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Review Article

Molecularly-Targeted Strategy and NF-κB in Lymphoid Malignancies

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Molecularly-targeted therapy is a promising strategy for the treatment of cancer. Nuclear factor (NF)-κB is a transcription factor that is constitutively activated in various lymphoid malignancies and may therefore be a good therapeutic target. Lymphoid malignancies arise from different stages of normal lymphocyte differentiation and acquire distinct pathways for constitutive NF-κB activation. However, no NF-κB inhibitor has yet been successfully applied in clinical medicine. This review focuses on the concept of molecularly-targeted therapeutics with small molecule drugs, molecular mechanisms of constitutive NF-κB activation in lymphoid malignancies, and the development of NF-κB inhibitors. A future perspective regarding the development of NF-κB inhibitors is also included. 〔*J Clin Exp Hematop 53(3) : 185-195, 2013*〕

Keywords: molecularly-targeted therapy, lymphoid malignancies, nuclear factor-κB

INTRODUCTION

Over the past decade, considerable advancements in molecular biology have facilitated a greater understanding of the mechanisms of cancer and the development of molecularly-targeted antineoplastic therapy with small molecule drugs. For example, all-trans-retinoic acid for acute promyelocytic leukemia and imatinib for chronic myelocytic leukemia (CML) have resulted in marked improvement in outcomes for many patients.[1,2] In the field of lymphoid malignancies, the proteasome inhibitor, bortezomib, has improved outcomes for patients with multiple myeloma (MM).[3] The anaplastic lymphoma kinase (ALK) inhibitors such as crizotinib for patients with anaplastic large cell lymphoma (ALCL) will show us another success story.[4] Although there are an increasing number of such compounds that are being applied in clinical medicine, molecularly-targeted therapies for lymphoid malignancies remain limited.

The successful development of molecularly-targeted therapy requires a classification of each subtype of the specific cancer based on the major signaling pathways that underlie their pathogenesis. Nuclear factor-κB (NF-κB) is constitutively activated in various lymphoid malignancies and may be a potential therapeutic target.[5] The present review focuses on the concept of molecularly-targeted therapeutics with small molecule drugs, molecular mechanisms of constitutive NF-κB activation in lymphoid malignancies, and the development of NF-κB inhibitors.

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MOLECULAR TARGETING OF CANCER AND ITS THEORETICAL BACKGROUND

Molecularly-targeted therapy is a promising antineoplastic modality. Recent studies have advanced our knowledge of the theoretical background of molecularly-targeted therapy with small molecule drugs, including the concepts "oncogene addiction", "oncogene amnesia", "oncogenic shock", and "rehabilitation".[6–9]

Oncogene addiction and amnesia

Cancer cells bear many persistent abnormalities in oncogenes and tumor suppressor genes that can vary between different types of cancer cells and that can trigger deregulation of various signaling pathways. Although many signal transduction pathways are affected, there is typically only a few signaling pathways that are central to the neoplastic phenotype. This notion is currently known as the "oncogene addiction" theory and is supported by the success of therapies that block discrete molecular pathways.[6,10] For example, CML is characterized by gene translocation t(9;22)(q34;q11), which fuses the Abelson (*Abl*) tyrosine kinase gene at chromosome 9 with the break point cluster (*Bcr*) gene at chromosome 22, thereby generating the chimerical tyrosine kinase, Bcr-Abl. Bcr-Abl constitutively transduces aberrant signals, and blockade of this molecule by imatinib induces apoptosis of CML cells, thereby showing that CML cells are "addicted" to signals produced by Bcr-Abl. Even in cells with "oncogene addiction", transformation and proliferation of cancer cells do not take place without a concomitant defect in safety systems that control checkpoint signals. This defect is called "oncogene amnesia" and is recognized as a cause of tumorigenesis.[7]

Oncogenic shock and rehabilitation

Cancer cells depend on addicted signals that promote their survival by stimulation of proliferation and maturation arrest and also depend on inhibition of safety systems. Our experience in molecularly-targeted therapy indicates that survival of cancer cells depends on the balance between pro-survival and apoptotic signals. Blockage of survival signals in the context of addiction causes imbalance between these two signals, and subsequent domination of apoptotic signals induces cancer cells death. This phenomenon is referred to as "oncogenic shock".[8]

