kinases and phosphatases

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Review

The Yin and Yang of IκB Kinases in Cancer

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Abstract: IκB kinases (IKKs), specifically IKKα and IKKβ, have long been recognized for their pivotal role in the NF-κB pathway, orchestrating immune and inflammatory responses. However, recent years have unveiled their dual role in cancer, where they can act as both promoters and suppressors of tumorigenesis. In addition, the interplay with pathways such as the MAPK and PI3K pathways underscores the complexity of IKK regulation and its multifaceted role in both inflammation and cancer. By exploring the molecular underpinnings of these processes, we can better comprehend the complex interplay between IKKs, tumor development, immune responses, and the development of more effective therapeutics. Ultimately, this review explores the dual role of IκB kinases in cancer, focusing on the impact of phosphorylation events and crosstalk with other signaling pathways, shedding light on their intricate regulation and multifaceted functions in both inflammation and cancer.

Keywords: IκB kinases; IKKs; NF-κB

1. Introduction

The NF-κB (Nuclear Factor-κB) pathway is a linchpin of cellular responses to external stimuli, especially in the realms of immune and inflammatory processes [1]. Within the broader context of the NF-κB signaling pathway, the IκB kinases (IKKs) (Table 1), particularly IKKα and IKKβ, occupy a pivotal position in the intricate regulatory network of these pathways. Traditionally recognized for their roles in immune surveillance and defense, the IKKs have recently emerged as enigmatic figures in the landscape of cancer biology [2–5]. Their Janus-faced nature, promoting or suppressing tumorigenesis depending on context, has prompted an intensive exploration of their molecular mechanisms within the context of cancer and the possibility of targeting them [6].

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Table 1. Types of IκB kinases.

Type of IκB Kinase	Role in NF-κB Pathway	Function in NF-κB Regulation	Targets
IKKα (Inhibitor of κB Kinase Alpha) [7]	Non-Canonical NF-κB pathway	Phosphorylates p100, leading to partial proteasomal processing into p52. Initiates non-canonical gene transcription. Involved in cellular senescence.	p100
IKKβ (Inhibitor of κB Kinase Beta) [8]	Canonical NF-κB pathway	Phosphorylates IκBα and IκBβ, marking them for degradation. Releases p50-RelA dimers for nuclear translocation. Associated with chronic inflammation and tumor promotion.	IκBα, IκBβ
IKKε (Inhibitor of κB Kinase Epsilon) [9]	Both canonical and non-canonical pathways	Regulates NF-κB activation, particularly in response to viral infections. Can promote cell survival.	-
TBK1 (TANK-binding kinase 1) [10]	Non-Canonical NF-κB pathway	Activates IKKα and promotes non-canonical NF-κB signaling. Also involved in antiviral immune responses.	IKKα
IKKζ (Inhibitor of κB Kinase Zeta (MAIL)) [11]	Both canonical and non-canonical pathways	Modulates NF-κB signaling and immune responses. May play a role in inflammation and autoimmunity.	-
NEMO (NF-κB Essential Modulator) [12]	Central scaffold protein	Acts as an essential scaffold for IKKα and IKKβ, facilitating their activation. Essential for canonical NF-κB activation.	IKKα, IKKβ

The NF-κB pathway, with its intricate family members, represents a dynamic signaling network that orchestrates cellular responses to a multitude of extracellular signals [13]. The fundamental aspect of this pathway revolves around the NF-κB transcription factors, comprising various members such as p65 (RelA), RelB, c-Rel, p105/p50, and p100/p52. These members of the NF-κB family combine in different dimeric forms, each playing specific roles in overseeing signaling pathways, particularly those involved in immune responses [14–16].

Central to the regulation of NF-κB is the presence of inhibitory proteins referred to as IκBs, responsible for maintaining NF-κB dimers in an inactive state within the cell's cytoplasm [17]. The activation of the pathway involves the phosphorylation of IκBs, tagging them for degradation by the proteasome machinery. This process liberates NF-κB dimers, allowing them to migrate into the nucleus and commence gene transcription (Figure 1) [18].

The NF-κB pathway, essential for various physiological processes, exists in multiple branches. Primarily, there are two well-characterized pathways: the canonical (or classical) and non-canonical (or alternative) [19]. These pathways differ in terms of the stimuli that activate them, the proteins involved, and the nature of their functions. The effective enhancement of NF-κB involves a complex regulation process mediated by the IκB kinase (IKK) complex. This intricate system orchestrates the phosphorylation of IκB proteins, leading to their ubiquitination and subsequent degradation via the proteasome [20–22]. This series of events ultimately results in the liberated NF-κB complexes translocating into the nucleus.

Within the nucleus, these NF-κB complexes engage with specific DNA sequences, thereby governing the transcription of genes involved in diverse processes, including immune responses, cellular growth regulation, and the modulation of cell survival [23–25]. Notably, within the context of cancer, NF-κB-dependent genes encompass those responsible for encoding cytokines, chemokines, cyclin D1, matrix metalloproteinases, and antiapoptotic proteins such as Bcl-xL [26–28].

