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Review

Inhibiting NF-κB activation by small molecules as a therapeutic strategy

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ABSTRACT

Because nuclear factor-κB (NF-κB) is a ubiquitously expressed proinflammatory transcription factor that regulates the expression of over 500 genes involved in cellular transformation, survival, proliferation, invasion, angiogenesis, metastasis, and inflammation, the NF-κB signaling pathway has become a potential target for pharmacological intervention. A wide variety of agents can activate NF-κB through canonical and noncanonical pathways. Canonical pathway involves various steps including the phosphorylation, ubiquitination, and degradation of the inhibitor of NF-κB (IκBα), which leads to the nuclear translocation of the p50–p65 subunits of NF-κB followed by p65 phosphorylation, acetylation and methylation, DNA binding, and gene transcription. Thus, agents that can inhibit protein kinases, protein phosphatases, proteasomes, ubiquitination, acetylation, methylation, and DNA binding steps have been identified as NF-κB inhibitors. Because of the critical role of NF-κB in cancer and various chronic diseases, numerous inhibitors of NF-κB have been identified. In this review, however, we describe only small molecules that suppress NF-κB activation, and the mechanism by which they block this pathway.

1. Introduction

The nuclear factor-κB (NF-κB) signaling pathway plays a major role in the development, maintenance, and progression of most chronic diseases. NF-κB controls the expression of genes involved in a number of physiological responses, including immune inflammatory responses, acute-phase inflammatory responses, oxidative stress responses, cell adhesion, differentiation, and apoptosis [1]. Recent studies have suggested that NF-κB dysregulation is associated with many diseases including AIDS, atherosclerosis, asthma, arthritis, diabetes, inflammatory bowel disease, stroke, muscle wasting and viral infections. Mounting evidence indicates that NF-κB acts as a link between inflammation and cancer progression [2–11], making NF-κB essential to and a potential drug target in hematological malignancies and solid tumors [12,13].

NF-κB was first identified in 1986 by Sen and Baltimore [6] in the nucleus bound to an enhancer element of the immunoglobulin kappa light chain gene in B cells [6,14]. It is now known to be ubiquitous in nature present in all the cell types and is evolutionary conserved. It belongs to the family of Rel proteins that includes c-Rel, RelA (p65), RelB, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100) all of which can form hetero- or homodimers [15–17].

NF-κB activation is tightly regulated mainly through its localization. In resting cells, NF-κB proteins are kept in the cytoplasm in association with inhibitory IκB proteins including IκBα, IκBβ, and IκBε [16] among which IκBα is the most abundant. NF-κB signaling occurs through the canonical (classical) pathway initiated by NF-κB1 (p50/p105) and a noncanonical (alternative) pathway initiated by NF-κB2 (p52/p100) (Fig. 1). Before the active NF-κB is translocated into the nucleus, NF-κB1 and NF-κB2 are cleaved to the active p50 and p52 subunits, respectively. While the classical pathway depends on IKK complex consisting of IKKα, IKKβ, IKKγ and the inhibitory subunit IκBs, the alternative pathway depends on IKKα homodimers and NF-κB inducing kinase (NIK) [18–20]. During classical activation, the IKK complex specifically phosphorylates IκBs on two conserved N-terminal serine residues which target them for E2- and E3-ligase-mediated polyubiquitination and subsequent 26S proteasomal mediated degradation. This process releases and activates NF-κB which now translocates to the nucleus. The activation of alternative pathway, which is commonly associated with RelB results in regulated processing of the p100 precursor protein to p52 and subsequent translocation of p52-RelB

Abbreviations: AgR, antigen receptor; ATM, ataxia-telangiectasia mutant; BAFF, B-cell activating factor; BCL, B-cell lymphoma; BCR, B cell receptor; CARMA, CARD-containing MAGUK protein; CD40L, CD40 ligand; CK, casein kinase; DSBS, Double-stranded DNA breaks; ECSIT, evolutionary conserved signaling intermediates on Toll pathways; EGF, epidermal growth factor; EGFR, EGF receptor; ELKS, glutamate, leucine, lysine, serine-rich protein; GSK, glycogen synthase kinase; Hsp90, heat shock protein 90; IκB, inhibitor of NF-κB; IKK, IκB kinase; IRAK, IL-1R-associated kinase; LTβ, lymphotoxin β; LPS, lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; MAPK, mitogen activated protein kinase; MAPK/Erk, kinase kinase; MyD88, myeloid differentiation factor; NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase; NEMO, NF-κB essential modulator; PDK, Phosphoinositide-dependent kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; RANKL, receptor activator of NF-κB ligand; RIP, receptor-interacting protein; Syk, Spleen tyrosine kinase; TAB, TAK1-binding protein; TAK, transforming growth factor-β-activated kinase; TCR, T cell receptor; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFR1, TNF receptor 1; Tpl2, tumour progression locus-2; TRADD, TNF-receptor-associated death domain protein; TRAF, TNF-receptor-associated factor

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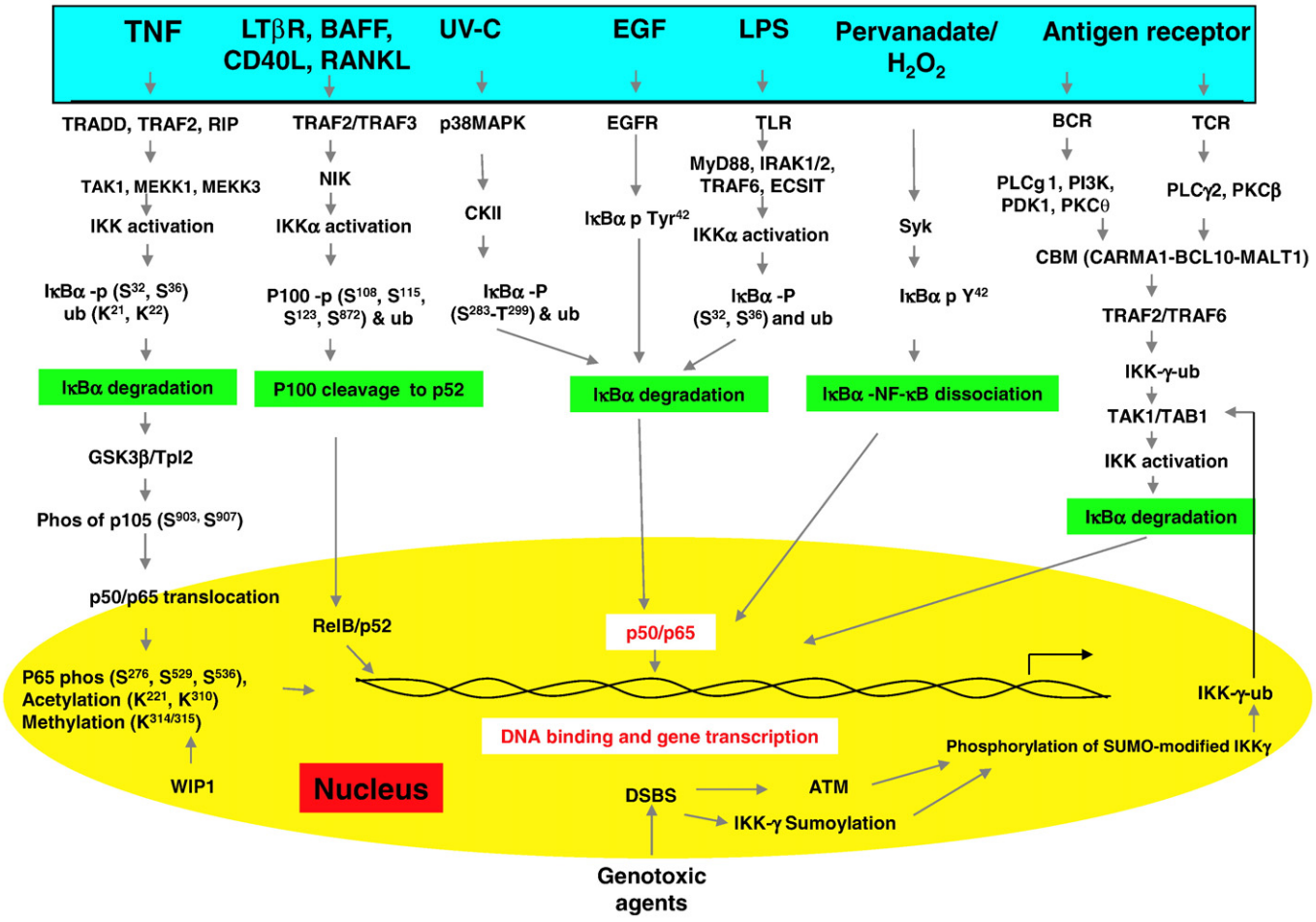
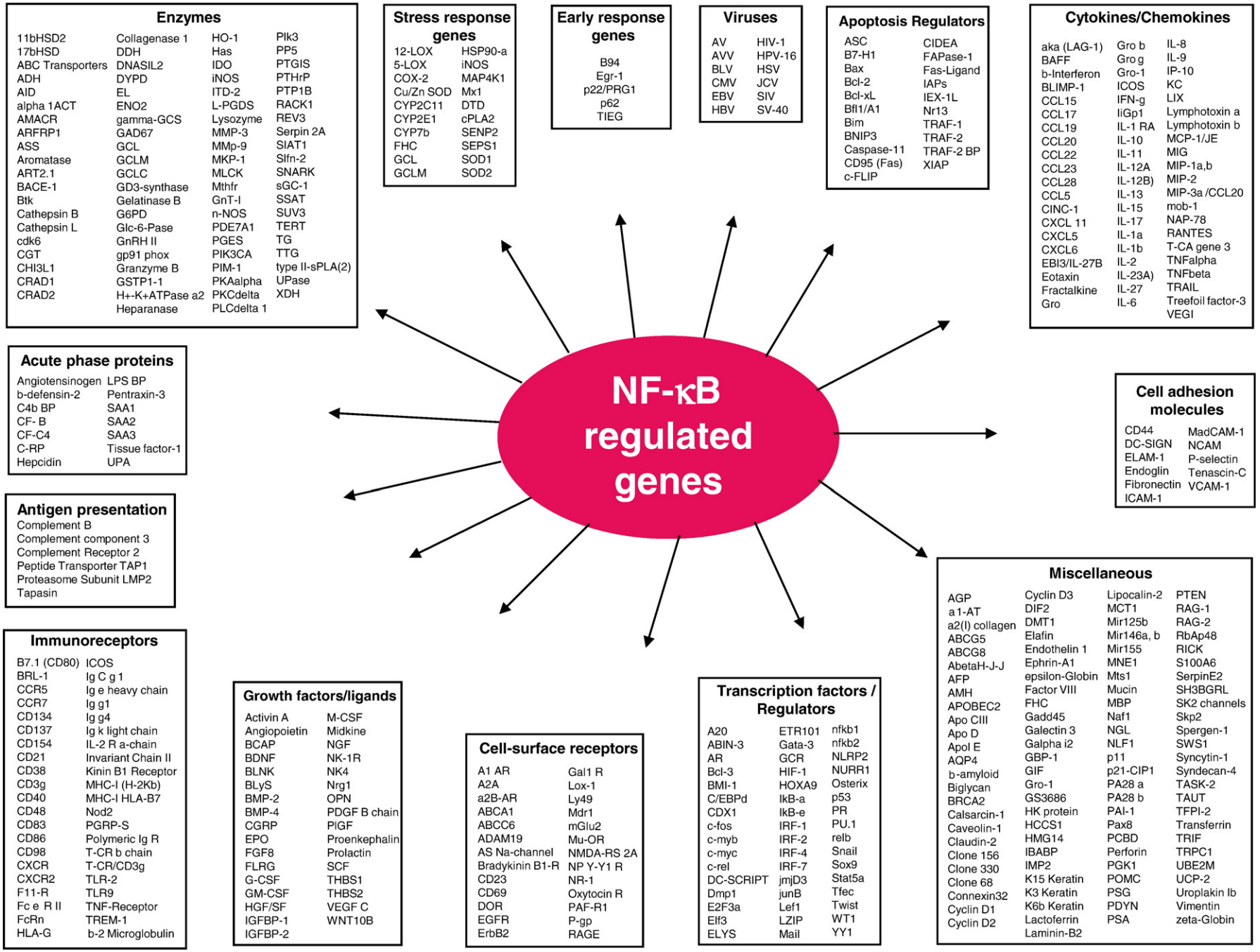


