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Review Article

UNLOCKING THE THERAPEUTIC POTENTIAL: EXPLORING NF-κB AS A VIABLE TARGET FOR DIVERSE PHARMACOLOGICAL APPROACHES

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ABSTRACT

NF-κB is a vital transcription factor that responds to diverse stimuli like cytokines, infections, and stress. It forms different dimers, binds to specific DNA sequences, and regulates gene expression. It operates through two pathways: canonical (for inflammation and immunity) and non-canonical (for specific processes). These pathways tightly control activity of NF-κB and impacting gene expression. Aberrant NF-κB activation is linked to cancer and other diseases, making it a potential therapeutic target. This review explores the role of NF-κB in disease and its therapeutic potential in various conditions. Intricate signal transduction processes lead to NF-κB activation by phosphorylating IκB proteins, allowing NF-κB dimers to enter the nucleus and influence gene expression. This dynamic regulation involves co-activators and interactions with other transcription factors, shaping complex gene expression programs.

Understanding the multifaceted functions off NF-κB is crucial as its deregulation is associated with a range of diseases, including cancer, autoimmune disorders, and inflammatory conditions. Exploring recent studies offers insights into potential therapeutic strategies aimed at modulating NF-κB activity to restore health and combat various pathological conditions. This Comprehensive review is based on the role of NF-κB in disease pathogenesis and therapeutic implications.

Keywords: NF-κB, Canonical pathway, Non-canonical pathway, Autoimmune disorder and Inflammatory conditions

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INTRODUCTION

NF-κB, denoted as the nuclear factor kappa-light-chain-enhancer of activated B cells, represents a pivotal transcription factor that becomes active in response to various stimuli, including cytokines, viral infections, and cellular stressors like hypoxia [1]. The intricate NF-κB network comprises a quintet of protein monomers, namely p65/RelA, RelB, cRel, p50, and p52. These monomers possess the ability to join forces, forming either identical or mixed dimers and exhibiting diverse affinities towards DNA binding [2]. Upon receiving external signals, cells undergo signal transduction processes that culminate in the phosphorylation of IκB, facilitating the release and nuclear translocation of NF-κB heterodimers to regulate gene expression [3].

The NF-κB family of transcription factors controls gene transcription by binding to specific DNA response elements in promoters or enhancers. These response elements, called B sites or B DNA, share a common consensus sequence. While the consensus sequence is well-defined, NF-κB dimers can also bind to DNA sequences that deviate from this consensus. X-ray crystal structures have provided insights into the molecular basis of target selection *in vitro*. However, *in vivo*, NF-κB dimers face additional challenges in selectively binding to DNA due to the complex chromatin environment [4].

NF-κB regulates gene expression through two distinct pathways: canonical and non-canonical. The canonical pathway responds to external stimuli and is linked to inflammation, immune response, cell processes, and survival. Activation of the canonical pathway relies on phosphorylation-dependent activation of the IKKs complex. In contrast, the non-canonical NF-κB pathway is selectively activated by a limited number of TNF superfamily receptors, suggesting a more specialized role for this branch of the pathway in biological processes [5]. The tightly orchestrated pathways in place exert stringent control over the levels and dynamics of the transcriptionally active NF-κB dimer repertoire, both in a constitutive manner and in response to external stimuli. Consequently, these pathways govern extensive programs of gene expression by engaging co-activators or collaborating with other transcription factors. The activation pathways employ multiple mechanisms to effectively modulate NF-κB activity, encompassing the degradation of IκB inhibitor proteins, the processing of NF-κB precursor proteins, and the expression of NF-κB monomer proteins [2]. Excessive stimulation and overactive engagement of the NF-κB pathway significantly propel the relentless advancement of cancer, thereby presenting a grave and formidable menace to the well-being of humanity [6]. When the body faces an infection or injury, NF-κB gets activated and helps initiate the body's defense mechanisms. It triggers the production of molecules like cytokines, which are important for the immune response. However, if NF-κB becomes overactive or stays activated for a long time, it can lead to chronic inflammation and contribute to various health issues, including cancer. It was observed that ZnO-NP (zinc oxide nanoparticles) has a strong binding affinity with NF-κB, suggesting a potential interaction between these nanoparticles and the protein. This interaction may have implications for the regulation of inflammation and immune responses in the body [7].

The current review focuses on the role of NF-κB in disease induction as well as healing. Moreover, this article includes the recent studies held on NF-κB.

Search methodology

This review encompasses information collected from peer-reviewed journal articles sourced from databases like PubMed, Google Scholar, Nature Journal, and Science Direct, covering the period between 1998 and 2023. Keywords such as "NF-κB," "Family of NF-κB," "Pathways," "Clinical Uses," "Role of NF-κB in Disease," "Therapeutic Applications of NF-κB" and "Recent Studies on NF-κB" were employed during the search process. The review offers a comprehensive understanding of the multifaceted functions of NF-κB and the latest insights into its potential therapeutic applications. Additionally, it delves into the structure and composition of the NF-κB family, shedding light on the complexities of its DNA binding and interaction with other cellular components.