Even if molecularly-targeted therapies are highly successful, complete eradication of cancer cells from the body is difficult. In the case of CML, a cancer stem cell population appears to be resistant to imatinib, and suspension of imatinib therapy results in re-growth of CML cells. However, a certain proportion of patients with Bcr-Abl expression below the levels of detection do not experience recurrence. This indicates the importance of a rehabilitation step by the microenvironment, which surrounds the small residual number of cancer cells and inhibits their re-growth.[11] Recent studies indicate that immunomodulatory agents, which promote further reduction of residual cancer cells, are excellent complements of molecularly-targeted therapy ; this concept is known as "rehabilitation".[9] A schematic representation of oncogene addiction, oncogene amnesia, oncogenic shock and rehabilitation in relation to cancer treatment is presented in Fig. 1.

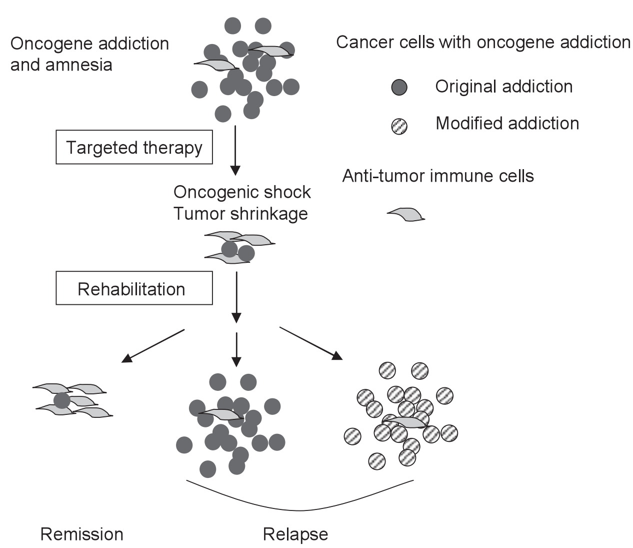

Fig. 1. A schematic representation of oncogene addiction, oncogene amnesia, oncogenic shock and rehabilitation in the process of cancer treatment. After shrinkage of the tumor cell burden by molecularly-targeted therapy, the rehabilitation process takes place. In the case of treatment failure, the original clone or modified clone with altered addiction expands, and recurrence occurs.

NUCLEAR FACTOR-κB (NF-κB)

NF-κB is a transcription factor that was originally described by Baltimore and co- investigators in 1986 as a molecule that binds to the promoter region of the immunoglobulin κ chain. NF-κB is induced by many diverse stimuli, including inflammatory cytokines, growth factors, oxygen stress and pathogens that are involved in many different biological phenomena (e.g., immune response, inflammation, cell proliferation, apoptosis and bone metabolism).[12]

Mechanisms of activation

NF-κB consists of five family members [i.e., RelA (p65), c-Rel, RelB, p50/p105 and p52/p100] and forms homo- or hetero-dimers. The regulatory factor, inhibitor of κB (IκB) localizes NF-κB within the cytoplasm. Both p105 and p100 possess a hybrid feature of NF-κB and IκB. These proteins are processed to NF-κB p50 and p52 by degradation of the IκB domain, respectively. Upon stimulation, signals converge on the IκB kinase (IKK), and degradation of IκB releases NF-κB and enables it to enter the nucleus, where NF-κB binds to the consensus sequence GGGRNNYYCC (R, purine ; Y, pyrimidine ; N, any base) in the promoter region of target genes and promotes gene expression. Major NF-κB pathways consist of the canonical (classical) and non-canonical (alternative) pathways (Fig. 2). NF-κB inducing kinase (NIK) in the non-canonical pathway can also activate the canonical pathway. Previous reports indicates that IKKα-mediated activation of IKKβ is involved in this process, although this notion remains controversial.[13,14]

A unique IκB protein, B cell leukemia/lymphoma 3 (BCL-3), regulates the third pathway. BCL-3 forms a complex with the p50 or p52 homodimer, both of which are processed from their precursor by IKK or related signals. This complex enters the nucleus and acts to repress or activate target genes. Phosphorylation by glycogen synthase kinase 3 (GSK3) and deubiquitination by cylindromatosis (CYLD) promotes and inhibits translocation of BCL-3 into the nucleus, respectively.