Fig. 1. Schematic representation of major NF-κB activation pathways. In the classical pathway, binding of TNFα to the receptor triggers the sequential recruitment of the adaptors TRADD, TRAF2 and RIP to the membrane. TRAF2 then recruits the IKK complex composed of IKKα, IKKβ and IKKγ (NEMO) through mediation of kinases like TAK1, MEKK1, MEKK3. Activation of the IKK complex leads to the phosphorylation and ubiquitination of IκBα at specific residues followed by its degradation via the proteasome pathway. The p105 subunit of NF-κB then undergoes GSK3β and Tpl2 mediated phosphorylation at S^{903} and S^{907} and subsequent degradation. The heterodimer p50–p65 is then released and migrates to the nucleus where it undergoes a series of posttranslational modifications including phosphorylation, acetylation and methylation and binds to specific κB sites and activates NF-κB target genes [49,209,210]. The alternative pathway is IKKγ independent and is triggered by binding of the CD40, RANK, LTβR, BAFF ligands to their receptor, leading to recruitment of TRAF proteins and the sequential activation of NIK and IKKα. Activation of IKKα then induces the processing of the inhibitory protein p100. p100 proteolysis releases p52 which then translocates to the nucleus and triggers transcription of NF-κB target genes [211]. NF-κB activation in response to UV-C does not depend on IKK activation and relies on sequential recruitment of p38MAPK and CKII. Activated CKII phosphorylates IκBα at C-terminus (S^{283}–T^{299}). The phosphorylated IκBα undergoes ubiquitination and degradation leading to release of active NF-κB in to the nucleus [212,213]. EGF induced NF-κB activation proceeds without serine phosphorylation and ubiquitination of IκBα and is IKK independent. It relies on phosphorylation of IκBα at Tyr^{42} through mediation of tyrosine kinases that triggers its proteasome mediated degradation and subsequent release of active NF-κB to the nucleus [214]. NF-κB activation in response to bacterial endotoxin LPS involves Toll like receptor and is mediated through recruitment of MyD88, TRAF6 and ECSIT. Recruitment of these adaptors leads to sequential activation of IRAK1/2 and IKK and eventual release of active NF-κB [215]. NF-κB activation by pervanadate and H_2O_2 induces phosphorylation of IκBα at Tyr^{42} by protein tyrosine kinase like Syk. The Tyr phosphorylation does not lead to IκBα degradation but makes the binding weak thereby dissociating the IκBα and releasing active NF-κB to the nucleus [216,217]. Antigen receptor viz., T-cell receptor and B-cell receptor mediated signaling to NF-κB activation depends on recruitment of a trimolecular protein complex CARMA1-BCL10-MALT1. In this pathway PKCθ (in T cells) and PKCβ (in B cells) along with other kinases act upstream to the trimolecular complex to promote IKKγ polyubiquitination and consequent IKK activation. Activation of IKK through this pathway involves mediation of TRAF2, TRAF6, TAK1 and TAB1 [218,219]. A novel pathway of NF-κB activation originating from the nucleus is associated with DNA damage. Double-stranded DNA breaks in response to genotoxic agents initiate signals that trigger SUMOylation of nuclear-localized IKKγ , preventing its nuclear export. Concomitantly, these breaks activate ATM which phosphorylates SUMO-modified IKKγ, promoting the removal of SUMO and enhancing IKKγ ubiquitination. Ubiquitinated IKKγ then translocates to the cytoplasm, where it activates IKK in cooperation with ATM and the ELKS protein, leading to IκBα phosphorylation and degradation, p65 nuclear translocation and induction of NF-κB dependent target genes [220-223]. NF-κB can also be regulated by phosphatases. WIP1, a Ser/Thr phosphatase was recently shown to negatively regulate NF-κB activation by dephosphorylating p65 at Ser^{536} [80].

heterodimers to the nucleus [19]. Although NF-κB activation occurs mainly through canonical and non-canonical pathways, during the past decade a number of pathways for NF-κB activation has been elucidated (Fig. 1).

Once in the nucleus, activated NF-κB undergoes a series of posttranslational modifications, including phosphorylation, acetylation, and methylation. These modifications regulate both the strength and duration of NF-κB activity. RelA/p65 is directly phosphorylated by cAMP-dependent protein kinase (PKA) at Ser^{276}, casein kinase II (CKII) at Ser^{529}, and IKK at Ser^{536} [21,22]. RelA dephosphorylation by protein phosphatase 2A (PP2A) has been reported to decrease NF-κB activity [23]. RelA is subject to inducible acetylation by p300/CBP, and acetylated RelA interacts weakly, if at all, with IκBα [24,25], but maintains its nuclear localization and NF-κB transcriptional response. RelA is also subject to methylation by lysine methyltransferase Set9 (also called Set7 or KMT7) at $Lys^{314/315}$ [26].

Fig. 2. A list of gene products regulated by NF-κB. These genes include transcription factors, cell-surface receptors, growth factors, immunoreceptors, acute phase proteins, enzymes, stress response genes, early response genes, viruses, apoptosis regulators, cytokines/chemokines and cell adhesion molecules. For more information, see http://www.nf-kb.org.