NF-κB family

The various constituents comprising the NF-κB protein, assemblage-specifically RelA (p65), RelB, c-Rel, p50 (derived from p105 precursor), p52 (derived from p100 precursor), and Relish-converge harmoniously via a universally preserved domain for DNA binding and dimerization, recognized as the Rel homology region (RHR). As depicted in fig. 1, this RHR equips them with the capability to form either homo-or heterodimers. Notably, RelA (p65), RelB, and c-Rel stand out by possessing a Trans-activation domain (TAD) at their C-termini, which empowers them to activate the expression of target genes. In contrast, p50 (p105 precursor), p52 (p100 precursor), and Relish adopt an alternative structure characterized by an extensive Ankyrin repeat-containing domain (ARD) at their C-termini. This distinct arrangement limits their capacity to independently trigger target gene expression as homodimers [8]. Collectively, they possess an revolutionaries conserved amino-terminal Rel homology domain (RHD) spanning 300 amino acids. Intricate segments embedded within this RHD serve as prerequisites for pivotal functions encompassing dimerization, affinity for DNA engagement, affinity for IkB interaction, and facilitation of nuclear migration [9].

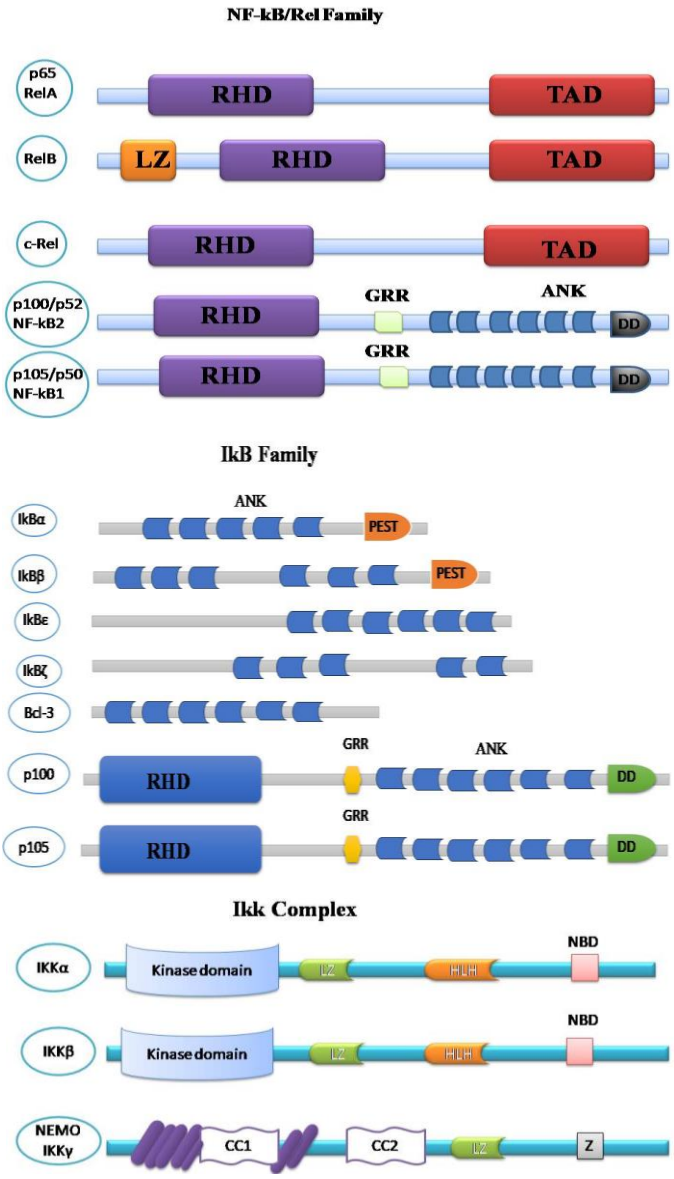

Fig. 1: NF-κB family consists of five members: p65 (RelA), RelB, c-Rel, p100 (p52), and p105 (p50)

These members play crucial roles in cellular processes through their involvement in signal transduction and gene expression regulation. The structure of each subunit is characterized by distinct domains, including the REL homology domain (RHD), Trans-activation domain (TAD), Aneurin repeat domain (Ank), death domain (DD), and Leucine zipper domain (LZ). In the case of p50 and p52, which are generated from the processing of p105 and p100, respectively, C-terminal residues are cleaved, producing the mature forms. To regulate the activity of NF-κB, phosphorylation events are crucial. Phosphorylation sites are distributed across the subunits and are associated with specific structural motifs. These phosphorylation events modulate NF-κB's function by influencing its interaction with other proteins, its nuclear translocation, and its ability to bind to DNA and initiate gene transcription. It's worth noting that the location of phosphorylation sites varies across the subunits and is linked to their respective structural motifs. The phosphorylation sites have been identified based on the human protein sequence. Overall, the phosphorylation of NF-κB subunits is a key mechanism that fine-tunes their activity and function in cellular processes [9].

Structure of NF-κB

Interconnected at their core, all NF-κB proteins share a fundamental trait: an N-terminal region termed the Rel homology domain (RHD). This domain serves as a versatile hub, encompassing the ability to bind to DNA and facilitate dimerization. Anchored within this domain is a Nuclear localization sequence (NLS), a critical ticket that grants these proteins access to the nucleus. Once within this inner sanctum, the RHD empowers them to forge connections with specific DNA sites known as κB sites. These interactions, in turn, bestow upon them the authority to govern the initiation or suppression of transcription for select target genes, thus molding the intricate tapestry of biological outcomes.