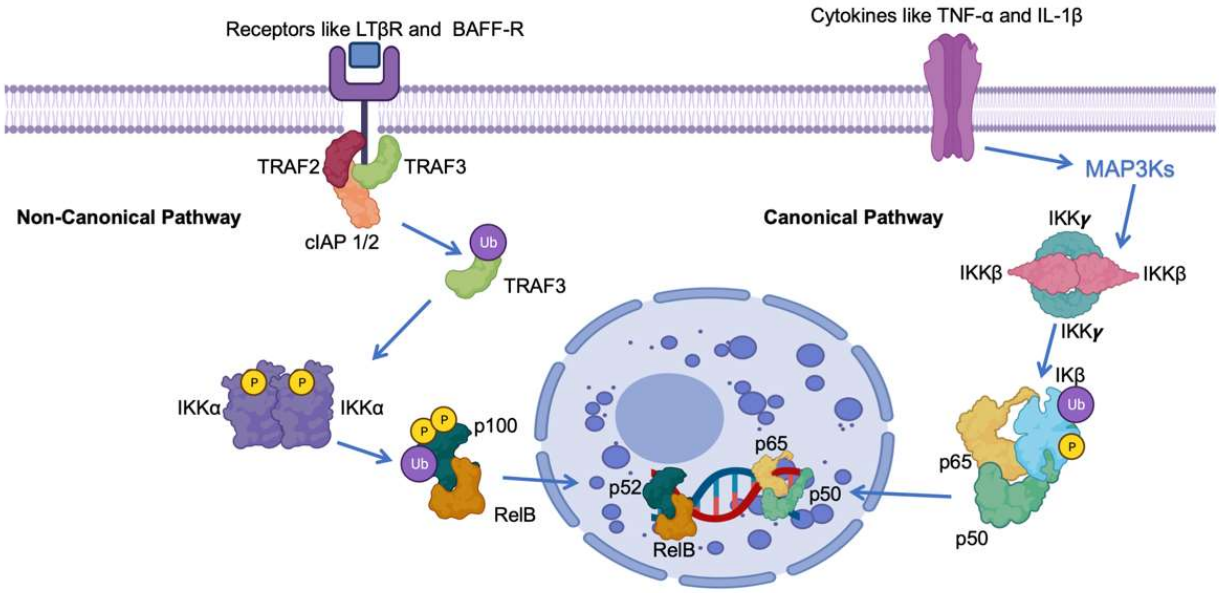


Figure 1. Schematic representation of the roles of IκB in the canonical and non-canonical NF-κB pathway. The NF-kB pathway involves key proteins such as Tumor Necrosis Factor Receptor-Associated Factor 3 (TRAF3), Precursor protein 100 (p100), V-rel avian reticuloendotheliosis viral oncogene homolog B (RelB), Nuclear Factor NF-kappa-B p52 subunit (p52), Nuclear Factor NF-kappa-B p65 subunit (p65), Cellular Inhibitor of Apoptosis Protein 1/2 (cIAP 1/2), B-cell Activating Factor Receptor (BAFF-R), and Lymphotoxin Beta Receptor (LTβR). Ub indicates ubiquitination, IKK α ((IkappaB kinase alpha). P indicates phosphorylation.

2. Canonical NF-κB Pathway

In the Canonical Nuclear Factor-kappa B (NF-κB) pathway, activation is initiated by a diverse array of stimuli, encompassing proinflammatory cytokines like Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), as well as microbial products like lipopolysaccharides (LPSs) (Figure 1) [29–32]. Key to this pathway is the activation of IKKβ, which subsequently phosphorylates and targets IκBα and IκBβ for degradation. As a result, this liberation allows for the movement of p50-RelA dimers into the nucleus. Once in the nucleus, these dimers function as transcription factors, overseeing the expression of genes linked to inflammation, immune responses, and cell survival (Figure 1) [33–35].

3. Non-Canonical NF-κB Pathway

Conversely, the Non-Canonical NF-κB pathway is typically triggered by a unique group of receptors, which encompass the lymphotoxin-β receptor (LTβR) and B-cell activating factor receptor (BAFF-R) [36]. This pathway is reliant on the conversion of p100 to p52, a process orchestrated by the activation of IKKα. Subsequently, the p52-RelB dimers relocate to the nucleus, assuming critical roles in the development of secondary lymphoid organs, B-cell maturation, and the organization of lymphoid tissues (Figure 1) [37–39].

NIK, or NF-κB-inducing kinase, holds a crucial position in regulating the non-canonical NF-κB signaling pathway [40]. Initially acknowledged for its role in activating the canonical NF-κB pathway, the absence of NIK did not hinder the TNF-induced IKKβ/p65/p50 activation. However, it was later discovered to be essential for triggering the non-canonical NF-κB pathway [41–43]. The regulation of NIK predominantly occurs post-translationally. Structurally, NIK encompasses four domains: a TRAF3-binding N-terminal region, a negative regulatory domain (NRD), a core kinase domain, and a C-terminal domain responsible for binding with proteins like IKKα and p100 [44–46].

Initially recognized as a mediator following TNF and IL-1 receptor activation, NIK's kinase activity was deemed crucial in facilitating this particular process. Additionally,

it mediates stimulation through various receptors like CD27, CD30, CD40, LTβR, and BAFFR [47–50]. The overexpression of NIK activates NF-κB, protecting cells from TNF-induced apoptosis, while kinase-dead NIK mutants inhibit NF-κB activation by TNFα [51–53].

Under normal conditions, NIK binds to TRAF2/3 and cIAP1/2, leading to its continuous ubiquitination and degradation [54]. Stimulation by cytokines (such as CD40L, TWEAK, LTα/β, or LPS) sequesters TRAF2/3, allowing the cIAP1-mediated ubiquitination of TRAF3 [55]. The subsequent degradation of TRAF3 leads to the accumulation of newly synthesized NIK within the cell. This stabilization and buildup of NIK are crucial for initiating the noncanonical NF-κB pathway [56–58]. Upon receptor activation, NIK triggers IKKα phosphorylation at Ser-176 and Ser-180, activating it to phosphorylate p100. The phosphorylation of p100 prompts the binding to ubiquitin ligase β-TrCP, resulting in partial proteasomal processing to p52. This processing removes the inhibitory C-terminal ankyrin repeat domain of p100, akin to the function of mature IκB proteins, thus maintaining RelB inactive in the cytoplasm. Subsequently, p52-RelB translocates to the nucleus to regulate transcription [59–62].