NF-κB regulated genes
Enzymes
11bHSD2
17bHSD
ABC Transporters
ADH
AID
alpha 1ACT
AMACR
ARFRP1
ASS
Aromatase
ART2.1
BACE-1
Btk
Cathepsin B
Cathepsin L
cdk6
CGT
CHI3L1
CRAD1
CRAD2
Collagenase 1
DDH
DNASIL2
DYPD
EL
ENO2
gamma-GCS
GAD67
GCL
GCLM
GCLC
GD3-synthase
Gelatinase B
G6PD
Glc-6-Pase
GnRH II
gp91 phox
Granzyme B
GSTP1-1
H+-K+ATPase a2
Heparanase
HO-1
Has
IDO
iNOS
ITD-2
L-PGDS
Lysozyme
MMP-3
MMp-9
MKP-1
MLCK
Mthfr
GnT-I
n-NOS
PDE7A1
PGES
PIK3CA
PIM-1
PKAalpha
PKCdelta
PLCdelta 1
Plk3
PP5
PTGIS
PTHrP
PTP1B
RACK1
REV3
Serpin 2A
SIAT1
Slfn-2
SNARK
sGC-1
SSAT
SUV3
TERT
TG
TTG
type II-sPLA(2)
UPase
XDH
Stress response genes
12-LOX
5-LOX
COX-2
Cu/Zn SOD
CYP2C11
CYP2E1
CYP7b
FHC
GCL
GCLM
HSP90-a
iNOS
MAP4K1
Mx1
DTD
cPLA2
SENP2
SEPS1
SOD1
SOD2
Early response genes
B94
Egr-1
p22/PRG1
p62
TIEG
Viruses
AV
AVV
BLV
CMV
EBV
HBV
HIV-1
HPV-16
HSV
JCV
SIV
SV-40
Apoptosis Regulators
ASC
B7-H1
Bax
Bcl-2
Bcl-xL
Bfl1/A1
Bim
BNIP3
Caspase-11
CD95 (Fas)
c-FLIP
CIDEA
FAPase-1
Fas-Ligand
IAPs
IEX-1L
Nr13
TRAF-1
TRAF-2
TRAF-2 BP
XIAP
Cytokines/Chemokines
aka (LAG-1)
BAFF
b-Interferon
BLIMP-1
CCL15
CCL17
CCL19
CCL20
CCL22
CCL23
CCL28
CCL5
CINC-1
CXCL 11
CXCL5
CXCL6
EBI3/IL-27B
Eotaxin
Fractalkine
Gro
Gro b
Gro g
Gro-1
ICOS
IFN-g
IiGp1
IL-1 RA
IL-10
IL-11
IL-12A
IL-12B)
IL-13
IL-15
IL-17
IL-1a
IL-1b
IL-2
IL-23A)
IL-27
IL-6
IL-8
IL-9
IP-10
KC
LIX
Lymphotoxin a
Lymphotoxin b
MCP-1/JE
MIG
MIP-1a,b
MIP-2
MIP-3a /CCL20
mob-1
NAP-78
RANTES
T-CA gene 3
TNFalpha
TNFbeta
TRAIL
Treefoil factor-3
VEGI
Acute phase proteins
Angiotensinogen
b-defensin-2
C4b BP
CF- B
CF-C4
C-RP
Hepcidin
LPS BP
Pentraxin-3
SAA1
SAA2
SAA3
Tissue factor-1
UPA
Cell adhesion molecules
CD44
DC-SIGN
ELAM-1
Endoglin
Fibronectin
ICAM-1
MadCAM-1
NCAM
P-selectin
Tenascin-C
VCAM-1
Antigen presentation
Complement B
Complement component 3
Complement Receptor 2
Peptide Transporter TAP1
Proteasome Subunit LMP2
Tapasin
Miscellaneous
AGP
a1-AT
a2(I) collagen
ABCG5
ABCG8
AbetaH-J-J
AFP
AMH
APOBEC2
Apo CIII
Apo D
Apol E
AQP4
b-amyloid
Biglycan
BRCA2
Calsarcin-1
Caveolin-1
Claudin-2
Clone 156
Clone 330
Clone 68
Connexin32
Cyclin D1
Cyclin D2
Cyclin D3
DIF2
DMT1
Elafin
Endothelin 1
Ephrin-A1
epsilon-Globin
Factor VIII
FHC
Gadd45
Galectin 3
Galpha i2
GBP-1
GIF
Gro-1
GS3686
HK protein
HCCS1
HMG14
IBABP
IMP2
K15a Keratin
K3 Keratin
K6b Keratin
Lactoferrin
Laminin-B2
Lipocalin-2
MCT1
Mir125b
Mir146a, b
Mir155
MNE1
Mts1
Mucin
MBP
Naf1
NGL
NLF1
p11
p21-CIP1
PA28 a
PA28 b
PAI-1
Pax8
PCBD
Perforin
PGK1
POMC
PSG
PDYN
PSA
PTEN
RAG-1
RAG-2
RbAp48
RICK
S100A6
SerpinE2
SH3BGRL
SK2 channels
Skp2
Spergen-1
SWS1
Syncytin-1
Syndecan-4
TASK-2
TAUT
TFPI-2
Transferrin
TRIF
TRPC1
UBE2M
UCP-2
Uroplakin Ib
Vimentin
zeta-Globin
Immunoreceptors
B7.1 (CD80)
BRL-1
CCR5
CCR7
CD134
CD137
CD154
CD21
CD38
CD3g
CD40
CD48
CD83
CD86
CD98
CXCR
CXCR2
F11-R
Fc e R II
FcRn
HLA-G
ICOS
Ig C g 1
Ig e heavy chain
Ig g1
Ig g4
Ig k light chain
IL-2 R a-chain
Invariant Chain II
Kinin B1 Receptor
MHC-I (H-2Kb)
MHC-I HLA-B7
Nod2
PGRP-S
Polymeric Ig R
T-CR b chain
T-CR/CD3g
TLR-2
TLR9
TNF-Receptor
TREM-1
b-2 Microglobulin
Growth factors/ligands
Activin A
Angiopoietin
BCAP
BDNF
BLNK
BLyS
BMP-2
BMP-4
CGRP
EPO
FGF8
FLRG
G-CSF
GM-CSF
HGF/SF
IGFBP-1
IGFBP-2
M-CSF
Midkine
NGF
NK-1R
NK4
Nrg1
OPN
PDGF B chain
PlGF
Proenkephalin
Prolactin
SCF
THBS1
THBS2
VEGF C
WNT10B
Cell-surface receptors
A1 AR
A2A
a2B-AR
ABCA1
ABCC6
ADAM19
AS Na-channel
Bradykinin B1-R
CD23
CD69
DOR
EGFR
ErbB2
Gal1 R
Lox-1
Ly49
Mdr1
mGlu2
Mu-OR
NMDA-RS 2A
NP Y-Y1 R
NR-1
Oxytocin R
PAF-R1
P-gp
RAGE
Transcription factors / Regulators
A20
ABIN-3
AR
Bcl-3
BMI-1
C/EBPd
CDX1
c-fos
c-myb
c-myc
c-rel
DC-SCRIPT
Dmp1
E2F3a
Elf3
ELYS
ETR101
Gata-3
GCR
HIF-1
HOXA9
IkB-a
IkB-e
IRF-1
IRF-2
IRF-4
IRF-7
jmjD3
junB
Lef1
LZIP
Mail
nfkb1
nfkb2
NLRP2
NURR1
Osterix
p53
PR
PU.1
relb
Snail
Sox9
Stat5a
Tfec
Twist
WT1
YY1

Activated NF-κB binds to specific DNA sequences in target genes, which are designated as κB elements, and regulates the transcription of over 500 genes involved in immunoregulation, growth regulation, inflammation, carcinogenesis, and apoptosis (Fig. 2). NF-κB is frequently constitutively activated in patients with chronic inflammatory conditions such as cancer and pulmonary, cardiovascular, autoimmune, skin, and neurodegenerative diseases [27]. NF-κB's ability to control multiple genes involved in human diseases makes the NF-κB signaling pathway a novel target for therapy [28,29].

Due to the various levels of regulation, NF-κB signaling pathway can be potentially targeted at various levels including kinases, phosphatases, ubiquitination, nuclear translocation, DNA binding, protein acetyl transferases and methyl transferases (Fig. 3).

2. Inhibitors of the NF-κB activation pathway

Given NF-κB's relevance in human diseases and the fact that many drugs interfere with NF-κB signaling, the NF-κB signaling pathway provides a highly attractive target for the therapeutic development. More than 700 inhibitors of the NF-κB activation pathway, including antioxidants, peptides, small RNA/DNA, microbial and viral proteins, small molecules, and engineered dominant-negative or constitutively active polypeptides have been described (Table 1). Several of these molecules act as general inhibitors of NF-κB activation, while other molecules target specific steps; some molecules possibly target multiple steps in the NF-κB pathway (Fig. 3).

2.1. Inhibition of protein kinases

NF-κB activation requires the phosphorylation, polyubiquitination, and subsequent degradation of its inhibitory subunit, IκBα. Hence, inhibiting IκBα phosphorylation ultimately inhibits NF-κB's transcriptional activity [30]. IκBα phosphorylation is carried out by IKK, a serine/threonine protein kinase composed of three basic subunits: the kinases IKKα, IKKβ, and the regulatory subunit IKKγ (NEMO). The IKK activation is usually the first common step in the integration of many NF-κB-activating pathways; therefore, one strategy for inhibiting NF-κB activation is to block IKK activation. However, although more than 150 agents have been shown to inhibit NF-κB activation at the IKK step, few studies have investigated the mechanism by which a given agent can inhibit IKK or its activation. The few IKK inhibitors for which a mechanism of action is known can be divided into three general groups: adenosine triphosphate (ATP) analogs, which show some specificity for interacting with IKK; compounds that have allosteric effects on IKK structure; and compounds that interact with a specific cysteine residue (Cys-179) in the activation loop of IKKβ. ATP analogs include natural products such as β-carboline and synthetic compounds such as SC-839, which has an approximately 200-fold preference for IKKβ compared to IKKα [28,31]. Compounds that have allosteric effects on IKK structure include BMS-345541, a synthetic compound that binds to an allosteric site on both IKKα and IKKβ and has an approximately 10-fold greater inhibitory effect on IKKβ than on IKKα [32]. Compounds that interact with Cys-179 IKKβ include thiol-reactive compounds such as parthenolide, arsenite, and certain epoxyquinoids [33–36]; these compounds' interactions with Cys-179 are believed to interfere with phosphorylation- induced IKKβ activation because Cys-179 is located between Ser^{177} and Ser^{181}, which are required for IKKβ activation in response to upstream signals such as tumor necrosis factor (TNF) and lipopolysaccharide (LPS) [37,38].