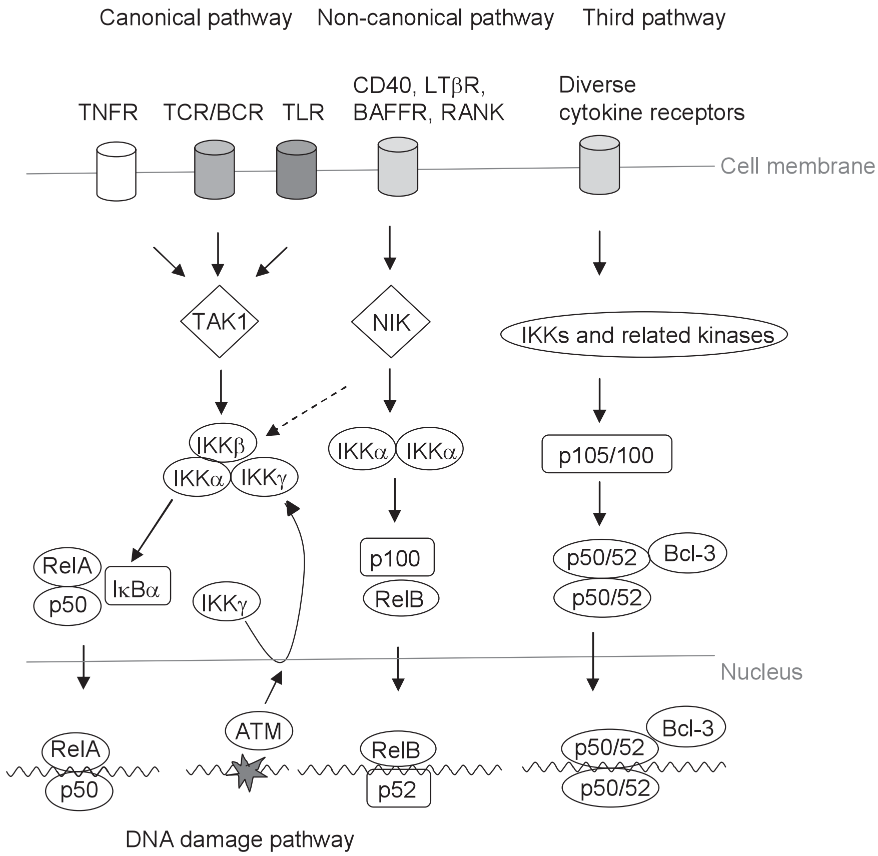

Fig. 2. Nuclear factor (NF)-κB pathways. Canonical (classical) and non-canonical (alternative) pathways are the major NF-κB pathways. There are a third pathway that is regulated by the unique protein, bcl-3, and a pathway triggered by DNA damage.

However, the manner in which this pathway is regulated is poorly understood.

DNA damage caused by diverse stimuli, such as chemotherapeutic agents and radiation, triggers ataxia telangiectasia mutated (ATM) and activates the IKK complex via ubiquitination of IKKγ. This inducible NF-κB protects cells from apoptosis and blunts the effect of the treatment. The different pathways are indicated in Fig. 2.[12,15-17]

Roles in cancer

NF-κB participates in the regulation of more than 500 genes and plays a central role in cancer biology by virtue of its actions on proliferation, anti-apoptosis, vascular regeneration, inflammation, metastasis, and infiltration. Signaling pathways involved in cancer cells are frequently linked to NF-κB. Constitutive activation of NF-κB is a hallmark of various type of cancers that originate from the hematopoietic system as well as solid organs.[18,19] This has led to the investigation of the molecular events responsible for constitutive activation of NF-κB.[20] Lymphoid malignancies frequently show strong and constitutive activation of NF-κB, which suggests that NF-κB plays a very important role in the development of lymphoid cells and their neoplastic transformation.[21] In other words, the "oncoge addiction" of malignant lymphoid cells may frequently be dependent on NF-κB. Experimental data also supports the notion of "NF-κB addiction" of lymphoid malignancies, all of which suggest that constitutive activation of NF-κB is a promising therapeutic target for lymphoid malignancies.