NIK interacts with and activates both IKKα and IKKβ, phosphorylating IKKα to a greater extent. Consequently, NIK acts as an upstream kinase for the IKK complex, facilitating signaling from multiple cytokine receptors [63–65]. Several other kinases, including MEKK1 and TAK1, were identified as IKK kinases, sometimes acting alongside NIK. TAK1, for instance, can activate NIK/IKK/NF-κB signaling independently of NIK in certain contexts [66]. Additionally, proteins like TRAF2, 5, and 6, as well as TBK-1, contribute to NF-κB activation by acting upstream of NIK. Moreover, Bcl10 has been reported to phosphorylate NIK under specific inflammatory conditions in human colonic epithelial cells treated with carrageenan (CGN) [22,67,68].

4. The Dark Side: IκB Kinases as Tumor Promoters

4.1. IKKα (Inhibitor of κB Kinase Alpha)

IKKα plays a multifaceted role in cancer, impacting both its initiation and progression, along with metastasis. In colorectal cancer cells (HT29), IKKα exhibits abnormal activation within the nucleus of tumor cells [69]. Here, it binds to specific genes reliant on Notch signaling, such as hes1 and herp2. The nuclear IKKα phosphorylates a nuclear co-repressor, SMRT, causing its release from chromatin and the subsequent expression of Notch-dependent genes [70], leading to more aggressive growth and proliferation. Pan-IKK inhibition re-establishes SMRT chromatin binding, curbing Notch-related gene expression, and restraining tumor growth in experimental models [71].

Additionally, IKKα phosphorylates N-CoR, akin to SMRT, facilitating its nuclear export from CRC cells [72]. The active nuclear IKKα isoform, IKKα(p45), is crucial for preventing apoptosis and thereby fostering tumor growth, specifically in HCT116 cells. Mechanistically, the association between active TAK1, BRAF, a complex containing IKKα(p45), and NEMO leads to SMRT and Histone H3 phosphorylation, which is vital for BRAF-mediated transformation independent from NF-κB signaling [73].

In keratinocytes, evidence demonstrates IKKα's involvement in cancer initiation independently of NF-κB [74]. The deletion of IKKα induces skin squamous cell carcinoma in mice, affecting 14-3-3σ expression and prompting aberrant cell proliferation, disrupting skin homeostasis, and promoting cell transformation [75]. Additional studies support IKKα's tumor suppressor role in the skin, linking its activity to the transforming growth factor beta (TGFβ) pathway. Moreover, a specific variant of nuclear IKKα in keratinocytes leads to more aggressive tumors upon exposure to chemical carcinogens [76,77].

Basal cell carcinomas (BCCs) are the most prevalent among human cancers affecting the skin [78]. While the noncanonical NF-κB pathway relies on IKKα, its specific role in BCC remains unclear. One study indicated that, within both BCC and non-malignant conditions, IKKα is present in the nucleus. Within BCC, the nuclear IKKα directly interacts with the promoters of inflammation factors and LGR5, a marker for stem cells. This interaction leads to an increase in LGR5 expression through the activation of the STAT3

signaling pathway, thereby contributing to cancer progression. The activation of the STAT3 pathway influences the LGR5 expression in a manner dependent on IKKα, as demonstrated by the interplay between STAT3 and IKKα. Moreover, suppressing the IKKα impedes the tumor growth and transition from the epithelial stage to the mesenchymal stage. This finding highlights IKKα's role as a genuine chromatin regulator in BCC. Its heightened expression facilitates oncogenic transformation by promoting the expression of genes related to stemness and inflammation. Consequently, these findings offer a fresh perspective on how IKKα may participate in the progression of BCC tumors within an inflammatory microenvironment [79].

Moreover, in a study by Mahato and colleagues [80], they have shown that the suppression of IKKα in prostate cancer cells using synthetic siRNAs affects tumor cell growth and invasiveness. In this study, the authors designed three synthetic siRNAs targeting the specific regions of IKKα mRNA and evaluated their ability to silence IKKα in PC-3 and DU145 cells. A range of assays, including wound healing, migration, proliferation, and cell cycle analysis, were employed to investigate how IKKα siRNAs biologically impacted prostate cancer cells. Interestingly, their results uncovered potent siRNAs that could silence IKKα by up to 70%, resulting in decreased wound healing, migration, invasion, and cell attachment capabilities in prostate cancer cells. Additionally, this study observed comparable anti-invasive effects in the presence of RANKL. However, silencing IKKα had minimal effects on cell proliferation and cell cycle distribution. These findings strongly indicate that IKKα significantly influences prostate cancer invasion and metastasis while playing a minor role in cell proliferation. Targeting IKKα using siRNA emerges as a promising therapeutic approach for managing prostate cancer by reducing invasion and metastasis without directly impacting cell proliferation [81,82].

Moreover, IKKα contributes to progesterone-induced tumor promotion in breast cancer, downstream of RANKL induction, and fosters metastatic spread relying on RANKL produced by tumor-infiltrating regulatory T cells. It phosphorylates Estrogen Receptor α, its coactivator AIB1/SRC3, and induces targets like cyclin D1 and c-myc, driving breast cancer cell proliferation [83]. Clinical observations link IKKα expression in breast cancer cells with patient outcomes regardless of cellular localization. In triple-negative breast cancer (TNBC) cells, IKKα mediates Notch signaling triggered by the Notch ligand Jagged1, a pivotal pathway for TNBC Cancer Stem Cell survival [84]. Combining therapies targeting the intersection of Notch, AKT, and NF-κB pathways holds promise for therapeutic applications against cancer stem cells in TNBC [85].