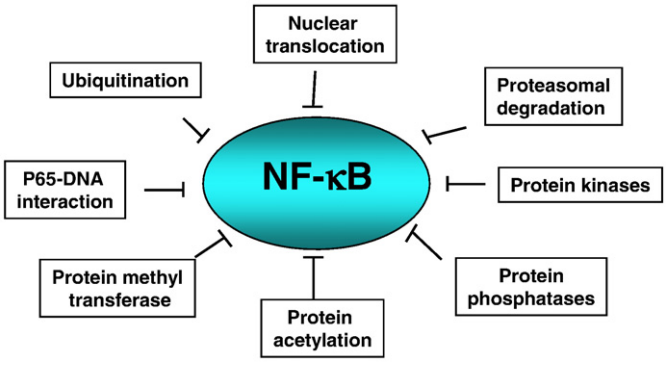


Fig. 3. Potential targets for inhibition of NF-κB activation pathway. NF-κB can be targeted at various steps including protein kinases, protein phosphatases, ubiquitination step, acetylation step, methylation step, nuclear translocation step and DNA binding step.

Gene-based inhibitors can also block IKK activation. Specifically, mutations at the ATP-binding site or in the kinase activation loop can create dominant-negative IKKα and IKKβ, which are capable of blocking NF-κB activation [39–43]. Because of their distinct roles in the canonical and non-canonical NF-κB activation pathways, dominant-negative IKK mutants can show stimulus-dependent inhibition [44]. Adenoviral-mediated delivery of an IKKβ dominant-negative kinase has been shown to have therapeutic potential for airway inflammatory diseases such as asthma [45,46]. NEMO can also serve as a target for inhibiting the IKK complex. In particular, introducing a cell-permeable 10 amino-acid peptide that corresponds to the NEMO-binding domain of IKKβ can block the binding of NEMO to IKK in response to TNF in the canonical pathway [47].

While activation of NF-κB by many stimuli depends on the phosphorylation of IκBs at N-terminal sites by the IKK complex, the mechanism of NF-κB activation by ultraviolet (UV) radiation involves the IKK-independent phosphorylation of IκBα at a cluster of C-terminal sites that are recognized by casein kinase II (CKII). CKII activity toward IκBα depends on p38 mitogen-activated protein kinase (MAPK) activation. CKII's role as a key survival signal that activates NF-κB and protects tumor cells from apoptosis suggests that CKII may be an attractive target for the treatment of diverse cancers. Apigenin, a plant flavonoid, and emodin, a plant anthraquinone, are competitive inhibitors of CKII that directly interact with the nucleotide-binding sites of CKII [48].

Besides phosphorylating and subsequently degrading the molecules that inhibit NF-κB, protein kinases can also target the functional domains of NF-κB proteins themselves to optimally activate NF-κB. NF-κB proteins can be phosphorylated in the cytoplasm or nucleus by such kinases as glycogen synthase kinase 3β (GSK3β) [49], TRAF-associated NF-κB activator (TANK)-binding kinase 1 (TBK1) [50,51], PKAc [21], mitogen- and stress-activated protein kinase-1 (MSK-1) [52], MAP3K NIK[53], Tpl2, PKC-θ [54], PI3K, Akt [55–57], p38 MAPK [58], protein tyrosine kinase, PKC-δ [59], RHO-kinase 2 [60], mitogen-activated protein kinase kinase 3 (MEKK3) [61], and receptor tyrosine kinases such as epidermal growth factor receptor, human epidermal growth factor receptor 2 [62]. Antagonistic antibodies or kinase inhibitors that target these molecules may decrease NF-κB activation. Some kinase inhibitors that have the potential to inhibit NF-κB activation include SB203580 and PD0980589 (MAPK inhibitors) [58]; denbinobin (TAK1 inhibitor) [63]; tyrosine kinase inhibitors [62]; rhein, (an MEKK inhibitor) [64,65]; TNAP, betaine (NIK inhibitors) [66–68], epoxyquinol B (a TAK1 crosslinker) [69]; M2L (an extracellular signal-regulated kinase 2 inhibitor) [70,71]; CCK-8 (a p38 kinase kinase inhibitor) [72], KSR2 (an MEKK3 inhibitor) [73], golli BG21 (a PKC inhibitor) [74].

2.2. Inhibition of NF-κB activation by protein phosphatases

Because protein phosphorylation is a dynamic process whereby phosphatases counterbalance kinase action, phosphatases may be used to inhibit NF-κB activation. Protein phosphatase 2A is a serine/threonine phosphatase that has been reported to dephosphorylate and modulate the activity of IKKβ [75]. Cytosine arabinoside, a pyrimidine analogue used to effectively treat acute leukemia, has been reported to induce apoptosis by activating protein phosphatases

Table 1
A list of small molecules as inhibitors of NF-kB pathway.

A. Upstream NF-κB	ox-LDL	Cyclopentenones	*Poncirus trifoliata* fruit extract	JM34	**Natural product**
Natural product	Panduratin A	CYL-19 s	Probiotics	KIOM-79	Actinodaphine
15d-PGJ(2)	PEITC	CYL-26z	Prostaglandin	Leptomycin B	Anthocyanins
Calagualine	Petrosaspongiolide M	Diaylpyridine derivative	Resiniferatoxin	Neomycin	*Arnica montana* extract
Conophylline	Phytic acid	DPE	Stinging nettle extracts	Nucling	Artemisinin
Evodiamine	Piceatannol	Epoxyquinone	Thiopental	Oregonin	Baicalein
Geldanamycin	Pinosylvin	Gabexate mesilate	Tipifarnib	OXPAPC	Bambara groundnut
Perrilyl alcohol	*Plagius flosculosus* extract	Gleevec	Titanium	Paeoniflorin	β-lapachone
PSK	Plumbagin	Hydroquinone	TNP-470	Phallacidin	Biliverdin
Rocaglamides	Pomegranate extract	Ibuprofen	*Trichomomas vaginalis*	Piperine	Brazilian
Viral protein	Prostaglandin A1	IQCAD	TG-rich lipoproteins	Pitavastatin	Calcitriol
Adenovirus E1A	Quercetin	Indolecarboxamide	Ursodeoxycholic acid	*Platycodi radix* extract	Campthothecin
NS5A (Hep-C virus)	Rengyolone	Isobutyl nitrite	*Xanthium strumarium* extract	Probiotics	*Sutherlandia frutescens*
Protein	Rosmarinic acid	Jesterone dimer	β- PEITC	Rapamycin	Capsiate
Erbin overexpression	Rottlerin	15-deoxyspergualine analog	8-MSO	*Rhubarb aqueous* extract	Catalposide
Golli BG21	Saikosaponin-d	Methotrexate	β-lapachone	*Salvia miltiorrhoza* extract	Cat's claw bark
KSR	*Salvia miltiorrhoza* extract	MLB120**	***Peptide***	*SH* extract	Cheongyeolsaseuptang***
MAST205	Sanguinarine	Monochloramine	Penetratin	Selenomethionine	Chitosan
NPM-ALK oncoprotein	*SAm* extract	MX781 (Retinoid antagonist)	VIP	Shenfu	Chicory root
Hep-C virus protease	Staurosporine	4-HPR	***Protein***	*Sophorae radix* extract	CSPDP
PEDF	Sesquiterpene lactones	Nafamostat mesilate	Activated protein C	Sopoongsan	Clarithromycin
Rituximab	Scoparone	NSAIDs	HSP-70	*Sorbus commixta* extract	Cloricromene
TNAP	Silibinin	PS-1145 (MLN1145)	Interleukin-13	Sphondin	C-K and Rh(2)
Synthetic	Silymarin	PQD	Intravenous Ig	*T. polyglycosides*	*Cortex cinnamomi* extract
Betaine	Sulforaphane	Pyridooxazinone derivative	Murr1 gene product	Younggaechulgam-tang***	Cryptotanshinone
Desloratadine	Sulindac	SC-514**	Neurofibromatosis-2 protein	α-pinene	Cytochalasin D
LY29 and LY30	Tetrandine	Scytonemin	PACAP	***Peptide***	Black rice extract
MOL 294**	Theaflavin	Sodium salicylate	SAIF	NCPP	Danshenshu
Pefabloc	Thienopyridine	Statins (several)	ST2 (IL-1-like receptor)	PN50	Diterpenoids
Rhein	Tilianin	Sulfasalazine	α-MSH	RelA peptides (P1 & P6)	Ent-kaurane diterpenoids
					Epinastine hydrochloride
SMI and FP	Ursolic acid	Sulfasalazine analogs	γ-glutamylcysteine synthetase	***Viral Protein***	Epoxyquinol A
B. IKK activity and IkB phosphorylation	Vesnarinone	Survanta	***Bacterial/Viral Protein***	3C protease (EMC virus)	Erythromycin
Natural product	Wedelolactone	Thalidomide	K1L (Vaccinia virus protein)	Canine Distemper Virus	Evodiamine
[6]-gingerol	Withanolides	THI 52	Nef (HIV-1)	MNF (myxoma virus)	Fish oil
1'-Acetoxychavicol acetate	Xanthoangelol D	YC-1*	Vpu protein (HIV-1)	***Protein***	*Fomes fomentarius* extracts
20(S)-Protopanaxatriol	Zerumbone	***Others***	YopJ	C5a	Fucoidan
4-Hydroxynonenal	β-carboline	Lead	***Synthetic***	DQ 65-79	Gallic acid
Acetyl-boswellic acids	γ-mangostin	Mild hypothermia	1-Bromopropane	Fox1j	*Ganoderma lucidum*
Anandamide	γ-Tocotrienol	Saline (low Na+)	Acetaminophen	GILZ	Garcinol
Anethole	***Peptide***	**C. IkB degradation**	Diamide	HSCO	Geranylgeraniol
Apigenin	IKKβ peptide	***Natural product***	Dobutamine	HSP-72	Ginkgolide B
Artemisia vestita[1]	NEMO CC2-LZ peptide	5'-methylthioadenosine	E-73	Interleukin-10	Glycyrrhizin
Baoganning	***Protein***	*Artemisia iwayomogi* extract	Ecabet sodium	Interleukin -11	Halofuginone
Betulinic acid	Anti-thrombin III	Alachlor	Gabexate mesilate	Interleukin -13	Hematein
Black raspberry extracts	Chorionic gonadotropin	Amentoflavone	Glimepiride	MTS-SR-IκBα	Herbal compound 861
Buddlejasaponin IV	FHIT	*Antrodia camphorata*#	Hypochlorite	Onconase	Hydroxyethyl starch
Cacospongionolide B	HB-EGF	*Artemisia capillaries* extract	Losartin	RASSF1A gene	Hydroxyethylpuerarin
Calagualine	Hepatocyte growth factor	Aucubin	LY294002	ROR-alpha	Hypericin
Cardamomin	Interferon-α	Baicalein	Pervanadate	Surfactant protein A	Kamebakaurin
Cardamonin	Interleukin-10	Blackberry extract	Phenylarsine oxide	TAT-SR- IκBα	Linoleic acid
Casparol	PAN1	Buchang-tang***	Phenytoin	ZAS3 protein	Lithospermi radix
Cobrotoxin	PTEN	Capsaicin	Ro106-9920**	ZUD protein	Macrolide antibiotics
Cycloepoxydon	SOCS1	Catalposide	Sabaeksan	β-amyloid protein	Mediterranean plant extracts
Decursin	***Viral Protein***	Cyclolinteinone	U0126 (MEK inhibitor)	***Synthetic***	2-methoxyestradiol
Dehydroascorbic acid	Adenovirus	Dihydroarteanniun	***Others***	BMD	6-MITC
Dexanabinol	Core protein (Hep-C virus)	Docosahexaenoic acid	Vagus nerve stimulation	Carbaryl	Nicotine
Digitoxin	Cytomegalovirus	Emodin	Low level laser therapy	CGS 25462	*Ochna macrocalyx* bark ext.
Diosgenin	E7 (Papillomavirus)	*Ephedrae herba* (Mao) extract	Zinc	DHMEQ	Oridonin
Diterpenes	MC159	Equol	**D. IκB upregulators/**	Diltiazem	PC-SPES (8 herb mixture)
Docosahexaenoic acid	MC160	Erbstatin	**NF-κB translocation**	Dioxin	PGG
Falcarindol	NS5B (Hep-C virus)	Estrogen	***Natural product***	Dipyridamole	Pepluanone
Flavopiridol	vIRF3 (KSHV)	Ethacrynic acid	PGG	Disulfiram	*Phyllanthus amarus* extracts
Furonaphthoquinone	***Synthetic***	Fosfomycin	15-deoxyspergualin	Enalapril	Plant compound A
Garcinone B	AIDCA derivative	Fungal gliotoxin	2',8''-biapigenin	mEET	Polyozellin
Glossogyne tenuifolia extract	TDZD	Gamisanghyulyunbueum***	5F (from *Pteri syeminpinnata*)	Fluvastatin	Prenylbisabolane 3
Glycine chloramine	TPCA-1	Genipin	*Agastache rugosa* leaf extract	Indole-3-carbinol	Prostaglandin E2
Guggulsterone	Pyridine derivatives	Genistein	Alginic acid	JSH-23	PSK
Herbimycin A	ACHP	Glabridin	*Antrodia camphorata* extract	KL-1156	Quinic acid
Honokiol	Acrolein	Glucosamine sulfate	Apigenin	Leflunomide	Sanggenon C
Hypoestoxide	AGRO100*	Glutamine	Astragaloside IV	Levamisole	Sesamin
Indirubin-3'-oxime	Amino-pyrimidine	Gumiganghwaltang***	AT514 (serratamolide)	MEB	Shen-Fu#
Isorhapontigenin	AS602868**	Isomallotochromanol	Atorvastatin	Moxifloxacin	Silibinin
		Isomallotochromene			
Kahweol	Aspirin	*Kochia scoparla* fruit extract	Blue honey suckle extract	Omapatrilat	Sinomenine