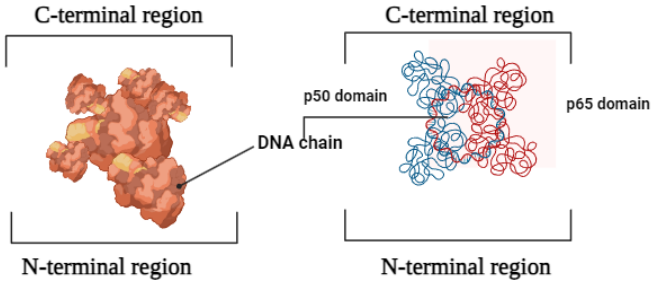

Fig. 2: Structure of NF-κB: NF-κB, typically formed as a P50-P65 dimer, acts as a transcription factor. Its N-terminal regions make specific DNA contacts, while C-terminal regions facilitate dimerization and stabilize DNA binding, resembling a molecular vise for precise gene regulation. This versatile molecule orchestrates diverse cellular responses in reaction to various stimuli [10]

The NF-κB superfamily can be categorized into two subfamilies: the NF-κB proteins, including vertebrate p100 and p105, and the Rel proteins comprising RelA, RelB, and c-Rel [11].

Consequently, it encompasses a multitude of NF-κB proteins, which predominantly exhibit an exhaustive array of combinations by engaging in the assembly of both homodimers and heterodimers, each bearing distinct specificities for DNA target sites. The demarcation between these two subfamilies can be traced through phylogenetic analysis, achieved via the alignment of their Rel homology domains (RHDs) and the sequences extending towards the C-terminal of RHDs. In finer detail, NF-κB proteins are characterized by the inclusion of C-terminal inhibitory ankyrin (ANK) repeat domains, whereas Rel proteins boast C-terminal trans-activation domains.

Origins of NF-κB generation mechanisms

The assembly of NF-κB dimeric transcription factors involves the combination of five monomers, as illustrated in fig. 4. Within the realm of potential dimers, twelve are anticipated to interact with the DNA κB element. In contrast, three dimers (RelB: RelB, RelB: RelA, and RelB: cRel) intertwine with low affinity, resulting in their inability to bind to DNA [12].

Among the 12 dimers capable of binding to DNA, 9 encompass at least one activator protein-RelA, cRel, or RelB-where RelA exhibits the highest potency and RelB the lowest. Generally, these dimers serve as transcriptional activators. Conversely, the remaining three dimers—the abundant p50:p50 homodimer and the less prevalent p52:p52 and p50:p52 homodimers and heterodimers-might act as activators when in concert with co-activators such as Bcl3 and IκBζ.

The exploration of mechanisms orchestrating the genesis of NF-κB dimers has garnered recent attention, signifying their significance in comprehending the diverse NF-κB dimer repertoires across various cell types during differentiation and development. Notably, instances of dimer repertoire shifts have been documented; for instance, in B cells, the predominant RelA: p50 configuration during the pre-B stage shifts to a prevailing cRel: p50 state in mature B-lymphoid cells. Furthermore, terminally differentiated B cells exhibit pronounced up-regulation of RelB and p52 [13].

In the intricate tapestry of monocyte lineages, the RelA: p50 dimer takes precedence. However, a unique scenario emerges in GM-CSF-derived inflammatory dendritic cells, where an atypical character comes to the fore-the RelB: p50 dimer. The genesis of this exceptional dimer has been unveiled to rely on two pivotal elements: the sustained high expression of RelB and the consequential activation of NIK [14].

ANK repeats, present either within the architecture of NF-κB proteins themselves or within a distinct cohort of NF-κB inhibitors (IκBs), intricately govern the precise cellular localization of NF-κB. Through their interaction with the Rel homology domain (RHD), these ANK repeats confine NF-κB to the cytoplasmic domain. Activation of the pathway by a suitable upstream signal triggers the degradation of the ANK repeat inhibitor, thereby granting the NF-κB dimer unrestricted access to the nucleus for DNA binding [14, 15]. Notably, NF-κB p100 and p105 proteins also possess a C-terminal death domain (DD), a pivotal feature facilitating interactions with other components of the DD superfamily. These interactions often serve as adaptors in signaling pathways or function as entities that recruit other proteins into intricate signaling assemblies [15].

NF-kB signaling illuminating pathways

Canonical NF-κB signaling pathway

The canonical NF-κB signaling pathway, also known as the NEMO-dependent pathway, involves the activation of the NEMO-associated IKK complex. This complex consists of the scaffold protein NEMO and two IκB kinases (IKK1/2). Activation of the IKK complex occurs through phosphorylation of serines in the activation T-loop, mediated by NEMO-dependent mechanisms. NEMO facilitates the multiplication of IKK subunits, allowing for trans-auto phosphorylation and activation [16, 17]. It also recruits upstream kinases like TAK1, leading to mutual activation and positive feedback. NEMO's ubiquitin-binding domain enables recruitment of IKK to non-degradative K63-linked ubiquity chains, characteristic of inflammatory signaling.