4.2. IKKβ (Inhibitor of κB Kinase Beta)

In contrast to IKKα, IKKβ is predominantly associated with the canonical NF-κB pathway. One of its key functions is the phosphorylation of IκBα and IκBβ. This phosphorylation event marks IκB proteins for degradation, allowing the release of p50-RelA dimers [86]. The degradation of IκB proteins leads to the liberation of NF-κB, a transcription factor crucial in orchestrating the expression of pro-inflammatory genes. This includes genes responsible for cytokine and chemokine production, thus fostering a sustained and amplified inflammatory response within the tumor microenvironment [87]. This persistent inflammation, driven by IKKβ, creates a milieu that nurtures tumor growth, angiogenesis, and metastasis [88].

The released dimers subsequently move into the nucleus, where they commence the transcription of genes linked with the canonical NF-κB pathway. Notably, the activation of IKKβ is frequently prompted by proinflammatory stimuli, connecting it to persistent inflammation [89]. This linkage further underscores IKKβ's significance in fostering tumor progression, the formation of new blood vessels (angiogenesis), and the spread of cancer to distant sites (metastasis), highlighting its critical role in the context of cancer. However, it is important to note that the outcome of this inflammatory response is context-dependent, either influencing the promotion of tumor formation or the initiation of an immune reaction against tumors [90].

To date, diverse chemical inhibitors targeting IKKβ have been discovered, each employing distinct mechanisms [91] (see Table 2). Most of these inhibitors mimic ATP, displaying reversible, ATP-competitive behavior, often exhibiting some preference for inhibiting IKKβ over IKKα and other kinases [92]. Yet, due to the structural similarity of protein kinase ATP-binding sites, these ATP mimics can inadvertently affect other kinases, causing unintended effects at concentrations required to inhibit their primary target in cells [93]. Specifically, some commonly used 'specific' IKKβ inhibitors, such as Bay 11-7082 and TPCA-1, have been found to induce significant off-target effects [94]. For instance, Bay 11-7082 disrupts NF-κB by irreversibly deactivating the E2-conjugating enzymes Ubc13 and UbcH7, as well as the E3-ligase LUBAC, rather than directly inhibiting IKK activity. Similarly, TPCA-1 hampers the STAT3 signaling by directly binding to the STAT3 Src Homology 2 (SH2) domain, alongside its IKKβ inhibitory activity [95].

Table 2. The selected compounds of natural and synthetic origin that were investigated for their effects on IKKβ in various cancer cell lines. They modulate IKKβ activity, leading to a suppression of NF-κB signaling, and the consequent downregulation of genes associated with inflammation, cell survival, and proliferation.

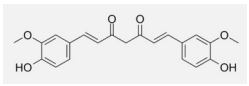
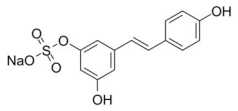
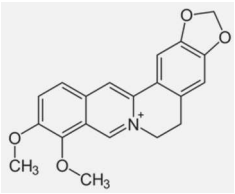
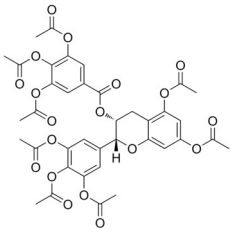
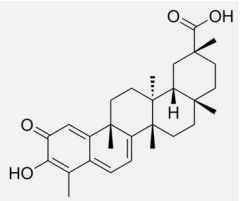
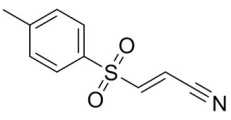
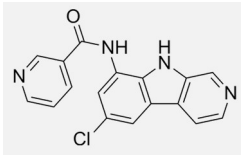
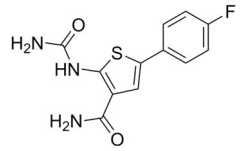
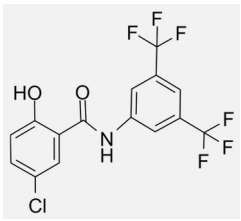
Compound Name	Source or Synthesis	Cell Line/Organism	Concentration (μM)	Incubation Time (h)	Observed Effect on IKKβ/Target	Structure
Curcumin [96]	Turmeric (Plant)	Various cancer cell lines (e.g., MCF-7, A549)	10–50	12–48	Inhibition of IKKβ phosphorylation and NF-κB activation, leading to reduced pro-inflammatory and pro-survival gene expression.	
Resveratrol [97]	Red grapes (plant)	Human prostate cancer cells (e.g., PC-3)	50–100	24–72	Suppression of IKKβ activity, resulting in reduced NF-κB-mediated transcription and anti-proliferative effects.	
Berberine [98]	Berberis pant	Various cancer cell lines (e.g., HCT-116, MDA-MB-231)	10–100	12–48	Inhibition of IKKβ phosphorylation, blocking NF-κB activation, and reducing the expression of pro-inflammatory and anti-apoptotic genes.	
EGCG (epigallocatechin-3-gallate) [99]	Green tea (plant)	Various cancer cell lines (e.g., A549, HCT-116)	20–100	24–48	Suppression of IKKβ phosphorylation, leading to decreased NF-κB activity and inhibition of pro-survival and pro-inflammatory pathways.	
Celastrol [100]	Thunder of god vine (plant)	Human beast cancer cells (e.g., MDA-MB-231)	0.5–1	6–24	Inhibition of IKKβ activity, blocking NF-κB signaling, and promoting apoptosis in cancer cells.	
BAY 11-7082 [101]	Synthetic compound	Multiple cancer cell lines (e.g., HeLa, U87)	5–20	2–24	Direct inhibition of IKKβ activity, leading to the suppression of NF-κB signaling and the downregulation of pro-survival and pro-inflammatory genes.	