DEREGULATION OF NF-κB IN LYMPHOID MALIGNANCIES

Constitutive activation of NF-κB in lymphoid malignancies was initially described in studies conducted around the year 2000. Subtypes in which this has been demonstrated include diffuse large cell lymphoma (DLBCL) of activated B-cell (ABC) type,[22] mucosa-associated lymphoid tissue (MALT) lymphoma,[23] mantle cell lymphoma (MCL),[24] B-precursor acute lymphocytic leukemia (ALL), classical Hodgkin lymphoma (cHL),[25] MM[26] chronic lymphoid leuke-

Table 1. Lymphoid malignancies and molecules involved in constitutive nuclear factor-ϰB (NF-ϰB) activation

Lymphoid malignancies	Molecules triggering aberrant NF-ϰB activation
ABC-diffuse large B-cell lymphoma	Activating mutations in CD79A/B and CARD11 Inactivating mutations of A20 Activating mutations in p100
MALT lymphoma	Chimerical c-IAP2-MALT1 Induction of BCL10 and MALT-1 by chromosomal translocations
Classical Hodgkin lymphoma	CD30, CD40, RANK, TACI, BCMA, LMP-1, c-Rel Inactivating mutations of IϰB and A20
Multiple myeloma	TACI, BCMA Various genetic aberrations (e.g., CD40, LTβR, NIK, TRAF2, TRAF3, p50, p100, CYLD)
Chronic lymphocytic leukemia	CD40, TACI, BCMA, GSK3β
B-precursor acute lymphocytic leukemia	Chimerical Bcr-Abl Activating mutations in Ras
Mantle cell lymphoma	TACI, BCMA
Adult T-cell leukemia/lymphoma	Tax, NIK
Pleural effusion lymphoma	v-FLIP

ABC, activated B-cell; MALT, mucosa associated lymphoid tissue; CARD11, caspase recruitment domain-containing protein 11; c-IAP2, chimerical cellular inhibitor of apoptosis protein 2; BCL10, B-cell lymphoma/leukemia 10; RANK, receptor activator of NF-ϰB; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; BCMA, B-cell maturation antigen; LMP-1, latent membrane protein-1; IϰB, inhibitor of ϰB; LTβR, lymphotoxin-β receptor; NIK, NF-ϰB inducing kinase; TRAF, tumor necrosis factor receptor-associated factor; CYLD, cylindromatosis; GSK3β, glycogen synthase kinase 3β; NIK, NF-ϰB inducing kinase; v-FLIP, viral FLICE-inhibitory protein [FLICE, Fas-associating protein with death domain (FADD)-like interleukin-1β-converting enzyme (ICE)].

mia (CLL)[27] and lymphoid malignancies strongly associated with viruses, i.e. adult T-cell leukemia/lymphoma (ATLL)[28] and primary effusion lymphoma (PEL).[29] These malignancies arise from different stages of normal lymphocyte differentiation and have distinct pathways for NF-ϰB activation.

Defective mutation in negative regulators of NF-ϰB signaling (i.e., A20, cylindromatosis, IϰB, etc.) is responsible for NF-ϰB activation in some of these lymphoid malignancies. Loss of these signals alone is not solely responsible for changes in NF-ϰB signaling.[30] Instead, these mutations may be a consequence of positive selection of cells bearing these mutations and loss of control during malignant transformation. These mutations may cooperate with upstream signals and thereby result in constitutive NF-ϰB signaling. Table 1 summarizes lymphoid malignancies characterized by strong and constitutive NF-ϰB activation and the molecules involved in this process. Most of the molecules involved are clustered within canonical and non-canonical pathway. Positions of each molecule in the NF-ϰB pathway are indicated in Fig. 3.

