



## Review

### Activation of NF- $\kappa$ B signalling pathway by inflammatory regulators and associated drug discovering

Dr. ShiQin Xu<sup>\*</sup>, Dr. XiaoHong Li<sup>\*</sup>, Prof. XiaoFeng Shen<sup>\*</sup>, Prof. XiRong Guo<sup>\*\*</sup>, Prof. YuZhu Peng<sup>\*\*</sup>, Dr. YuSheng Liu<sup>\*</sup>, Dr. QingSong Zhao<sup>\*</sup>, Dr. ShanWu Feng<sup>\*</sup> and Dr. FuZhou Wang<sup>\* $\Psi$</sup>

<sup>\*</sup>Department of Anesthesiology and Critical Care, Affiliated Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing, Jiangsu, China

<sup>\*\*</sup>Institute of Pediatrics, Affiliated Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing, Jiangsu, China

(Received 25 February 2009 and accepted 12 April 2009)

**ABSTRACT:** Intracellular signalling transduction plays a pivotal role in cell activation, and the regulation of gene transcription needs the involvement of series of nuclear factors. Nuclear transcription factor- kappa B, one of the key factors in mediating gene expression, takes an essential part in a body of physiological and pathological processes. Endotoxin lipopolysaccharides, proinflammatory cytokine tumor necrosis factor-alpha, ligand-dependent immunocellular B cell receptor and inflammation-associated bradykinin are four typical NF- $\kappa$ B activation pathways. Activating or inhibitory drugs focused on NF- $\kappa$ B may be strongly related with the therapy of associated diseases, and the exploration of effective and economical drugs concentrated on NF- $\kappa$ B is crucial.

**KEY WORDS:** Nuclear factor- $\kappa$ B; Inhibitor factor- $\kappa$ B; Inflammatory signalling; Drug discovery

## INTRODUCTION

Transcription factor NF- $\kappa$ B was initially described as a mediator of the expression of the kappa light-chain gene in the nuclei of murine mature B cell lines and plasmacytomas, but has subsequently been found in many other cells. Even viruses have been found that could take direct advantage of NF- $\kappa$ B's powerful transcriptional effect. The high level of interest in NF- $\kappa$ B / Rel is focused on their broad roles in inducibly and coordinately controlling gene transcription of significant biomedical importance. Herein we concentrate on understanding the functional roles of NF- $\kappa$ B and I- $\kappa$ B in immune regulation, signalling pathways activated by lipopolysaccharide (LPS), tumor necrosis factor-

alpha (TNF- $\alpha$ ), ligand-dependent immunocellular B cell receptor (BCR) and bradykinin (BK), and associated drug discovering.

## NF- $\kappa$ B FAMILY, STRUCTURE, AND GENERAL ROLES

NF- $\kappa$ B is the prototype of a family of dimeric transcription factors made from monomers which have approximately 300 amino-acid Rel regions that bind to DNA, interact with each other, and bind the I- $\kappa$ B inhibitor. All currently known members of NF- $\kappa$ B / Rel proteins family include RelA (p65), RelB, c-Rel, v-Rel, p50, p52, Dorsal, Dif, Relish, etc. The activated form of NF- $\kappa$ B is a heterodimer, generally, which consists of two proteins, a p50 subunit and a p65 subunit, playing the key role in various courses of transcription. In unstimulated cell, p50/p65 heterodimer, the classical member of the Rel family of transcription factor, is found in cytoplasm and is bound to I- $\kappa$ B $\alpha$ , I- $\kappa$ B $\beta$ , and I- $\kappa$ B $\gamma$ , which keep it from entering the nuclei. Rel family involved in oncogenesis is not new, they also are part of activated NF- $\kappa$ B, and the

<sup>$\Psi$</sup> Correspondence at: Department of Anesthesiology and Critical Care, Affiliated Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, No. 123, Tianfei Xiang, Mochou Road, Nanjing 210004, Jiangsu, China. Email: [zfwang50@njmu.edu.cn](mailto:zfwang50@njmu.edu.cn) Phone No: 86-25-84460777-3301

different forms of Rel may activate different sets of target genes. The members of NF- $\kappa$ B / Rel family share the conserved Rel-homology domain, involved in specific DNA binding and dimerization.

NF- $\kappa$ B specially recognizes kappa B DNA element with a consensus sequence of 5'-GGGRNYYYCC-3' (R is an unspecified purine; Y is an unspecified pyrimidine; and N is any nucleotide). The crystal structure at 2.9 Å resolution of the p50/p65 heterodimer has a 5-base-pair 5'-GGGAC-3' subsite for p50, and a 4-base-pair 3'-TTCC-5' subsite for p65, each subunit consists of two immunoglobulin-like domains connected by a 10-amino-acid flexible linker. Base-specific binding by p50 to the subsite occurs through the residues Arg54, Arg56, Tyr57, Glu60, His64 and Lys241, and binding to the 3' subsite by the p65 subunit occurs through Arg33, Arg35, Tyr36, Glu39 and Arg187. All these results explain the different behavior of the p50/p65 heterodimer with heterologous promoters. The structural features of the p50 dimer-DNA complex are consist of 10 loops contribute to protein-DNA recognition.