Table 2. *Cont.*

Compound Name	Source or Synthesis	Cell Line/Organism	Concentration (μM)	Incubation Time (h)	Observed Effect on IKKβ/Target	Structure
PS1145 [102]	Synthetic compound	Various cancer cell lines (e.g., A549, MDA-MB-231)	1–10	4–24	Selective inhibition of IKKβ, resulting in the attenuation of NF-κB signaling and the reduction in pro-inflammatory and anti-apoptotic gene expression.	
TPCA-1 [103]	Synthetic compound	Human lung cancer cells (e.g., H1299)	1–5	6–24	Inhibition of IKKβ kinase activity, leading to the suppression of NF-κB-mediated transcription and anti-proliferative effects.	
IMD-0354 [104]	Synthetic compound	Prostate cancer cells (e.g., PC-3)	10–50	6–48	Inhibition of IKKβ activity, resulting in reduced NF-κB signaling and the downregulation of genes associated with cell survival and inflammation.	

Currently, the most potent ATP-competitive inhibitors for IKKβ include MLN-120B and BI605906, showcasing over 50-fold and over 300-fold selectivity for IKKβ over IKKα, respectively [105].

Recent research indicates potential toxicity and side effects correlated with IKKβ inhibition, such as the onset of inflammatory skin diseases and the heightened vulnerability of colonic epithelium to various stressors [106,107]. Severe liver malfunction has been observed in mice with IKKβ deficiencies, and intestinal and liver toxicity has surfaced in numerous clinical trials involving IKKβ inhibitors, potentially restricting their clinical applicability [108].

5. The Bright Side: IKKs as Tumor Suppressors

5.1. IKKα in Tumor Suppression

Despite its role in promoting cancer in some contexts, IKKα also has tumor-suppressive functions. It can induce cellular senescence in response to oncogenic stress, causing cells to enter a state of irreversible growth arrest [109]. Cells that undergo senescence not only cease dividing but also release substances referred to as the senescence-associated secretory phenotype (SASP). These substances attract immune cells, which in turn play a role in eliminating cells that could potentially develop into tumors [110].

A significant association exists between DNA damage-triggered senescence and the NF-κB-regulated SASP [111]. When exposed to genotoxic stress, the Ataxia telangiectasia mutated (ATM) kinase activates NF-κB by triggering the post-translational modifications (PTMs) of NEMO, which play a pivotal role in NF-κB activation. NEMO activation by ATM subsequently triggers the IKK complex, culminating in the nuclear translocation of NF-κB and the transcription of numerous genes related to SASP [112]. In melanoma, senescent cells produce a secretome characterized by the pro-invasive and pro-tumorigenic properties, relying on PARP-1 and NF-κB [113].

The expression of SASP components IL-6 and IL-8 necessitates IκBζ during both DNA damage-induced senescence and oncogene-induced senescence (OIS), establishing IκBζ as a crucial modulator of the proinflammatory SASP [114].

Multiple strands of evidence indicate that the continuous DNA damage response (DDR) is crucial for robust SASP production. The depletion of DDR elements like ATM, NBS1, or CHK2 inhibits the expression of IL-6, IL-8, and several GRO family members [115].

Consequently, it has been demonstrated, at least in specific experimental setups, that DDR activation—not just the presence of DNA damage itself—governs senescent states and SASP regulation [116].

Metformin, an anti-diabetic medication with diverse effects, also exerts activity on senescent cells [117]. One of its effects involves impairing the SASP of RAS-induced senescent cells without impeding proliferative arrest. This occurs through the inhibition of IKKα/β and IκB phosphorylation by metformin, preventing the nuclear translocation of p65 (RelA) [118]. Metformin negatively influences NF-κB without affecting other inflammatory pathways like p38, JNK, and IRF. The inhibition of SASP by metformin might contribute to the observed anti-aging effects post-metformin treatment [119].

5.2. IKKβ in Antitumor Immune Responses

One of the central mechanisms through which IKKβ contributes to antitumor immunity is the activation of immune cells, particularly T cells and dendritic cells (DCs) [2]. These immune cells play pivotal roles in orchestrating immune responses against cancer.

IKKβ activation in T cells enhances their responsiveness and effector functions. T cells are the foot soldiers of the immune system, responsible for recognizing and eliminating cancer cells [120]. The activation of the IKKβ/NF-κB pathway in T cells augments their activation and proliferation. This, in turn, leads to an increased pool of cytotoxic T lymphocytes (CTLs) that can effectively target and kill cancer cells [121]. Additionally, activated T cells can infiltrate the tumor microenvironment, exerting their antitumor effects directly at the site of malignancy.

T cells capable of recognizing tumor-associated antigens exhibit potential in eradicating tumors [122]. Despite their presence in cancer patients—both in circulation and within tumors—these tumor-reactive T cells often fail to prevent tumor progression over time, indicating a probable decline in their functional abilities [123]. The direct analysis of these tumor antigen-specific T cells revealed deficiencies in cytokine production and cytolytic activity. Efforts to intervene and restore T cell function have shown promise in clinical settings but frequently result in partial responses. Understanding the mechanisms underlying T cell dysfunction in cancer remains crucial for enhancing therapeutic efficacy [124].