(continued on next page)

Table 1 (*continued*)

Kava derivatives[2]	Azidothymidine	L-ascorbic acid	*Buthus martensi* extract	R-etodolac	Sword brake fern extract
Licorce extracts	BAY-11-7082	Leflunomide metabolite	Cantharidin	Rolipram	*Tanacetum larvatum* extract
Manumycin A	BAY-11-7083	Melatonin	Chiisanoside	SC236 (COX-2 inhibitor)	Tansinones
Monochloramine	Benzoimidazole derivative	Midazolam	Clarithromycin	Triflusal	Taurine + niacine
N-acetylcysteine	Benzyl isothiocyanate	Momordin I	*Cornus officinalis* extract	Volatile anesthetics	TZD MCC-555
Nitric oxide	BMS-345541	*Morinda officinalis* extract	Eriocalyxin B	**E. NF-kB DNA-binding**	Trichostatin A
				Inorganic Complex	
Nitrosylcobalamin	Carboplatin	*Mosla diantherra* extract	Gangliosides	Metals (chromium, cadmium, gold, lead, mercury, zinc, arsenic)	Triptolide
Oleandrin	CDDO-Me	*Opuntia ficus indica* extract	Glucocorticoids	Apocynin	Tyrphostin AG-126
Omega 3 fatty acids	CHS 828*	*Platycodin* saponins	*HP* extracts	Apple juice/extracts	Ursolic acid
Withaferin A	Compound 5	Polymyxin B	Hirsutenone	Arctigenin	Ligonberries
Xanthohumol	Compound A	Ritonavir	Human breast milk	Aretemisa p7F	Lupeol
Xylitol	***Synthetic***	Rosiglitazone	BZLF1 (EBV protein)	Astaxanthin	Magnolol
Yan-gan-wan#	ADP ribosylation inhibitor	Roxithromycin	SH gene products (PMV)	Benidipine	Maltol
Yin-Chen-Hao#	7-amino-4-methylcoumarin	DAAS	***Protein***	bis-eugenol	*Mangifera indica* bark extract
Yucca schidigera extract	Amrinone	Serotonin derivative	Antithrombin	*BG* compounds	Mangiferin
Peptide	Atrovastat	Simvastatin	NF-kappaB-repression factor	BHA	Melatonin
Ghrelin	Benfotiamine	SM-7368**	PIAS3	CAPE	Mn-SOD
Peptide YY	Benzamide	T-614	PTX-B	Carnosol	Mulberry anthocyanins
Rapamycin	Bisphenol A	Sulfasalazine	***Synthetic***	Carvedilol	Myricetin
Viral Protein	Caprofen	SUN C8079	17-AAG	Catechol derivatives	N-acetyl-L-cysteine
African Swine Fever virus	Carbocisteine	Triclosan plus CPC	TMFC	Celasterol	Nacyselyn
Sendai Virus-C,V proteins	Celecoxib	Tobacoo smoke	AQC derivatives	Cepharanthine	Naringin
E1B (Adenovirus)	Germcitabine	Verapamil	9-aminoacridine derivatives	Chlorogenic acid	N-ethyl-maleimide
ICP27 (HSV-1)	Cinnamaldehyde	***Others***	Chromene derivatives	Chlorophyllin	Nitrosoglutathione
H4/N5 (bracovirus)	2-methoxy CNA	Heat (fever-like)	D609	Cocoa polyphenols	NDGA
NS3/4A (Hep-C)	2-hydroxy CNA	Hypercapnic acidosis	Dimethylfumarate	Curcumin	Ochnaflavone
Protein	CDS	Hyperosmolarity	EMDPC	DHEA	Orthophenanthroline
Adiponectin	CP Compound	Hypothermia	Histidine	DHEA sulfate	Phenylarsine oxide
AIM2 overexpression	Cyanoguanidine	Alcohol	HIV-1 PI	Dehydroevodiamine	PhIP
Angiopoietin-1	HMP	**E. NF-kB transactivation**	Mesalamine	Demethyltraxillagenin	Phyllanthus urinaria
Antithrombin	α-difluoromethylornithine	***Natural products***	PEITC	Diethyldithiocarbamate	PMC
AvrA protein (Salmonella)	DTD	4'-DM-6-Mptox	Pranlukast	Diferoxamine	PTX
β-catenin	Evans Blue	4-phenylcoumarins	RO31-8220 (PKC inhibitor)	Dihydroisoeugenol	Pyrithione
Bromelain	Evodiamine	AHUP	SB203580 (MAPK inhibitor)	Dihydrolipoic acid	Pyrrolinedithiocarbamate
					Quercetin
CaMKK	Fenoldopam	Adenosine	Tetrathiomolybdate	Dilazep	Quinozolines
CD43 overexpression	FEX	c-AMP	Tranilast	Fenofibric acid	Rebamipide
FLN29 overexpression	Fibrates	*Artemisia sylvatica* extract	Troglitazone	DMDTC	Red wine
FLIP	FK778	Bifodobacteria	***Others***	Dimethylsulfoxide	Redox factor 1
G-120	Flunixin meglumine	Blueberry & berry mix	Low gravity	Disulfiram	Resveratrol
Gax (homeobox protein)	Flurbiprofen	BSASM	**F. Proteasome/protease**	Ebselen	Ginseng derivative
HIV-1 Resistance Factor	Hydroquinone	*BF* phenylpropanoids	***Natural product***	Edaravone	Rotenone
Interleukin 4	IMD-0354	cPrG.HC	Cyclosporin A	EGTA	Roxithromycin
SspH1 and IpaH9.8	JSH-21	Seaweed extract	Lactacystine	EPC-K1	S-allyl-cysteine
NDPP1 (CARD protein)	KT-90	*Fructus benincasae* extract	β-lactone	Epigallocatechin-3-gallate	Sauchinone
Overexpressed ZIP1	Lovastatin	Glucocorticoids	***Peptide***	Ergothioneine	Spironolactone
p8	Mercaptopyrazine	Gypenoside XLIX	ALLnL	Ethyl pyruvate	Strawberry extracts
p202a	Mevinolin,	Kwei Ling Ko[3]	LLM	*Ganoderma lucidum* polysaccharides	Taxifolin
p21 (Rec)	Monoethylfumarate	*LC* root	Ubiquitin ligase	Garcinol	Tempol
PIAS1	Moxifloxacin	Luteolin	Z-LLL	γ-glutamylcysteine synthetase	Tepoxaline
Pro-opiomelanocortin	Nicorandil	Manassantins A,B	Z-LLnV	*Ginkgo biloba* extract	tert-butyl hydroquinone
					Tetracylic A
PYPAF1 protein	Nilvadipine	*MI* bark extract	***Synthetic***	Glutathione	Vitamin B6
Raf Kinase inhibitor protein *Rhus verniciflua* fruits	NO-ASA	Mesuol	APNE	Hematein	Vitamin C
SLPI	Panepoxydone	Nobiletin	Boronic acid peptide	Hydroquinone	Vitamin D
Siah2	Peptide nucleic acids	Phomol	BTEE	Hydroquinone	Vitamin E derivatives
SIRT1 Deacetylase overexpression	Perindopril	Psychosine	3,4-dichloroisocoumarin	IRFI 042	Wogonin
Siva-1	PAD	Qingkailing#	Deoxyspergualin	Iron tetrakis	xanthohumol
Solana nigrum L.	α–PBN	Saucerneol D & E	DFP	Isovitexin	Yakuchinone A, B
Surfactant protein A	Pioglitazone	Shuanghuanglian#	Disulfiram	Kangen-karyu extract	α-lipoic acid
Tom1 overexpression	Pirfenidone	*Smilax bockii* extract	FK506 (Tacrolimus)	Ketamine	α-tocopherol
Transdominant p50	PNO derivatives	Trilinolein	Bortezomib	Lacidipine	α-torphryl acetate
Uteroglobin	Quinadril	*Uncaria tomentosum* extract	Salinosporamide A	Lazaroids	α-torphryl succinate
VEGF	Raloxifene	*WS* extracts	TLCK	L-cysteine	β-Carotene
	Raxofelast	Wortmannin	TPCK		
	Ribavirin	α-zearalenol	**G. Antioxidants**		
	Rifamides	***Viral Protein***	23-hydroxyursolic acid		
			Aged garlic extract		
			Anetholdithiolthione		