Additionally, NEMO itself can be ubiquitinated, particularly by linear ubiquitin chains produced by the LUBAC enzyme, facilitating the formation of transient signalsomes. Various inflammatory cytokines, pathogen-associated molecular patterns (PAMPs), or immune stimulatory signals can activate the NEMO-containing complex, resulting in the phosphorylation-dependent activation of IKK and subsequent degradation of IκB proteins. The degradation of IκBs releases NF-κB dimers, allowing them to accumulate in the nucleus and regulate gene expression. NEMO acts as a scaffold between IKK and IκBα, directing IKK activity towards IκBα. Negative feedback loops are essential for controlling NF-κB activity. IκBα, one of the target genes regulated by NF-κB, can translocate to the nucleus, bind to NF-κB, and inhibit its activity, leading to its cytosolic trafficking. This negative feedback loop prevents excessive NF-κB activity and enables reactivation when IKK activity persists. Another negative feedback mechanism involves IκBδ, which is induced by nuclear NF-κB and acts as an IκB, attenuating persistent signals. Other feedback mechanisms, such as IκBε and A20, contribute to the complex dynamics of NF-κB signaling. TNF, a cytokine involved in the pathway, exhibits both negative and positive feedback effects, with A20 playing a crucial role in integrating prior exposure to render the NF-κB pathway less sensitive to subsequent stimuli [18, 19].

Non-canonical NF-κB pathway

The non-canonical NF-κB pathway relies on NIK (NF-kB-inducing kinase) as a central signaling component. NIK is a mitogen-associated protein 3 kinase (MAP3K) that was initially thought to activate NF-κB in response to cytokines like TNF-α and IL-1. However, under normal physiological conditions, NIK is dispensable for NF-κB activation by TNF-α and IL-1. NIK is essential for the induction of p100 processing, which is a key step in the non-canonical NF-κB pathway. It activates IKKa, which phosphorylates and processes p100. NIK regulation involves dynamic ubiquitination and proteasome degradation mediated by TRAF3, and the TRAF-cIAP E3 complex serves as a NIK ubiquitin ligase. Additionally, some viral oncoproteins, like Tax and vFLIP, can induce p100 processing independently of NIK by interacting with p100 and IKKa, potentially activating IKKa through different mechanisms [20, 21].

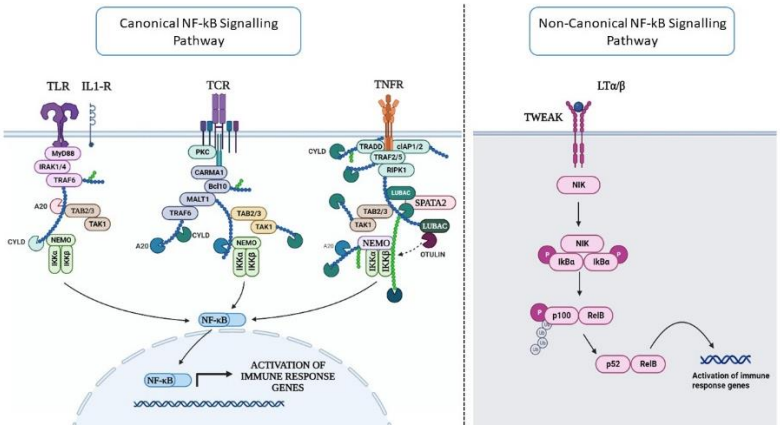

Fig. 3: Canonical and Non-Canonical NF-κB pathway, the canonical NF-κB pathway is activated by a wide range of stimuli, leading to the activation of IKK and subsequent translocation of p50/p65 dimers to the nucleus. In contrast, the non-canonical NF-κB pathway is activated by a specific subset of signals, leading to the processing of p100 and the formation of RelB/p52 dimers that regulate a distinct set of target genes. Both pathways play crucial roles in immune responses and inflammation, but they are initiated by different signals and involve different NF-κB subunits

Other signalling pathway

NF-κB regulation is complex, involving activation through canonical cytokine pathways and multiple signal transduction cascades related to cardiac hypertrophy and oxidative stress responses. It serves as a signaling integrator, interacting with MEKKs, IKK complex, and other factors to modulate gene expression in the heart [22]. MAPK cascades exhibit a high degree of evolutionary conservation across all eukaryotic cells. These kinases play a pivotal role in mediating the transmission of diverse extracellular signals to a spectrum of cellular processes, including growth, differentiation, apoptosis, and the inflammatory response. The activation of MAPK cascades, subsequently leading to the activation of NF-κB, has been comprehensively characterized within the cells of the mammalian immune system. NF-κB assumes a central role in the regulation of inflammation by governing the expression of genes responsible for encoding pro-inflammatory cytokines, chemokines, and inducible enzymes like inducible nitric oxide synthase (iNOS) in the immune cells of mammals.

The initiation of cell signaling pathways, including MAPK and NF-κB, in response to CpG oligodeoxynucleotides (CpG ODN), has been documented across various cell types. For instance, CpG ODN stimulation induces the production of Th1-like pro-inflammatory cytokines, interferons, and chemokines by plasmacytoid dendritic cells (PDCs), natural killer (NK) cells, and B cells [23]. Post-translational modifications of NF-κB, specifically through phosphorylation events, significantly enhance its capacity for transactivation. While there is substantial knowledge regarding the kinases responsible for phosphorylating NF-κB, the understanding of the phosphatases responsible for its dephosphorylation has remained limited. Through the application of a genome-scale siRNA screen, we have successfully identified the WIP1 phosphatase as a negative regulator of NF-κB signaling.