DLBCL and MALT lymphoma

The molecules responsible for the deregulated activation of NF-ϰB signaling are localized between the B-cell receptor (BCR) and the transforming growth factor-β-activated kinase 1 (TAK1). Activating mutations of CD79B, or less commonly of CD79A or caspase recruitment domain-containing protein 11 (CARD11), account for one-third of cases of NF-ϰB activation in activated B-cell (ABC)-like DLBCL.[31,32] One-quarter of ABC-like DLBCL cases are associated with genetic inactivation of A20. Although rare, production of mutant NF-ϰB2 (p100) lacking ankyrin repeats by deletion of the 3' end of the NF-ϰB2 gene is also associated with NF-ϰB activation. Many more alterations have been discovered in this subtype.[33,34]

Formation of chimerical cellular inhibitor of apoptosis protein 2 (c-IAP2)-MALT1 by t(11;18)(q21;q21) triggers constitutive NF-ϰB signaling independent of regulation of CARD11 and B-cell lymphoma/leukemia 10 (BCL10) by BCR in the case of MALT lymphoma that is unrelated to *Helicobacter pylori* infection.[35-37] Less commonly, constitutive induction of MALT1 and BCL10 by t(14;18)(q32;q21)[38] and t(1;14)(p22;q32),[23,39] respectively, also contributes to modification of NF-ϰB signaling.

cHL, MM and CLL

Molecules involved in cHL include the family of tumor necrosis factor receptors (TNFRs). Activation of TNFR molecules (i.e., CD30,[40-42] CD40,[40,43] transmembrane activator and CAML interactor [TACI], B-cell maturation antigen [BCMA],[44] and receptor activator of NF-ϰB [RANK][45]), and

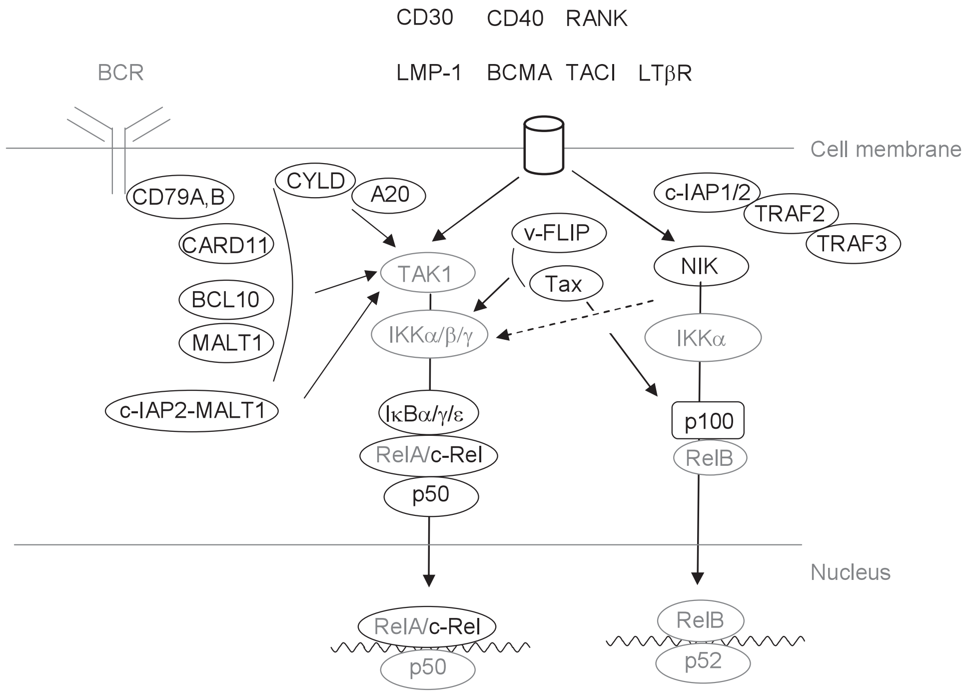

Fig. 3. The molecules committed to constitutively strong nuclear factor (NF)-κB activation in lymphoid malignancies and their positions within NF-κB pathways. Involved molecules indicated in Table 1 are illustrated in black font.