2A and 2B-A and dephosphorylating the p65 subunit of NF-κB [23,76]. Recently, OspF, a protein phosphatase from *Shigella flexneri*, was found to dephosphorylate MAPK and prevent histone H3 phosphorylation at Ser^{10} in a gene-specific manner to block the activation of a subset of NF-κB responsive genes [77]. Our previous studies have shown that protein tyrosine phosphatase (PTP) inhibitors can suppress NF-κB activation and that phenylarsine oxide, a specific PTP inhibitor, can promote tyrosine 42 phosphorylation of IκBα [78]. While some PTPs stimulate NF-κB activation, other PTPs negatively regulate NF-κB activation. For instance, PTEN, a tumor suppressor with phosphatase activity is known to inhibit NF-κB activation [79]. Recently, Chew et al. [80] found that WIP1, a Ser/Thr PP2C family of phosphatases, acts as a negative regulator of NF-κB activation. Overexpression of WIP1 was associated with decreased NF-κB activation, whereas WIP1 knockdown resulted in increased NF-κB activation. The group further showed that WIP1 target Ser^{536} of the p65 subunit of NF-κB.

2.3. Proteasome inhibitors and IκB ubiquitination blockers

The step before NF-κB leaves the cytoplasm involves the ubiquitination of IκB by the SCF-β-TrCP ubiquitin ligase complex followed by the rapid degradation of ubiquitinated IκB by the 26S proteasome [38]. Because IκBα degradation is an important step in the NF-κB activation pathway, inhibiting the proteasomes that degrade IκBα may also serve as a tool for pharmacological intervention. Very specific and potent proteasome inhibitors have been engineered by coupling boronic acid to dipeptides [81]. The dipeptide boronate, bortezomib, the most-studied proteasome inhibitor in clinical development, has been shown to inhibit proliferation and induce apoptosis in head and neck [82–84], prostate [85], pancreatic [86], gastric [87], and ovarian [88] cancers. Bortezomib's antitumor properties correlate in part with its ability to inhibit IκBα degradation [82,89]. Other well-known proteasome inhibitors include ALLnL, LLM, Z-LLnV, and Z-LLL, lactacystine, N-cbz-Leu-Leu-leucinal (MG132), MG115, and ubiquitin ligase inhibitors [90]. In addition, we recently identified a novel proteasome inhibitor, salinosporamide A (NPI-0052), which can suppress both constitutive and inducible NF-κB activation in a nanomolar range [91].

Several serine protease inhibitors with chymotrypsin-like specificity, including DCIC, TPCK, TLCK, BTEE, APNE, are also able to block proteasome function. However, unlike other protease inhibitors that block only IκB degradation, serine protease inhibitors can block IκB phosphorylation as well as degradation. However, not all serine protease inhibitors can inhibit NF-κB activation [92–94].

Among IκB ubiquitination blockers, the YopJ protein of the bacterial pathogen *Yersinia* deubiquitinates and stabilizes IκBα to prevent NF-κB nuclear translocation [95]. The small molecule R0196-9920 has been reported to inhibit IκBα ubiquitination and oral inflammation in mouse models [96,97]. Yaron et al. [97] blocked TNFα-induced IκBα degradation by microinjecting phosphopeptides that corresponded to IκBα's signal-dependent phosphorylation site. Presumably these phosphopeptides acted as competitive inhibitors for binding to the ubiquitin ligase complex essential to IκBα degradation. Inhibiting β-TrCP (the recognition subunit of the SCF E3 ligase complex) by specific RNAi treatment or by overexpression of dominant-negative β-TrCP mutants blocked NF-κB activity and sensitized breast cancer cells to chemotherapeutic agents [98]. Recently, A20 (TNFAIP3), a cytoplasmic zinc finger protein, was shown to inhibit NF-κB activation in the TNFR and TLR pathways. The ubiquitin editing property of A20 was shown to be essential for NF-κB inhibition [99].

Notes to Table 1:

15d-PGJ(2), 15-deoxy-prostaglandin J(2); 17-AAG, 17-allylamino-17-demethoxygeldanamycin; 20(S)-PPT, 20(S)-Protopanaxatriol; 4'-DM-6-Mptox, 4'-demethyl-6-methoxypodophyllotoxin; 6-MITC, 6-Methylsulfinyl) hexyl isothiocyanate; α-MSH, α-melanocyte-stimulating hormone; α-PBN, alpha-phenyl-N-tert-butylnitrone; ACHP, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile; AGRO100, G-quadruplex oligodeoxynucleotide; AHUP, 8-acetoxy-5-hydroxyumbelliprenin; AIDCA, (Amino)imidazolyl carboxaldehyde derivative; ALLnL, N-acetyl-leucinyl-leucynil-norleucynal; APNE, N-acetyl-DL-phenylalanine-b-naphthylester; AQC, 6-aminoquinazoline; BAY-11-7082, E3((4-methylphenyl)-sulfonyl)-2-propenenitrile; BAY-11-7083, E3((4-t-butylphenyl)-sulfonyl)-2-propenenitrile; *BF, Bupleurum fruticosum; BG, Bruguiera gymnorrhiza;* BHA, Butylated hydroxyanisole; BMD, N(1)-Benzyl-4-methylbenzene-1,2-diamine; BMT, o,o'-bismyristoyl thiamine disulfide; BSASM, plant extract mixture; BTEE, N-benzoyl L-tyrosine-ethylester; CaMKK, Calcium/calmodulin-dependent kinase kinase; CAPE, Caffeic Acid Phenethyl Ester; CDDO-Me, C-28 methyl ester of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid; CDS, Commerical peritoneal dialysis solution; CMP, Chinese medicinal preparations; CNA, Cinnamaldehyde; Compound 5, Uredio-thiophenecarboxamide derivative; CP Compound, 6-Hydroxy-7-methoxychroman-2-carboxylic acid phenylamide); CPC, cetylpyridinium chloride; cPrG.HC, Cycloprodigiosin hycrochloride; CSPDP, Chondrotin sulfate proteoglycan degradation product; CYL-19 s and CYL-26z, two synthetic alpha-methylene-gamma-butyrolactone derivatives; D609, phosphatidylcholine-specific phospholipase C inhibitor; DAAS, diacetoxy acetal derivative of santonin; DFP, diisopropyl fluorophosphates; DHEA, Dehydroepiandrosterone; DHMEQ, Dehydroxymethylepoxyquinomicin; DMDTC, Dimethyldithiocarbamates; DPE, 2-(3,4-dihydroxyphenyl)ethanol; DTD, 4,10-dichloropyrido[5,6:4,5]thieno[3,2- d':3,2- d]-1, 2, 3-ditriazine; EGTA, Ethylene glycol tetraacetic acid; EMC virus, encephalomyocarditis virus; EMDPC, Ethyl 2-[(3-methyl-2,5-dioxo(3-pyrrolinyl)) pyrimidine-5-carboxylate; EPC-K1, phosphodiester compound of vitamin E; FEX, Fexofenadine hydrochloride; FHIT, Fragile histidine triad protein; FLIP, FLICE-Like Inhibitory Protein; G-120, Ulmus davidiana Nakai glycoprotein; GILZ, Glucorticoid-induced leucine zipper protein; HB-EGF, Heparin-binding epidermal growth factor-like growth factor; HMP, 7-(4'-hydroxy-3'-methoxyphenyl)-1-phenylhept-4-en-3-one; *HP, Harpagophytum procumbens;* HSCO, Hepatoma Subtracted-cDNA library Clone One; IQCAD, Imidazolylquinoline-carboxaldehyde derivative; JSH-23, 4-Methyl- -(3-phenyl-propyl)-benzene-1,2-diamine; KL-1156, 6-Hydroxy-7-methoxychroman-2-carboxylic acid phenylamide; KSHV, Kaposi's sarcoma-associated herpesvirus; KSR, Kinase suppressor of ras; *LC, Ligusticum chuanxiong;* LLM, N-acetyl-leucinyl-leucynil-methional; LY294002, [2-(4-morpholinyl)-8-phenylchromone]; MAST205, a serine/threonine kinase; MC160, Mollusum contagiosum virus; MEB, 2-(4-morpholynl) ethyl butyrate hydrochloride; mEET, Mouse estrogen enhanced transcript; Mn-SOD,Manganese superoxide dismutase; MSO, 8-methylsulphinyloctyl; N-(4-hydroxyphenyl) retinamide [4-HPR; NDGA, Nordihydroguaiaritic acid; NCPP, NLS Cell permeable peptides; NFD-37, 2-Methyl-2-(2-methylpropenyl)-2,3-dihydronaphthoquinone [2,3-b]furan-4,9-dione; NH(2)Cl , monochloramine; NO-ASA, Nitric-oxide-donating aspirin; ox-LDL, Oxidized low density lipoprotein; OXPAPC, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; PACAP, Pituitary adenylate cyclase-activating polypeptide; PAD, 6(5H)-phenanthridinone; PEDF, pigment epithelium derived factor; PEITC , Phenethyl isothiocyanate; PGG, 1,2,3,4,6-penta-O-galloyl-β-D-glucose; PhIP, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; PI, protease inhibitor; PIAS1, protein inhibitor of activatated STAT1; Plant compound A, plant-derived phenyl aziridine precursor; PMC, (2,2,5,7,8-pentamethyl-6-hydroxychromane); PMV, Paromyxovirus; PNO, Pyridine N-oxide; PQD, Pyrazolo[4,3-c]quinoline derivative; PSK, Protein-bound polysaccharide; PTEN, phosphatase and tensin homolog; PTX, Pentoxyifylline (1-(5'-oxohexyl) 3,7-dimehylxanthine; PTX-B, pertussis toxin binding protein; Pyridine derivatives, 2-amino-3-cyano-4-aryl-6-(2- hydroxy-phenyl)pyridine derivatives; RH(2) & C-K, intestinal bacterial metabolites Rh(2) and compound K (C-K); RORalpha, Retinoic acid receptor-related orphan receptor-alpha; *SH, Sargassum hemiphyllum;* SAIF, Saccharomyces boulardii anti-inflammatory factor; SLPI, Secretory leucoprotease inhibitor; SMI and FP, Salmeterol and Fluticasone propionate; SOCS, suppressor of cytokine signaling proteins; SspH1 and IpaH9.8, Leucine-rich effector proteins of Salmonella & Shigella; TDZD, 1,2,4-thiadiazolidine derivative; TG, triglyceride; THI 52, 1-naphthylethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; TLCK, N-α-tosyl-L-lysine chloromethyl ketone; TMFC, 3,4,5-trimethoxy-4'-fluorochalcone; TNAP, TRAFs and NIK-associated protein; *; TP, Tripterygium polyglycosides;* TPCA-1, 2-[(aminocarbonyl)amino]-5-acetylenyl-3-thionphenecarboxamides; TPCK, N-α-tosyl-L-phenylalanine chloromethyl ketone; TZD, Thiazolidinedione; VEGF, Vascular endothelial growth factor; VIP, Vasoactive intestinal peptide; VVP, Vaccinia virus protein; *WS, Witheringia solanacea;* Z-LLL, N-carbobenzoxyl-L-leucinyl-L-leucinyl-L-norleucinal; Z-LLnV (carbobenzoxyl-leucinyl-leucynil-norvalinal.

[1] Tibetan medicine.
[2] Piper methysticum.
[3] Tortoise shell-Rhizome jelly.
* Anticancer drugs.
** Small molecules.
*** Oriental medicines.
[#] Traditional Chinese Medicine.

2.4. Blockage of NF-κB nuclear translocation

One approach for inhibiting NF-κB activation is to use small peptides that cross the cell membrane and block the nuclear translocation of the NF-κB complex [100–102]. For example, SN50, a forty-one-residue synthetic peptide that contains a hydrophobic membrane-translocating region and the nuclear localization sequence of NF-κB p50 [100], can enter cells and compete with NF-κB complexes for the machinery responsible for the nuclear translocation of NF-κB. SN50 effectively inhibits the LPS- and TNF-α–induced nuclear translocation of NF-κB in different cell lines [100, 103–106] and mitigates inflammatory responses *in vivo* [107,108]. However, SN50 also blocks the nuclear translocation of a number of other transcription factors [101]. Dehydroxymethylepoxyquinomicin, a fungal epoxyquinoid that has anti-inflammatory and antitumor activity in several mouse models, has been reported to be a specific inhibitor of NF-κB nuclear translocation [109].

2.5. Blocking NF-κB activation by inhibitors of p65 acetylation

The activated p65 subunit of NF-κB undergoes acetylation in the nucleus at multiple lysine residues including K^{122}, K^{123}, K^{218}, K^{221} and K^{310} [24,110]. The opposing activities of histone acetyltransferases and histone deacetylases (HDACs) regulate p65 complex acetylation [25]. Acetylation of p65 also depends on coactivators such as p300 and CREB-binding protein (CBP) [111]. The K^{221} and K^{310} acetylation are associated with increased NF-κB target gene transcription [111] and are required for p65 activation [25], which is supported by the observations that SIRT driven deacetylation at K^{310} inhibits NF-κB target gene transcription [112]. Additionally, K^{122} and K^{123} acetylation reduces p65 DNA binding affinity and increases IκB interaction and nuclear export [110]. Site-specific p300-mediated p65 acetylation thus regulates the specificity of NF-κB– dependent gene expression [110,113].

During the last 5 years, a number of compounds have been reported to inhibit NF-κB by inhibiting acetylation. Gallic acid obtained from natural products such as gallnuts, sumac, oak bark, and green tea was recently reported to possess anti-histone acetyltransferase activity, thus showing potential to downregulate NF-κB activation [114]. Daxx, a protein associated with the death domain of Fas receptor, has been reported to suppress NF-κB transcriptional activity by inhibiting p300/CBP-mediated p65 acetylation [115]. Anacardic acid derived from traditional medicinal plants can also inhibit NF-κB activation by inhibiting p65 acetylation [116].

2.6. Blocking NF-κB activation by methyltransferases

The RelA subunits of NF-κB undergo various posttranslational modifications that create specific marks to recruit different effectors to control NF-κB's temporal and spatial activation [117]. RelA is subject to monomethylation by lysine methyltransferase Set9 (also called Set7 or KMT7) at $Lys^{314/315}$ *in vitro* and *in vivo* in response to stimuli [26]. RelA methylation at these two residues negatively regulates NF-κB function by triggering the ubiquitination and proteasome-mediated degradation of promoter-associated RelA. RelA methylation also serves as a "death" signal for the destruction of DNA-bound, activated NF-κB [26]. Because RelA subunit methylation negatively impacts NF-κB function, designing a molecule that activates Set9 function could potentiate NF-κB inhibition.

2.7. Blockage of NF-κB to DNA binding

The most direct strategy for blocking NF-κB activation is to block NF-κB from binding to specific κB sites on DNA. Some sesquiterpene lactones (SLs) have been reported to inhibit NF-κB [118] by interacting with Cys-38 in the DNA-binding loop of RelA [119,120]. Most SLs can also inhibit DNA binding through an analogous Cys residue in the DNA-binding loops of p50 and c-Rel. Recently, a computer-based structural comparison of 103 SLs predicted that a methylene-carbonyl substructure is important for SL-based inhibition of RelA at Cys-38 [121]. Some SLs, including parthenolide, have been shown to inhibit IKKβ through the reactive Cys-179 in the kinase activation loop [34,120]. Thus, SLs, which target both IKK activity and NF-κB subunit DNA binding [36], have multistep inhibitory activity within the NF-κB signaling pathway.

Blocking specific NF-κB-DNA binding can also be accomplished with decoy oligodeoxynucleotides (ODNs). These ODNs have κB sites and competes for NF-κB dimer binding to specific genomic promoters [122–124]. These oligonucleotides have modifications to increase their stability and their affinity for NF-κB *in vivo* [125–127]. Decoy ODNs have been reported to have therapeutic potential in a number of animal models of inflammation and cancer; for example, directly injecting NF-κB decoy ODNs into implanted adenocarcinoma colon 26 tumors in mice inhibited cachexia without affecting tumor growth [128].