The regulatory influence exerted by WIP1 on NF-κB is observed in both p38-dependent and p38-independent manners. Overexpression of WIP1 leads to a dose-dependent reduction in NF-κB activation, whereas WIP1 knockdown results in heightened NF-κB activity. We have demonstrated that WIP1 directly acts as a phosphatase for Serine 536 on the p65 subunit of NF-κB. The phosphorylation of Serine 536 is widely recognized as crucial for the transactivation function of p65 since it is essential for the recruitment of the transcriptional co-activator p300. Consequently, WIP1-mediated regulation of p65 has a direct impact on the binding of NF-κB to p300 and, consequently, chromatin remodelling [24].

Regulation of NF-κB Pathway by TNF family

The signaling pathways of TNF family receptors and their role in NF-κB activation are complex and diverse. While some key factors involved in these pathways have been identified, there is still much to be understood, especially regarding the specific roles of TRAF proteins and atypical signaling mechanisms. Additionally, the function of regulatory ubiquitination in NF-κB signaling remains controversial and requires further investigation. It is crucial to approach these topics with caution and continue research to gain a comprehensive understanding of TNF family receptor signaling and NF-κB activation [25]. The regulation of NF-κB subunit phosphorylation introduces significant complexity to the control of these essential transcription factors, stemming from the multitude of phosphorylation sites and the potential involvement of multiple kinases targeting single sites. This intricacy is compounded by the generation of diverse modified NF-κB protein pools resulting from phosphorylation at different sites. This diversity underlies gene-specific impacts of NF-κB phosphorylation and context-dependent functional outcomes. The interplay of identified and unknown phosphorylation sites might collectively dictate the selectivity of NF-κB's transcriptional activity effects. While the DNA-binding site sequence influences the outcome of specific phosphorylation events, the interaction of phosphorylated NF-κB subunits with other factors plays an equally crucial role in determining functional outcomes [26].

Negative regulation of canonical NF-κB involves feedback mechanisms mediated by IκBα, IκBβ, and IκBε proteins that drive NF-κB dimers out of the nucleus, terminating transcriptional activity and preventing prolonged target gene expression. Canonical NF-κB is positively regulated through TRAF-mediated polyubiquitination and LUBAC-catalyzed linear (M1-linked) ubiquitination, involving different types of ubiquitin chains (K48-linked for degradation, M1, and K63-linked for signal transduction). Ubiquitination is a critical post-translational modification with over 600 E3 ligases in the human genome, influencing various cellular and immune response

processes [5]. The identification of kinase NIK has illuminated its central function in mediating NF-κB activation through Traf2, thereby harmonizing the signaling pathways of TNF/NGF and interleukin-1 receptors. This is underscored by NIK's adeptness in obstructing NF-κB induction across diverse receptors and their associated adaptors [27].

Coregulators of NF-κB pathway through chromatin modulation

NF-κB binding to DNA isn't enough for gene transcription. Coregulators, such as coactivators and corepressors, play vital roles in NF-κB signaling. AEG-1 acts as a coactivator, translocating to the nucleus upon TNFα treatment to facilitate NF-κB-mediated transcription. In contrast, ING4 is a corepressor, recruited to κB promoters simultaneously with NF-κB, leading to reduced p65 phosphorylation, decreased p300 recruitment, histone deacetylation, and increased HDAC-1 levels at these promoters [28, 29].

NF-κB transactivation termination

Properly ending NF-κB transcriptional activity is crucial to return it to its inactive state in the cytoplasm, ensuring the cell remains responsive to future stimuli. This is achieved through two main mechanisms:

1. NF-κB is shuttled back to the cytoplasm by newly synthesized IκBs, creating a negative feedback loop.

2. NF-κB activity is terminated in the nucleus through ubiquitination-dependent degradation of its subunits [30, 31].

These processes help maintain cellular responsiveness to stimuli. The most prevalent and well-understood mode of NF-κB regulation is the IκB negative feedback loop. NF-κB activation involves IκB degradation, allowing NF-κB complexes to enter the nucleus. However, as soon as NF-κB enters the nucleus and binds to its promoter, transcription of the NF-κB IA gene (encoding IκBα) is induced, leading to the production of newly synthesized IκBα. These IκBα molecules then enter the nucleus, disengage NF-κB from DNA, and transport it back to the cytoplasm. This negative feedback mechanism also applies to IκBβ and IκBε, albeit with different degradation and resynthesis rates. An oncoprotein called p28GANK was found to restrain NF-κB by retaining it in the cytoplasm through p65 nuclear export, dependent on ankyrin repeats in p28GANK, a common feature among IκB family proteins. This cycle of induction and suppression of IκB leads to oscillations in nuclear NF-κB, potentially influencing the expression pattern of specific NF-κB target genes [32, 33].