TNFR-like proteins (i.e., Epstein-Barr virus latent membrane protein-1 [LMP-1]) involve constitutive NF-κB signaling in cHL. Defective mutations in negative regulators (i.e., IκB[46,47] and A20[48]), and amplification of the *c-REL* locus may also involve constitutive NF-κB signaling in cHL.[49]

In terms of NF-κB target genes, primary mediastinal B-cell lymphoma and cHL have similar gene expression profiles.[50,51] Although the *c-REL* amplification and defects in A20 have been reported, the precise molecular mechanisms of constitutive NF-κB activation in primary mediastinal B-cell lymphoma remain unclear.[52] A recent report indicates involvement of NF-κB in the gene expression profile of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).[53]

In part, NF-κB activation in MM may be caused by signals from the bone marrow microenvironment ; activation of TACI and BCMA by their ligands, B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are conceivably involved in this process.[54,55] In addition, MM cells harbor various non-overlapping mutations (Table 1).[14,56]

Genetic alterations in the NF-κB pathway are rarely reported in CLL when compared with other lymphoid malignancies. CD40 is involved in NF-κB activation in neoplastic follicle and in bone marrow.[57,58] BAFF and APRIL activate NF-κB via their receptors, TACI and BCMA, in a paracrine or autocrine manner.[59] Aberrant accumulation of GSK3β in the nucleus is another mechanism responsible for NF-κB activation in CLL.[60]

ALL and MCL

Formation of chimerical *Bcr-Abl* by t(9;22) and activating *Ras* mutations involves constitutive NF-κB signaling in B-precursor ALL. *Bcr-Abl* is associated with 25-30% of adult cases and with 5% of child cases and is thought to activate NF-κB in an IKK-independent manner.[61-63] Ras mutations can mediate activation of the canonical pathway via direct degradation of IκBα[61]

NF-κB signaling in MCL drives BAFF and forms a positive feedback loop activating the canonical and alternative pathway via BCMA and TACI.[64] MCL also shows mono- and bi-allelic deletions of FAF1, which inhibits RelA and IKKβ[65] A20 is often inactivated in MCL by genomic mutations, deletions and increased methylation of the promoters.[66]

ATLL and PEL

Human T-cell leukemia/lymphoma virus type 1 (HTLV-1) tax triggers NF-κB signaling by associating with and activating IKK.[67,68] However, in ATLL cells, Tax expression is generally repressed by epigenetic or other mechanisms in HTLV-1 proviruses.[69,70] Tax is a major molecule that triggers NF-κB signaling during transformation of infected cells.

Recent studies suggest that NIK mediates constitutive NF-κB signaling, which is triggered by suppression of miR31, a negative regulator of NIK mRNA.[71,72] PEL is associated with Kaposi sarcoma-associated herpes virus (KSHV) infection, and association of viral FLICE-inhibitory protein (FLIP), a cellular homologue of FLIP, with IKK complex induces constitutive NF-κB signaling.[73]

DEVELOPMENT OF NF-κB INHIBITORS

As indicated in Fig. 4, targets of NF-κB inhibitors can be classified as follows : (a) ubiquitination, which transduces signals downstream (i.e., K63 type ubiquitination or straight chain ubiquitination), (b) kinase cascades, which phosphorylate IKK and mediate the phosphorylation of IκBα, (c) degradation of IκBα modified with K48 type ubiquitination at the proteasome, (d) nuclear translocation of NF-κB, (e) DNA binding of NF-κB, and (f) acetylation or methylation of NF-κB.

There are more than 800 NF-κB inhibitors. However, some of these inhibitors can only be used in the laboratory due to toxicity or pharmacodynamics limitations.[74] NF-κB inhibitors can be classified as old drugs, which have already been used in clinical practice and were only recently discovered to have inhibitory properties, and new drugs, which have been purposely developed as NF-κB inhibitors. As of yet, none of these new NF-κB inhibitors have been successfully translated into clinical medicine. An overview of the current status of representative NF-κB inhibitors is described in Table 2.