One critical pathway for T cell function involves the activation of IκB kinase β (IKKβ) and the subsequent activation of NF-κB. In the tumor environment, T cell-NF-κB activity is often hindered, leading to reduced functionality in T cells isolated from cancer patients [125]. Recent studies conducted with mouse models exhibiting compromised NF-κB downstream of the T cell receptor (TCR) underscored the critical importance of T cell-NF-κB activation in the release of cytokines, specific targeting, and the destruction of antigens, and the in vivo eradication of tumors [126]. This indicates that reduced T cell-NF-κB activity induced by growing tumors compromises anti-tumor T cell responses, fostering a cycle favoring tumor growth. Consequently, exploring methods to stimulate T cell-intrinsic NF-κB activity becomes a compelling avenue for enhancing anti-tumor immunity [127,128].

In a study by Evaristo et al. [129], novel genetic mouse models expressing constitutively active IKKβ (caIKKβ) specifically in T cells were employed. The results demonstrated that the T cell-specific expression of caIKKβ significantly improved tumor control, even in cases of established tumors. Thus, stimulating T cell-intrinsic NF-κB appears crucial in responding to cancer growth, suggesting that the therapeutic manipulation of the IKKβ/NF-κB axis holds promise for boosting anti-tumor immune responses.

DCs are antigen-presenting cells that play a critical role in initiating and shaping antitumor immune responses. IKKβ activation in DCs enhances their ability to capture, process, and present tumor antigens to T cells [130]. This process, known as antigen presentation, is a crucial step in initiating an adaptive immune response against cancer. The activation of the IKKβ/NF-κB pathway in DCs results in the upregulated expression of co-stimulatory molecules and cytokines that are necessary for efficient T-cell priming [131].

IKKβ activation in DCs leads to the upregulation of co-stimulatory molecules, such as CD80 and CD86 [132]. These molecules interact with their corresponding receptors on

T cells, providing essential co-stimulatory signals that are required for T-cell activation and proliferation. The enhanced expression of these co-stimulatory molecules by IKKβ-activated DCs amplifies the effectiveness of T-cell priming and the subsequent antitumor immune response [133].

Baratin et al., 2015 [134] conducted a comparative analysis of the transcriptomes of NLT-DCs within the skin and their migratory counterparts located in the draining lymph nodes (LNs). Through this investigation, they identified a novel gene network that is regulated by the NF-kB pathway and is specific to migratory dendritic cells. Their findings demonstrate that the targeted deletion of IKKβ, a key activator of NF-kB, in dendritic cells, hampers the accumulation of NLT-DCs in LNs and impairs the conversion of regulatory T cells in vivo. These outcomes are closely associated with disruptions in immune tolerance and the onset of autoimmune responses.

The activation of IKKβ leads to a heightened production of proinflammatory cytokines like interleukin-12 (IL-12) and interferon-gamma (IFN-γ) by DCs [135]. These cytokines serve a pivotal function in fostering an immune environment that supports anti-tumor immunity. IL-12, for instance, can skew the immune response towards a Th1 phenotype, characterized by enhanced cytotoxic activity and IFN-γ production by T cells. IFN-γ, on the other hand, has direct antitumor effects and can activate other immune cells to contribute to tumor eradication [136].

6. Distinct Phosphorylation Events and Kinases

Serine/threonine phosphorylation by IKKα and IKKβ plays a pivotal role in regulating the NF-κB pathway. When NF-κB is inactive, it is typically sequestered in the cytoplasm by inhibitor proteins known as IκB (Inhibitor of κB) [137]. The phosphorylation of serine residues within IκB proteins, especially IκBα and IκBβ, is a critical event orchestrated by IKKβ. This phosphorylation serves as a recognition signal for the E3 ubiquitin ligase, which ubiquitinates IκBα and IκBβe [138].

Tyrosine-phosphorylated STAT dimers represent the culmination of these intricate processes. Once formed, these dimers are ready to exert their transcriptional influence. STAT dimers translocate from the cytoplasm into the cell nucleus. Inside the nucleus, they bind to specific DNA sequences known as enhancer elements or response elements in the regulatory regions of target genes [139]. This binding event is specific to the dimer's composition and the cytokine signals received.

The binding of tyrosine-phosphorylated STAT dimers to these regulatory elements serves as a molecular switch, initiating the transcription of genes associated with immune responses and inflammatory processes [140]. The regulated genes often encode critical immune effectors, signaling molecules, and cytokines, shaping the cell's response and ultimately contributing to the immune and inflammatory outcomes observed in response to cytokine stimulation. Importantly, the activation of tyrosine kinases, such as JAKs, indirectly stimulates the NF-κB pathway [141]. This occurs through the cooperative efforts of transcription factors like STATs, which activate the gene expression related to immune responses. These genes may include those encoding proinflammatory cytokines and chemokines [142].

The coordination of various signaling pathways, involving both tyrosine phosphorylation and serine/threonine phosphorylation events, ensures that the cellular response is robust, efficient, and finely tuned to the needs of the immune system [143]. For instance, in viral infection, the release of interferons triggers the activation of JAK–STAT signaling, leading to the transcription of antiviral genes [144]. At the same time, the activation of the NF-κB pathway stimulates the production of proinflammatory cytokines, which, in turn, serve to attract immune cells to the site of infection. The interplay between these signaling pathways optimizes the host's response to the viral threat, underscoring the complexity of cross-talk mechanisms in immune regulation [145].

In the non-canonical NF-κB activation pathway, IKKα primarily phosphorylates a different substrate, p100. This phosphorylation leads to a unique processing event that is crucial for the activation of non-canonical NF-κB [146].