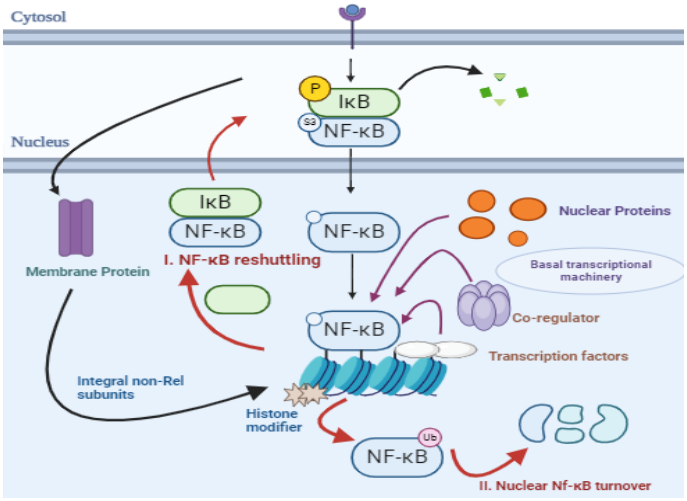

Fig. 4: The regulation of NF-κB within the nucleus is a highly sophisticated process; once NF-κB gains access to the nucleus, its transcriptional activity undergoes meticulous control by various nuclear regulators, represented in blue. These regulators include non-Rel subunits like RPS3 (S3) found within the NF-κB complex, proteins originally localized in the nucleus or trans-located from the cell membrane, as well as other transcription factors and chromatin modifiers, all of which play essential roles in regulating function off NF-κB. There are two distinct mechanisms, highlighted in red, that are employed to terminate the transactivation of NF-κB. The first pathway involves IκB-mediated relocation, which returns NF-κB to the cytoplasm. The second mechanism relies on ubiquitination-dependent nuclear degradation to effectively put an end to nuclear activity of NF-κB [34]

Dynamics of NF-κB via imaging

Live cell imaging has significantly advanced our understanding of the NF-κB system. It has unveiled the intricate dynamics of NF-κB activation in response to various stimuli, shedding light on its role in immune responses and inflammation by controlling cytokine and chemokine production. These studies have demonstrated that NF-κB activation leads to diverse gene expression patterns influenced by factors such as oscillations, stimulus-specific dynamics, and even chromatin modifications. Single-cell assays and RNA measurements have further emphasized the importance of NF-κB dynamics in regulating gene expression. While challenges remain, this dynamic perspective offers valuable insights into the complex relationship between NF-κB dynamics and transcriptional control, paving the way for deeper exploration of this vital signaling pathway [35].

Impact of NF-κB on disease pathogenesis

In inflammation

NF-κB is a crucial regulator of pro-inflammatory gene expression, inducing cytokines, chemokines, and inflammatory mediators in diseases like rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis, psoriasis, and asthma. Increased NF-κB activity, along with elevated pro-inflammatory cytokine production, is detected in affected tissues. Genetic alterations in NF-κB and IκB have not been directly linked, suggesting dysregulation of NF-κB activation mechanisms may contribute to its aberrant activity in these diseases [36]. NF-κB has been viewed as an attractive target for new anti-inflammatory medications. However, genetic studies in mice have revealed that role of NF-κB is complex, as it can both promote and inhibit inflammation through various mechanisms, affecting leukocyte activity and apoptosis. Additionally, NF-κB plays a part in regulating the intensity and duration of the inflammatory response. To determine the potential of NF-κB as a therapeutic target for inflammatory diseases, further investigations are required to understand its diverse functions in different contexts [37].

In cancer

NF-κB and STAT3 each regulate numerous genes involved in cell proliferation, survival, stress responses, and immune functions, with overlapping target genes and complex positive and negative

crosstalk between the two transcription factors [38]**.** In the mouse DEN model, hepatocyte death caused by DEN leads to the release of IL-1α, triggering NF-κB signalling in Kupffer cells. These activated Kupffer cells then produce a variety of cytokines and growth factors, including IL-6 [39]. The released IL-6 acts on hepatocytes, activating STAT3 in them. The genes activated by STAT3 play a crucial role in compensatory hepatocyte proliferation and contribute to the development of liver tumorigenesis. This interconnected signalling pathway demonstrates the complex interplay between NF-κB, IL-6/STAT3, and hepatocyte responses in liver injury and tumour formation [40]. Scientific evidence supports the anticancer role of zinc compounds that target NF-κB. Zinc inhibits NF-κB activation through zinc finger-containing proteins, reversible inhibition of cyclic nucleotide phosphodiesterase (PDE), and increased expression of peroxisome proliferator-activated receptor (PPAR). This inhibits inflammatory reactions and free radical generation. Zinc also eliminates cancer-causing mutant forms and inhibits cancer cell migration, particularly when chelated. This research suggests that chelated zinc compounds like zinc acetate and zinc orotate have potential as effective cancer treatments, paving the way for novel chemotherapy options [41].

In congenital diaphragmatic hernia (CDH)

CDH affects new-born's (1 in 2500 births), causing lung issues. We studied CDH's lung development problem linked to NF-κB-related inflammation. Both rat and human CDH lungs showed active NF-κB during abnormal development, especially in airway linings. Dexamethasone tested as, an anti-inflammatory drug on rat lung tissue affected by CDH. It improved lung growth and normalized NF-κB activity. Curcumenol, another substance, had a similar positive effect on lung development and NF-κB. In pregnant rats with CDH foetuses, giving dexamethasone improved lung growth and normalized NF-κB activity in the baby rats. This indicates excessive activity off NF-κB in CDH lungs of rats and humans. Treatments like dexamethasone or NF-κB-targeting substances could potentially aid lung development in CDH cases. Further research is needed for confirmation [42].