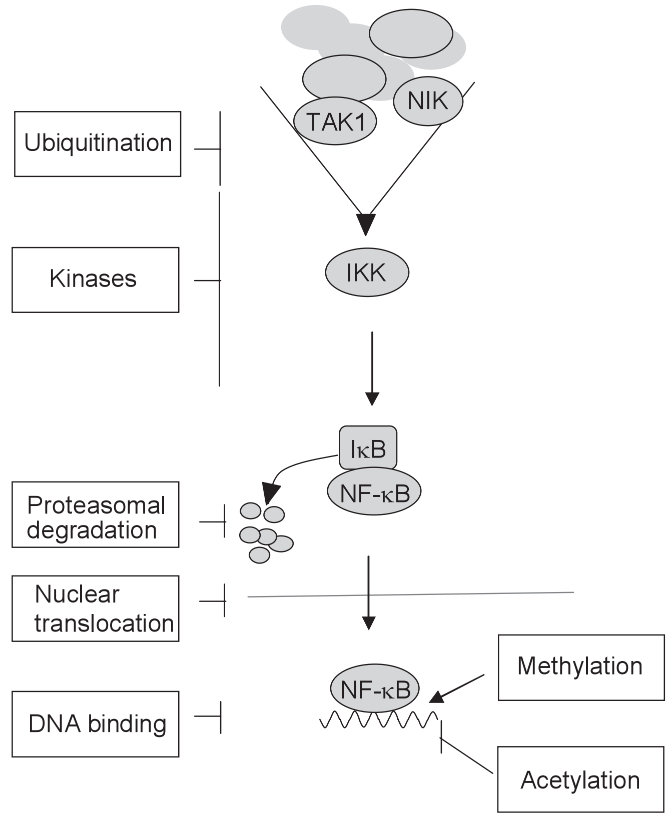

Fig. 4. Potential targets for the development of nuclear factor (NF)-κB inhibitors. Inhibition is more specific when a compound is directed against more unique targets in NF-κB pathways.

Old drugs

This group includes classical drugs, such as steroids and non-steroidal anti-inflammatory agents. Most of these old drugs have an NF-κB inhibitory effect as a part of their original effect. Non-steroidal anti-inflammatory agents, such as aspirin, sulindac and selective COX-2 inhibitors, exert an NF-κB inhibitory effect by inhibiting multiple steps in the NF-κB pathway,[75,76] and several reports suggest that these compounds can prevent cancer, including cHL.[77]

Glucocorticoids, such as dexamethasone and prednisolone, are widely used as anti-inflammatory and immunosuppressive agents and for the treatment of lymphoid malignancies. Two mechanism of actions have been proposed for their effects : IκBα transcription mediated by glucocorticoid receptor (GR)[78,79] and histone acetylation or methylation by the GR-RelA complex.[80]

Sulfasalazine (SSZ), a synthetic anti-inflammatory drug used for rheumatoid arthritis and inflammatory bowel disease, inhibits NF-κB by direct inhibition of adenosine triphosphae (ATP) binding to IKKα and IKKβ[81] Thiol-reactive drugs, represented by arsenic trioxide and gold compound auranofin, inhibit NF-κB by modifying IKKβ Cys-179.[82,83] These drugs have been used for the treatment of acute promyelocytic leukemia (APL) and rheumatoid arthritis, respectively.

Tamoxifen, a selective estrogen regulator modulator (SERM),[84] a ligand for peroxisome proliferators-activated receptor (PPAR),[85] derivatives of macrolides (rapamycin and everolimus[86]), immunomodulators (thalidomide and lenalidomide[87]) and dietary agents (culcumin[88]) inhibit NF-κB, although the mechanisms by which they produce this effect are unclear.

New drugs

Pharmaceutical companies are developing specific NF-κB inhibitors, and most of these drugs target a key molecule that has a critical role in signal transduction in the NF-κB pathway. Most of these drugs are inhibitors for IKK, especially IKKβ[89] Other drugs include inhibitors of the nuclear translocation and the DNA binding of NF-κB. Although some of these drugs have entered in clinical trials, most are not being currently studied for cancer. Bortezomib, a proteasome inhibitor, was previously thought to inhibit NF-κB, but more recent reports indicate that this compound activates NF-

Table 2. Old and new nuclear factor-κB (NF-κB) inhibitors, and their major targets in NF-κB pathways