The phosphorylation of p100 by IKKα is followed by its partial proteasomal processing. This processing event results in the generation of a smaller protein fragment, p52. Importantly, p52 contains the DNA-binding domain necessary for transcriptional activity, allowing it to function as an NF-κB transcription factor [147]. The p52 subunit combines with other proteins, like RelB, to create dimers that then move into the nucleus. This sequence of events triggers the activation of the non-canonical NF-κB pathway, which functions differently compared to the canonical pathway [148].

The mechanism behind the phosphorylation of the IκB kinase T-loop remains a significant unanswered query. Suggestions have arisen proposing the involvement of IKK kinases (IKKKs) in this process, drawing an analogy to other signaling pathways [149]. One prominent example is TAK1, known for its involvement in the JNK pathway [150]. In cell-free assays, TAK1, along with the adaptor proteins TAB 1 and TAB 2, has been identified as a TRAF6-regulated IKK activator [151]. TAB 2's role in recruiting TAK1 to the K63-linked polyubiquitin chains of upstream regulators likely induces IKKβ phosphorylation through proximity-driven mechanisms [152]. However, TAK1 is not a universal IKKK but rather functions as a regulatory module impacting the IKK activation based on stimuli and cell type. Another potential IKKK, MEKK3 [153], has been proposed as it can phosphorylate IKK in vitro, and its deficiency correlates with the reduced NF-κB activation in response to various stimulations like TNF, IL-1, or TLR. IL-1-induced NF-κB activation has been linked to MEKK3 alongside TAK1 [154]. However, it is also suggested that IKK subunits might undergo activation through trans-autophosphorylation rather than via an IKKK. Recent structural and composition analyses support these possibilities, indicating that trans-autophosphorylation and IKKK-dependent phosphorylation might work sequentially or in parallel to achieve optimal kinase activation [155].

The dimeric NF-κB transcription factor, consisting of Rel family subunits that bind to DNA, plays a pivotal role in immune and inflammatory responses. NF-κB has recently been identified as a protector against apoptosis induced by tumor necrosis factor (TNF) and various genotoxic agents [156]. Typically, NF-κB dimers are confined within the cytoplasm due to their interaction with inhibitory IκB proteins. These proteins bind to the Rel homology domain (RHD), which is responsible for the dimerization, nuclear translocation, and DNA binding functions of NF-κB/Rel proteins [157]. When cells are stimulated by proinflammatory cytokines (e.g., IL-1, TNF), bacterial lipopolysaccharide (LPS) or phorbol ester (TPA), specific IκBs (such as IκBα and IκBβ) undergo rapid phosphorylation at certain N-terminal residues. This phosphorylation leads to their subsequent polyubiquitination and degradation via the 26S proteasome [158].

The breakdown of these inhibitory IκB proteins liberates the NF-κB dimer, enabling its migration into the nucleus to commence gene transcription [159]. Altering the phosphorylation sites on IκBα through specific mutations prevents its phosphorylation, ubiquitination, and subsequent degradation. Mutants like IκBα(A32/36) act as powerful inhibitors of NF-κB activation. Efforts to comprehend the regulation of this pathway have concentrated on identifying the responsible protein kinase(s). The IκB kinase (IKK) complex, a 900 kDa protein kinase complex, phosphorylates IκBα and IκBβ at sites crucial for their ubiquitination and degradation [160]. Another protein kinase complex phosphorylating IκB has been described, but its relationship with IKK remains unclear. IKK's activity is rapidly stimulated by IL-1 or TNF and is dependent on its phosphorylation [161]. One component of the IKK complex, IKKα, an 85 kDa polypeptide containing a protein kinase domain and protein interaction motifs, has been molecularly identified. IKKα's expression is vital for NF-κB activation by various stimuli. IKKα has been isolated as a NIK-interacting protein, suggesting its role in NIK-mediated NF-κB activation [162]. While a catalytically inactive IKKα mutant can inhibit NF-κB activation, it can still interact with other IKK components to form a functional but less active IκB kinase complex.

Ubiquitination is a post-translational modification that tags proteins for degradation by the proteasome [163]. Following ubiquitination, IκBα and IκBβ are targeted for proteasomal degradation. As a result, they are rapidly degraded, freeing NF-κB from its sequestration. The released NF-κB transcription factors can subsequently migrate to the cell nucleus and initiate the transcription of genes [164].

The activation of IKKs appears to hinge on induced proximity from densely organized signaling complexes and the binding of adapter proteins like NEMO or TAB proteins. Non-degradative polyubiquitination, essential for IKK complex activation, triggers these processes [165].

TRAF6 stands as the initial ubiquitin E3 ligase identified, catalyzing K63-linked auto-ubiquitination alongside Ubc13 and Uev1A, subsequently initiating IKK activation. TRAF6 participates in numerous NF-κB-stimulating signaling pathways, including those triggered by IL-1R, TLR, TCR, RIG-I-like receptor, and DNA double-strand breaks [166]. In IL-1 signaling, TRAF6's enzymatic activity, rather than auto-ubiquitination, is essential for NF-κB activation. TRAF6 not only self-ubiquitinates but also mediates the K63-linked polyubiquitination of various pathway components like IRAK1, MALT1, and TAK1 [167]. Moreover, it is suggested that TRAF6 generates free, unanchored K63-linked polyubiquitin, serving as a docking platform in IKK activation [168]. Several K63-specific E3 ligases involved in distinct NF-κB signaling cascades were identified, such as TRAF2/5, or TRIM25 in the TNFR, IL-1R/TLR, and RIG-I pathways. Additionally, several proposed NF-κB pathway regulators are substrates of inducible K63 ubiquitination, including Bcl10, NOD2, and ELKS [169].