In drug addiction

NF-κB, a key regulator of numerous neural pathways involving neurotransmission, hormonal responses, and chemotactic signals, appears to play a vital role in the intricate functioning of neural systems impacted by chronic alcohol abuse. This inference is supported by insightful findings from microarray analyses of post-mortem human brain samples. Notably, NF-κB activity exhibits complex interactions with diverse neurotransmitter and signaling systems in the brain, contributing to the immediate effects of alcohol consumption. Over time, alcoholism induces adaptive changes in neuronal function, which likely stem from alterations in gene expression, as suggested by the work of Nestler and Aghajanian in 1997. Moreover, intriguing discoveries from microarray studies reveal distinct expression patterns of NF-κB in the brains of individuals afflicted with alcohol addiction [43]. Furthermore, NF-κB emerges as a mediator of withdrawal symptoms arising from prolonged morphine administration, as demonstrated by studies utilizing NF-κB inhibitors to mitigate precipitated withdrawal behavior in rodents [44]. Equally compelling are analogous observations in an *in vitro* model measuring guinea pig isolated ileum contractions [45].

These collective findings underscore the multifaceted role of NF-κB in both alcohol-related neural adaptations and opioid withdrawal processes, paving the way for deeper insights into potential therapeutic interventions for alcoholism and substance abuse disorders. The potent role played by nuclear factor kappa B in drug addiction is demonstrated by their wide distribution of mRNA expression and protein throughout the brain, such as locus coeruleus, amygdala, stria terminals and ventral tegmental area in alcohol dependence-induced withdrawal [46, 47].

In neurotoxicity

Specifically, prolonged exposure to alcohol increases NF-κB DNA-binding levels in conjunction with elevated cytokine expression [48]. However, the majority of preclinical research on NF-κB has examined its role in neurotoxicity [49], particularly when induced by high concentrations of alcohol[50]. Conversely, alcohol intake is attenuated by inhibition of IKK, a kinase involved in NF-κB activation. Taken together, these findings support the notion that NF-κB positively modulates alcohol dependence-induced withdrawal syndrome in rodents. The deleterious effect of chronic exposure of alcohol on NF-κB function and whether NF-κB activity contributes to the behavioural changes in alcohol addicts still obscure [51].

In allergic Asthma

NF-κB, a widely distributed transcription factor, becomes activated subsequent to its phosphorylation, facilitated by IκB kinase. This activation leads to the dissociation of its inhibitor, kappa-B subunit alpha (IκBα). Notably, NF-κB plays a pivotal role in the development of pulmonary inflammation by inducing the expression of important mediators, namely, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Furthermore, it is worth emphasizing that iNOS and COX-2 themselves participate in the activation of NF-κB. Consequently, NF-κB can subsequently trigger the production of other inflammatory mediators and cellular responses. Hence, it becomes evident that the regulation of iNOS and COX-2 is imperative for the effective control of inflammation within the pulmonary and airway regions [52].

Non-alcoholic fatty liver disease

Long-term exposure of mice to a high-fat diet can lead to liver issues, including a condition called steatosis, where the liver accumulates excess fat. This process can cause dysfunction in the liver's cellular powerhouses, the mitochondria, due to the impact of reactive oxygen species (ROS), resulting in impaired fatty acid metabolism and increased damage. Steatosis itself can be triggered by various factors, such as high levels of fatty acids and glucose, insulin resistance, and increased fat synthesis. Importantly, this condition is closely associated with liver inflammation, which is partly regulated by a protein called NF-κB. NF-κB acts as a genetic switch, controlling the genes responsible for inflammation and immune responses in the liver, further complicating the health of the organ due to a high-fat diet's long-term effects [53].

Suppression of the NF-κB signalling pathway by viruses

Viruses employ various strategies to inhibit the activation of NF-κB, a critical transcription factor involved in the host's antiviral response. These strategies primarily target different components of the NF-κB signaling pathway. Some viruses reduce the production of mRNA and protein levels of receptors and adaptor proteins, such as RIG-I and MAVS, thereby hindering NF-κB activation. Others employ a common viral strategy of degradation through the proteasome pathway, targeting proteins like MyD88, TRIF, TRAF6, and MAVS, effectively blocking NF-κB signaling. Additionally, viruses can interfere with the functions of these proteins through direct interactions, disrupting the NF-κB pathway. Some viruses inhibit IKKs, essential for IκBα phosphorylation, and prevent NF-κB activation. Viral proteins also target IκBα, either by modulating posttranslational modifications or preventing its degradation. Lastly, viruses can prevent p50/p65 dimer from entering the nucleus by binding to these subunits or blocking nuclear transport receptors. These intricate strategies collectively enable viruses to evade the host's immune response by inhibiting NF-κB transcriptional activity at various stages of the signaling cascade [54].