Drugs	Targets in NF-κB pathway
Old drugs	
Glucocorticoids	IκB, RelA
SERMs	
Tamoxifen, Raloxifene	IKK, RelA
PPAR ligands	
Ciglitazone	IκBα, IκBβ
Macrolides	
Everolimus	IκBα
Thalidomide	IKKβ
Thiol-reactive drugs	
Arsenic trioxide	IKKβ
Auranofin	IKKβ
NSAIDs	
Aspirin	IKK, RelA, COX-2
Dietary agents	
Culcumin	IKK
New drugs	
IKK inhibitors	
PS-1145	IKKβ
ACHP	IKKβ
SPC-839	IKKβ
BMS-345541	IKKβ
Nuclear translocation inhibitors	
DHMEQ	NF-κB
Proteasome inhibitors	
Bortezomib	Proteasome

SERM, selective estrogen regulator modulator; PPAR, peroxisome proliferators-activated receptor; NSAIDs, non-steroidal anti-inflammatory drugs; IKK, inhibitor of κB kinase; PS-1145, β-carbolin; ACHP, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile; SPC-839, quinazoline; DHMEQ, 5-dehydroxymethyl derivative of epoxyquinomicin C; IκB, inhibitor of κB; COX-2, cyclooxygenase-2.

κB.[90] Therefore, further characterization of the mechanism of action of this compound is required.

IKK inhibitors

Many IKK inhibitors have been described, and most have more potent activity against IKKβ than against IKKα. Most common IKK inhibitors, which includes β-carbolin (PS-1145) and quinazoline (SPC-839) exert their effect by inhibiting incorporation of ATP into IKK.[91,92] ACHP [2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile] also exerts its effect by competing with ATP for incorporation to IKK.[93] BMS-345541, which is a quinoxaline derivative, inhibits kinase activity by an allosteric effect without affecting ATP binding.[94] The epoxiquinon A monomer, the jesteron dimer, and parthenolide all target Cys-179 in IKKβ[95,96] Recent reports suggest that the anti-cancer effect of IKKβ inhibitors is hampered by activation of the non-canonical pathway.[97] Furthermore, several reports indicate the involvement of IKK in pathways other than NF-κB, thereby raising the question about the specificity and potential off-target effects of IKKβ inhibitors.[98,99]

Inhibitors of the nuclear translocation and DNA binding of NF-κB

The targets of these small numbers of drugs are downstream of IKK and are shared within the canonical and non-canonical NF-κB pathway. SN-50 is a peptide consisting of 26 amino acids that includes the nuclear translocation signal of NF-κB p50 and that competitively inhibits nuclear translocation of NF-κB into the nucleus.[100] However, SN-50 also inhibits other transcription factors, such as AP-1, because of similarities in amino acids alignment. The chroman analog, KL-1156, prevents the nuclear translocation step of RelA.[101] DHMEQ, a 5-dehydroxymethyl derivative of epoxyquinomicin C isolated from *Amycolatopsis sp.*, is a unique NF-κB inhibitor that acts at the level of the translocation of NF-κB into the nucleus and DNA binding.[102,103] DHMEQ directly binds to NF-κB, and its effect is more potent on NF-κB with the activation domain (i.e., RelA, c-Rel and RelB) than on NF-κB without the activation domain (i.e., p50 and p52). We previously described the efficacy of DHMEQ on various lymphoid malignancies, including MM, CLL, ATLL, cHL and PEL.[28,104-107] IKKβ inhibitors that target the Cys-179 of IKKβ also target Cys within the DNA binding domain of NF-κB and inhibit the binding of NF-κB into target DNA sequences.

CONCLUDING REMARKS

Preclinical studies suggest that NF-κB inhibitors may have utility for the treatment of cancers, especially in lymphoid malignancies in which there is constitutively strong NF-κB activity. Since NF-κB plays important roles in many biological phenomena, including immunity and hematogenesis, it is important to keep side effects to a minimum. For that purpose, when we try to translate a developed NF-κB inhibitor into clinical medicine, it is important to understand the molecular background of each cancer and the mechanisms of the action of the NF-κB inhibitors. Careful follow-up of side effects in clinical studies is also important. Reevaluation of old drugs may provide an avenue to identify an effective strategy with a lower incidence of side effects. Imatinib is called as “a magic cancer bullet” because it is very effective. Thus, if an NF-κB inhibitor can be successfully translated into clinical medicine, the compound will deserve to be called as “a miracle cancer bullet”.

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