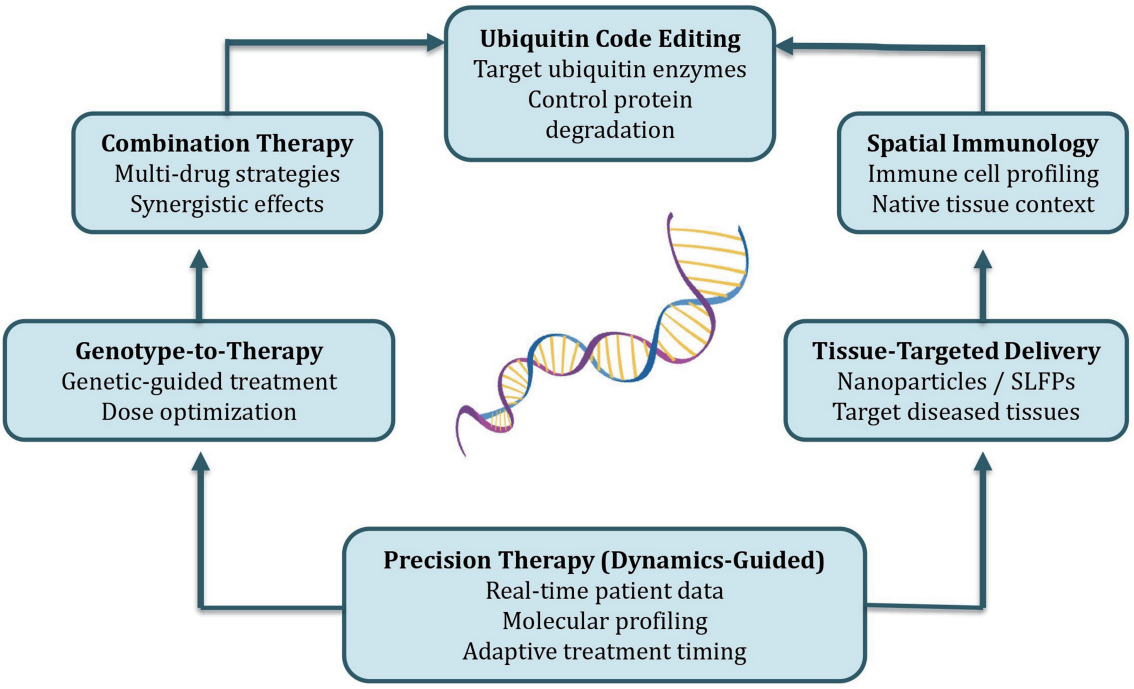

Fig. 3. Future directions in precision immunotherapy and ubiquitin-targeted strategies.

signal relays, and dynamic feedback regulation, enables rapid and context-specific gene expression in response to diverse stimuli. However, dysregulation of NF-κB—whether by genetic mutations or persistent environmental triggers—underlies the pathophysiology of many immunological disorders, including autoimmune illnesses such as rheumatoid arthritis, IBD, and SLE, allergic disorders, and primary immunodeficiencies. Advances in molecular understanding have revealed how defects in key pathway components such as NEMO/IKBKG, LUBAC, and A20/TNFAIP3 can manifest as distinct syndromes of immunodeficiency and autoinflammation, highlighting the clinical importance of precise pathway control. Therapeutically, both established (e.g., cytokine inhibitors, proteasome inhibitors, BTK inhibitors) and emerging strategies (e.g., IKK/NIK/MALT1 inhibitors, DUB modulators, RNA-based and nanoparticle therapies) aim to modulate NF-κB with increasing selectivity. Yet, the challenge remains to suppress pathological activation without compromising essential immune functions. The development of robust biomarkers and pathway activity readouts is critical for patient stratification and monitoring therapeutic response. Looking ahead, integrating insights from pathway dynamics, ubiquitin code editing, spatial immunology, and genotype-driven approaches promises more precise, effective, and safe interventions for NF-κB-driven diseases.

This review advances the field of NF-κB research by introducing a suite of novel conceptual frameworks and mechanistic insights that go far beyond the established knowledge found in previous comprehensive reviews. While earlier work thoroughly described canonical and noncanonical pathways, disease associations, and standard therapeutic strategies, this review pioneers new territory by conceptualizing the "ubiquitin code" as a programmable regulatory system, leveraging monogenic diseases as natural experiments to establish causality in pathway dysfunction, and integrating spatial and temporal regulation into a multi-dimensional model of NF-κB control. These advances collectively transform our understanding of NF-κB from a linear signaling cascade to a dynamic, precision-targetable network.

Limitations and gaps

This study provides a comprehensive overview of NF-κB signaling and its role in immunological diseases, but it has several limitations. While it details molecular mechanisms and therapeutic strategies, it lacks in-depth experimental validation for emerging therapeutic approaches, such as ubiquitin code editing or spatial immunology. Moreover, the study does not address the translational challenges of NF-κB inhibitors, especially regarding toxicity and specificity in clinical settings. Additionally, while it discusses biomarkers, it provides limited insight into their clinical applicability and validation. Future studies should focus on bridging preclinical findings with real-world therapeutic efficacy and safety, especially in diverse patient populations.

Conclusions

The NF-κB signaling pathway is a central regulator of immune responses, inflammation, and cell survival, integrating diverse signals through its canonical and non-canonical mechanisms. Its dysregulation underlies various diseases, including cancer and chronic inflammatory conditions, highlighting its potential as a therapeutic target, though precise modulation is essential to balance efficacy with the preservation of critical physiological functions.

Acknowledgments

The authors are thankful to the Institute of Professional Studies College of Pharmacy, Gwalior, Madhya Pradesh, India, and GLA University, Mathura, Uttar Pradesh, India.

Funding

None.

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study concept and design (YS, AS, JKG), acquisition of data (RM, AD), analysis, and interpretation of data (RM, AD, YS, AS), drafting of the manuscript (RM, AD), critical revision of the manuscript for important intellectual content (YS, JKG, SD), administrative, technical, or material support (PC), and study supervision (AS). All authors made a significant contribution to this study and have approved the final manuscript.

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