Targets for inhibition of NF-κB

The NF-κB signaling cascade, crucial in various disease conditions, is primarily initiated at the cell membrane through a range of receptors, including TNFR, IL1R, TLR, TCR, BCR, growth factor receptors, and TNFRSF members like RANK, Fn14, and BAFF receptors. While these cell surface receptors are ideal targets for inhibiting these pathways, they primarily involve protein-protein interactions and lack binding sites for small molecules, making them suitable for antibody-based therapies, siRNA, oligonucleotides, or peptides. Currently, the market offers biologics like monoclonal antibodies and recombinant/fusion proteins to target these

receptors, such as TNF blockers and IL1R antagonists. Small molecule inhibitors are less common, with limited success in clinical trials, exemplified by TLR4 and TLR7/8/9 antagonists and a preclinical TNFR small molecule inhibitor. The challenges and prospects of targeting these membrane receptors in therapeutic interventions are diverse, reflecting the complexity of NF-κB signaling modulation in disease contexts [55].

NF-κB as a target for various therapies

The Role of NF-κB in inflammatory diseases like cancer and autoimmune conditions is well-known, and ongoing research underscores its therapeutic potential across various illnesses. The first study of its kind investigates NF-κB activation pathways in preeclamptic placentas, revealing insights into potential mechanisms contributing to the disorder [56].

Table 1: Recently studied various NFF-kB inhibitors

NF-kB inhibitors	Target	Disease	Reference
Compound 51	• Suppress NF-κB activation • Reducing the levels of pro-inflammatory cytokines • Mitigating oxidative stress	Promising candidate for the development of anti-inflammatory drugs	[57]
BAY 11-7085	• Inhibitor of nuclear factor kappa B (NF-κB)	Alcohol dependence	[58]
B022	• Inhibitor of NF-κB	Liver inflammation and steatosis	[59, 60]
NIK SMI1 (small molecule inhibitor 1)	• Inhibition of BAFF-induced B-cell survival • Inhibits NIK in immune cells l	Lupus	[61]
dCp33 (NIK Specific Inhibitor Compound 33)	• Specifically inhibits non-canonical NF-κB pathway • Prevented bone loss	Osteoporosis	[62]
N-Acetyl-3-aminopyrazoles	• Selective inhibitor of NIK with IC50	Cancer	[63]
Dioscin	• Improve the expression of T3, T4, FT3, FT4, and TSH hormones • Down-regulate the levels of TGAb, TPOAb and TRAb • Inhibition of mTOR and TLR4/NF-κBsignaling pathways	Autoimmune thyroiditis (AIT)	[64]
Sirtuin 6 (SIRT6)	• Suppress the production of Reactive oxygen species (ROS) through deacetylation of NRF2, which results in NRF2 activation. • inhibit the inflammatory process through the downregulation of NF-kB transcription	Coronary artery disease (CAD)	[65]
MSC-Exos	• Facilitated M2 polarization via targating MAPK/NF-κb pathway • Reduced the M1-M2 polarization ratio	Facial nerve (FN) injury	[66]
Betulin	• Targeting MAPK, NF-κB, and Nrf2 Signalling Pathway	• Cardiovascular and liver diseases, cancer, diabetes, oxidative stress, and inflammation.	[67]
Trichostatin A (TSA)	• TSA treatment in BMMCs suppressed NF-κB expression, indicating that histone acetylation could modulate TNF-α and IL-13 secretion via NF-κB.	• Foot-and-mouth disease (FMD)	[68]

CONCLUSION

In conclusion, NF-κB, or nuclear factor kappa-light-chain-enhancer of activated B cells, is a multifaceted transcription factor that plays a pivotal role in cellular responses to a wide array of stimuli, including inflammation, infections, stressors, and more. Its intricate regulation involves a complex network of proteins and signaling pathways, allowing it to finely tune gene expression in response to diverse environmental cues.

Significance of NF-κB spans a broad spectrum of diseases, including inflammatory disorders, cancer, congenital defects, addiction, neurotoxicity, and asthma. Understanding its role in these contexts has opened doors for potential therapeutic interventions, ranging from biologics to small molecule inhibitors. These therapies aim to either activate or inhibit NF-κB's activity to restore cellular homeostasis, reduce inflammation, or target cancerous growth. Moreover, viruses have evolved various strategies to manipulate and evade the host immune response by targeting NF-κB signaling, highlighting the importance of this pathway in host defense.

Continued research into the complexities of NF-κB regulation and its impact on disease pathogenesis promises to unveil new therapeutic avenues and deepen our understanding of the intricate balance between immune response and disease development. Ultimately, harnessing the power of NF-κB regulation holds significant potential for improving the treatment and management of a wide range of health conditions.

Future perspectives

In modern research on cell communication, scientists are using advanced tools to closely examine tiny groups of cells. These tools allow them to understand how cells work in more detail than ever before. Traditional methods can't provide the level of detail needed to study how signals affect genes within single cells. So, researchers are using new techniques like CRISPR gene editing along with single-cell measurements and powerful imaging to directly see how certain genes are activated in individual cells. This approach can also help us study other factors involved in these processes. Furthermore, the integration of mathematical modelling with experimental data and *in vivo* imaging enhances our ability to predict cell behaviour, thus advancing drug discovery and personalized medicine. Future research will increasingly investigate the impact of tissue microenvironments on inflammation, facilitated by real-time, *in vivo* analysis of signaling processes within relevant contexts.

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CONFLICT OF INTERESTS

Declares none

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