2.8. Other mechanisms of NF-κB inhibition

2.8.1. By gene transfer

One strategy to block NF-κB activation is through the transfer of genes that code for proteins shown to suppress NF-κB activation. The most direct target is IκBα. IκBα mutation at specific phosphorylation sites (Ser^{32} and Ser^{36} replaced to alanine) and ubiquitination sites (Lys^{21} and Lys^{22} mutated to arginine) results in a nondegradable form of IκBα. This results in a stable cytoplasmic pool of IκBα, thereby preventing NF-κB activation [129–131]. Injecting a nonphosphorylatable form of IκBα into bone marrow macrophages has been shown to inhibit osteoclastogenesis and block bone resorption [132]. Additionally, specific C-terminal serine-to-alanine mutations are sometimes included to reduce the constitutive turnover of IκBα [133]. These super-repressor forms of IκBα can still interact with NF-κB dimers to keep the dimers in the cytoplasm permanently [131,133,134]. Such molecules have been used successfully to inhibit NF-κB activity and to study its role in tumor development [135,136] and to sensitize tumor cells to apoptosis-inducing agents [133,134]. Inhibiting NF-κB through the expression of an IκBα super-repressor (IκBαSR) has also been used to sensitize chemoresistant tumors to TNFα- and CPT-11-induced apoptosis, resulting in tumor regression [137], and to inhibit the proliferation of human head and neck carcinoma cells *in vitro* and *in vivo* [138]. However, IκBαSRs have also been shown to interact with and affect the activity of non-NF-κB pathway proteins including p53 [139], cyclin-dependent kinase 4 [140], and HDACs [141]. Furthermore, IκBαSR overexpression has been associated with the spontaneous development of squamous cell carcinoma in a murine model [142].

2.8.2. Antioxidants

Antioxidants were suggested as possible NF-κB inhibitors many years ago [143,1444]. Treatment with oxidants such as hydrogen peroxide can activate NF-κB in many cell types. In some cell types, antioxidants can inhibit the induction of NF-κB activity in response to a variety of stimuli (e.g., interleukin-1β, LPS, TNFα) [145,146]. However, using antioxidants as NF-κB inhibitors is now regarded with increasing scepticism because the NF-κB-inhibiting properties of pyrrolidine dithiocarbamate, a thiol-containing compound, cannot be attributed to its antioxidant function but rather to its effects as an inhibitor of IκB ubiquitin ligase activity [147]. The ways in which antioxidants block NF-κB activation remain unclear, but it is likely that they act at different steps in the NF-κB pathway in different cell types. Antioxidants have been suggested to inhibit NF-κB activation by scavenging reactive oxygen intermediates that act as signaling molecules to activate the NF-κB pathway and by directly inhibiting IKK kinase activity by modifying critical Cys residues in the IKK kinase activation loop [145,146]. Mitochondrial electron transport inhibitors that suppress reactive oxygen intermediate production (e.g., rotenone) and overexpression of antioxidizing enzymes (e.g., manganese superoxide dismutase and catalase) can block TNFα-induced NF-κB activation [148–150]. Caffeic acid phenethyl ester, a phenolic antioxidant, has been

reported to cause direct interference with DNA binding by NF-κB [151] that can be reversed by dithiothreitol [78]. Other antioxidants, *viz*., N-acetylcysteine, calcium chelators (e.g., EGTA, lacidipine), and vitamin C and E derivatives have been reported to inhibit hydrogen peroxide- or stimulus-induced NF-κB activation.

2.8.3. Bacterial, fungal, and viral proteins

Several microorganisms and viruses encode proteins that can inhibit NF-κB activation. Many viruses have developed a number of mechanisms to inhibit NF-κB signaling [152], and three viruses–African swine fever virus (ASFV) [153], rabbit myxoma virus [154], and insect *Microplitis demolitor* bracovirus [155]–encode IκB-like NF-κB inhibitors. The ASFV encodes the A238L IκB-like protein, which can stably interact with RelA to inhibit TNFα-, IFN-γ-, and phorbol ester-induced NF-κB–DNA binding [156]. The poliovirus 3C protease cleaves RelA to reduce NF-κB signaling [157]. In addition, several viruses have adaptor-like or small proteins that inhibit IKK activity [152]. For example, the MC160 protein of *Molluscum contagiosum* [158] and the nonstructural 5B protein of the hepatitis C virus [159] appear to be IKKα-specific and thus may specifically inhibit the noncanonical NF-κB pathway.

The YopJ protein, a Src homology 2 domain protein encoded by *Yersinia pseudotuberculosis*, inhibits NF-κB activation by preventing the phosphorylation and degradation of IκBα [160]. YopJ has also been shown to bind directly to IKKβ *in vitro* and *in vivo* [161]. The *Salmonella typhimurium* AvrA protein also inhibits NF-κB activation, although its mechanism of action may be different than that of the YopJ protein [162].

Gliotoxin produced by the fungus *Aspergillus fumigatus* has been reported to inhibit NF-κB activation by preventing IκB degradation [163]. Several other small molecules synthesized by microorganisms or designed derivatives of such compounds that have NF-κB-inhibiting potential include panepoxydone (from *Lentinus crinitus*) [164], 5,6 epoxycyclohexenone compounds (from *Amycolatopsis*), and cycloepoxydon [165]. Such compounds may affect distinct parts of the NF-κB pathway including DNA binding, nuclear translocation, and IκBα phosphorylation and degradation.

2.8.4. Anti-inflammatory and immunosuppressive agents

Various anti-inflammatory agents including glucocorticoids, non-steroid anti-inflammatory drugs (NSAIDs), and immunosuppressants have been developed to block NF-κB activation. Glucocorticoids, which are commonly used as anti-inflammatory drugs, strongly inhibit NF-κB activation by mechanisms that are not completely understood but likely include inhibition of DNA binding, IKK activity and transactivation [166]. The glucocorticoids dexamethasone, prednisone and methylprednisolone have been reported to inhibit NF-κB activation. In addition, estrogen and selective estrogen receptor modulators (SERMs) such as raloxifene can act through the estrogen receptor to inhibit NF-κB activation [167,168].

NSAIDs such as sodium salicylate (aspirin) and sulindac have been reported to inhibit NF-κB activation by inhibiting IκBα phosphorylation [169,170]. At higher concentrations, aspirin has been shown to block NF-κB activity by directly binding to and inhibiting the kinase activity of IKKβ by reducing its ability to bind ATP [171]. More recently, aspirin was reported to inhibit proteasome activity [172]. As such, high-dose aspirin therapy may have applications in treating diseases in which NF-κB activity is involved, including cancer [173], diabetes [174], and heart disease [175]. Other NSAIDs such as ibuprofen and indomethacin have also been reported to inhibit NF-κB activation in cell culture [176–179].

Several well known immunosuppressants are known to target NF-κB by distinct mechanisms, some precluding NF-κB nuclear translocation [180], some through inhibiting calcineurin [181], some by binding heat-shock proteins [182] and some by modulating the DNA binding or transactivation potential of NF-κB [183–186]. Examples of immunosuppressants having inhibitory effect on NF-κB activation include cyclosporin A (CsA) [180], FK506 [187,188], PG490 (diterpene triepoxide) [186] and deoxyspergualin [182].

2.8.5. p53 induction

It is known that p53 and NF-κB pathways play opposing roles in human cancer, with p53 acting as a tumor suppressor and NF-κB acting as a tumor activator. The crosstalk between p53 and NF-κB indicates that p53 and NF-κB repress each other's activities owing to their competition for transcriptional coactivator proteins p300 and CBP [189]. A recent study has proposed an additional mechanism of how CBP phosphorylation by IKKα determines whether CBP binds to p53 or NF-κB [190]. Although a number of studies have focused on identifying p53 activators and NF-κB inhibitors individually, few studies have investigated the molecules that target both the pathways simultaneously. Identifying molecules that simultaneously activate p53 and inhibit NF-κB would have great potential in combination therapy for cancer and various other diseases and could provide helpful tools to better understand the crosstalk between the p53 and NF-κB pathways. Quinacrine, an antimalarial drug, and other derivatives of 9 aminoacridine have been shown to simultaneously repress NF-κB and activate p53 in renal cell carcinoma [191]. Other molecules with similar potential include nutlins [192,193], cisplatin [194,195], leptomycin B [196,197], adenosine-2,3-dialdehyde [198], the NSAID JTE-522 [199], and the cyclin-dependent kinase inhibitors R-roscovitine [200,201]; and flavopiridol [202,203]. While most reports indicate antiapoptotic role of NF-kB, some suggest proapoptotic role of this transcription factor depending on the stimulus, cell type and subunit involved [204-206]. In addition, under certain circumstances, the apoptosis induced by p53 may involve the activation of NF-κB [207,208]. Thus, inhibition of NF-κB in tumors that exhibit wild type p53 may diminish, rather than augment a therapeutic response.

3. Conclusions and future perspective

NF-κB has been implicated in almost all chronic diseases, and more than 40,000 studies on NF-κB have been published with 9000 on its inhibitors. Although more than 700 different inhibitors (aspirin to IκBα super repressor) of this transcription factor have been reported, yet no NF-κB blocker has been approved for human use. Various steroids and NSAIDs have been found to block NF-κB, but their effects are highly pleiotropic. The molecules that block NF-κB activation lack specificity and thus interfere with NF-κB's physiological roles in immunity, inflammation, and cellular homeostasis. Additionally, whether the concentrations of inhibitors used in tissue culture experiments can be applied *in vivo* is often unclear. Therefore, one of the major challenges facing researchers is to develop NF-κB inhibitors aimed at treating different diseases based on their ability to target specific pathways or cells, thereby avoiding the risk of undesired side effects. Future studies should also focus on validating *in vitro* data *in vivo*.

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