TNFα signaling does not rely on K63-linked ubiquitination, suggesting the importance of alternative non-degradative polyubiquitination in this pathway [170]. For instance, the linear, M1-linked ubiquitination of NEMO and RIP1 by the LUBAC complex is crucial for NF-κB activation. LUBAC is associated with the TNFR1 signaling complex. LUBAC-mediated M1-linked ubiquitination contributes to various NF-κB activations but is dispensable for B-cell receptor signaling. Mutations affecting LUBAC components were linked to immune-related disorders, showcasing their physiological relevance [171].

Multiple ubiquitin linkages seem to play roles in NF-κB signaling, adding to the complexity of ubiquitin-mediated processes [172]. E3 ligases like cIAP1 and TRIM23 catalyze distinct ubiquitin chain types, and certain proteins show modifications with various ubiquitin linkages in response to stimuli. Additionally, the mono-ubiquitination of proteins like NEMO has been shown to impact NF-κB activation. These diverse modifications coordinate specific protein interactions in NF-κB signaling pathways, although many intricacies regarding these actions remain undiscovered [173].

7. Genetic and Epigenetic Regulation

While primary genetic mutations within the IκB kinase genes themselves are relatively rare occurrences in the realm of cancer, modifications affecting their upstream regulatory elements can exert profound and far-reaching effects. Somatic mutations affecting lysine 171 within the IKBKB gene, responsible for encoding the critical activating kinase (IKKβ) in the canonical NFκB signaling pathway, were observed in splenic marginal zone lymphomas and multiple myeloma. Lysine 171 is part of a positively charged pocket crucial for interaction with the activation loop phosphate in the naturally activated kinase [174].

Their findings demonstrate that both K171E IKKβ and K171T IKKβ variants function as kinases that remain constantly active, even in the absence of activation loop phosphorylation. Through predictive modeling and biochemical investigations, we elucidate why mutations in a positively charged residue within the cationic pocket of a kinase reliant on activation loop phosphorylation lead to persistent activation [175].

Utilizing transcription activator-like effector nuclease (TALEN)-based knock-in mutagenesis, we present evidence from a B lymphoid context indicating the involvement of K171E IKKβ in the development of lymphomas. Genetic mutations in TRAF proteins have the potential to engender the persistent and aberrant activation of the NF-κB pathway, a

phenomenon observed in various cancer types [176]. A notable instance is the frequent occurrence of mutations in the TRAF3 gene within the context of multiple myeloma, which leads to a chronic state of NF-κB pathway activation. The discernment of such genetic anomalies, often made possible through advanced techniques like whole-genome sequencing, not only advances our comprehension of the multifaceted terrain of cancer biology but also unveils promising therapeutic targets for potential intervention [177].

Multiple mechanisms contribute to NF-κB transcriptional regulation beyond its binding to κB regulatory elements in DNA. In non-neuronal cells, the signaling elements of the NF-κB pathway participate in gene expression control through histone phosphorylation and acetylation in coordination with histone deacetylases (HDACs). The IκB protein variant, IκBα, independently governs transcription by engaging with HDAC1 and HDAC3. Additionally, the IKKα subunit operates distinctly from the IKK complex, influencing the cytokine-induced gene expression by modulating histone H3 phosphorylation [178]. These investigations reveal the novel functions of NF-κB signaling components, like IκBα and IKKα, in autonomously regulating the chromatin structure and gene expression from NF-κB's direct DNA binding.

Previously formed memories are prone to disruption immediately post-recall, necessitating reconsolidation. While protein translation mechanisms are acknowledged for their role in memory reconsolidation, research into gene transcription mechanisms remains relatively limited in this context [179].

An interesting study [180] indicated that the retrieval of contextual conditioned fear memories activates the NF-κB pathway, regulating histone H3 phosphorylation and acetylation at specific gene promoters in the hippocampus, particularly mediated by IKKα rather than the NF-κB DNA-binding complex. Behaviorally, inhibiting IKKα's control over a chromatin structure or NF-κB DNA-binding complex activity results in impairments in fear memory reconsolidation. Elevated histone acetylation offsets this memory deficit when faced with the IKK blockade. These results offer new insights into IKK-mediated transcriptional mechanisms in the hippocampus essential for memory reconsolidation.

MicroRNAs (miRNAs) are another essential post-transcriptional regulator of IκB kinases [181]. One example is miR-21, a well-known oncogenic miRNA that plays a role in regulating the NF-κB pathway in various cancers. In certain scenarios, miR-21 targets PTEN (Phosphatase and Tensin Homolog), an inhibitor of the NF-κB pathway. This targeting leads to increased NF-κB activity in cancer cells, which, in turn, promotes cell survival, proliferation, and resistance to apoptosis [182].

8. Conclusions

IκB kinases, IKKα and IKKβ, represent a multifaceted and pivotal aspect of cancer biology, serving as central players in inflammation, immune responses, and tumorigenesis. Their dual role in cancer, which is shaped by myriad factors including distinct phosphorylation events, genetic and epigenetic regulation, and therapeutic implications, underscores the intricacies of their functions.

The potential of IκB kinases as therapeutic targets in cancer therapy is a burgeoning field. Precision medicine, which aims to individualize the treatment strategies based on genetic and molecular profiles, is at the forefront of this effort. While challenges such as resistance to IKK inhibitors persist, the development of combinatorial therapies and immunomodulation strategies offers hope for overcoming these obstacles.

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