A detailed understanding of the regulation of NF- $\kappa$ B will be greatly facilitated by the cloning of its gene. Cloning of the p50 DNA binding subunit of NF- $\kappa$ B disclosed that the NF- $\kappa$ B/ I- $\kappa$ B system is a unique exemplar of control over the function of a protein by cytoplasmic / nuclear partitioning. The NF- $\kappa$ B protein can be considered as a second messenger, which transmitting signals from the cell surface to the nucleus, just like the action pattern of glucocorticoids receptor. It's necessary to point out that expression of the NF- $\kappa$ B gene seems to be strongly regulates by TNF- $\alpha$  and phorbol esters at the level of mRNA abundance. Interestingly, factor KBF-1 that is bound by MHC-I enhancer sequences has similar DNA combining region. The p65 subunit of NF- $\kappa$ B serves as a receptor for the inhibitory subunits I- $\kappa$ B $\alpha$  and I- $\kappa$ B $\beta$  and exhibits  $\kappa$ B-specific DNA binding activity that is considerably weaker than that of the p50 subunit. The 65-KD protein showed identical mobility in native gels as purified p65 derived from authentic NF- $\kappa$ B. Meanwhile, I- $\kappa$ B exerts its inhibitory effect upon NF- $\kappa$ B primarily through interaction with p65 subunit.

#### NF- $\kappa$ B INHIBITOR FAMILY I- $\kappa$ B AND IKK

In resting cells, NF- $\kappa$ B is found in cytosol and is bound to I- $\kappa$ B $\alpha$ , I- $\kappa$ B $\beta$ , and I- $\kappa$ B $\gamma$  complex, which belong to the inhibitory protein family. Other I- $\kappa$ B-like proteins involve Bcl-3, I- $\kappa$ B- $\epsilon$ , I- $\kappa$ B- $\delta$  (p100), Cactus, and Relish etc<sup>1</sup>. NF- $\kappa$ B is activated through the phosphorylation of I- $\kappa$ B, and then causing its rapid degradation by proteasomes. A variety of stimuli can activate NF- $\kappa$ B by separating I- $\kappa$ B from them, including cytokines, activators of PKC,

Viruses, Oxidant and bacterial components, such as LPS, HSL, peptidoglycan, pneumolysin, flagellin, slime glycoprotein, bacterial DNA<sup>2-4</sup>. Nevertheless, complex formation between NF- $\kappa$ B and I- $\kappa$ B is rapidly and efficiently reversible in vitro, which fits well with the finding that induction of NF- $\kappa$ B is reversible *in vivo*.

I- $\kappa$ B kinases (IKKs) are required for the departure of I- $\kappa$ B from NF- $\kappa$ B, subsequently lead to conjugate with ubiquitin and proteasome-mediated degradation of the inhibitor. The activation of NF- $\kappa$ B needs phosphorylation of I- $\kappa$ B $\alpha$  at Ser32 and Ser36. In intact cells, phosphorylation of I- $\kappa$ B $\alpha$  is not sufficient for activation of NF- $\kappa$ B.

The predominant IKK complex found in cell lines contains two catalytic subunits, IKK $\alpha$  (IKK1), IKK $\beta$  (IKK2), and a chaperon subunit, NEMO (NF- $\kappa$ B essential modifier) or IKK $\gamma$ . IKK $\alpha$  and IKK $\beta$  are serine / threonine protein kinases, whereas NEMO contains several protein interaction motifs but no apparent catalytic domain. TNF- $\alpha$  stimulation showed that the ubiquitination of NEMO mediated by c-IAP-1 plays a crucial role in the activation of IKK complex. It's the conserved zinc finger of NEMO that required for both NEMO ubiquitination and IKK activation<sup>5</sup>, especially the key role of residue cysteine 417 at the zinc fingers domain of NEMO<sup>6</sup>. And differential phosphorylation of IKK $\gamma$ /NEMO by IKK $\beta$  and other kinases may be important in regulating IKK activity, the carboxyl terminus residues 144-159, 369 and 375 of IKK $\gamma$ /NEMO are the major sites of phosphorylation by IKK $\beta$ <sup>7</sup>. IKK $\gamma$ /NEMO is central to many immune, inflammatory and apoptotic pathway<sup>8</sup>. On the contrary, IKK $\gamma$ C417R exhibits negative effects on IKK activity and NF- $\kappa$ B activation in human THP.1 monocytes, consequently the cell sensitivity to TNF- and LPS-mediated apoptosis increased<sup>6</sup>. Furthermore, Delhase M et al. indicated that the autophosphorylation of a serine cluster located between the HLH (Helix-Loop-Helix) motif of IKK $\beta$  and its COOH-terminus decrease IKK activity. To IKK $\alpha$  activation, Ser176 of it represents the major site phosphorylated by NF- $\kappa$ B-inducing kinase (NIK). At the same time, NIK has an essential role in the thymic microenvironment in the establishment of central tolerance<sup>9</sup>.

Therefore, the phosphorylation of both the complexes of I- $\kappa$ B and IKK is a prerequisite for NF- $\kappa$ B's nuclear translocation.

#### NF- $\kappa$ B ACTIVATED SIGNALLING BY FOUR TYPICAL STIMULI

Generally, to activate NF- $\kappa$ B, that suitable environmental signals must bring about the release of NF- $\kappa$ B dimers from their cytoplasmic inhibitors, in particular from the prototypical inhibitor I- $\kappa$ B $\alpha$  and its close relatives, I- $\kappa$ B $\beta$ , and I- $\kappa$ B $\gamma$ <sup>10</sup>, it is a

first and necessary step in the activation process. An inducible degradation of I- $\kappa$ B $\alpha$  through a cytoplasmic, chymotrypsin-like protease, is required, that is to say, phosphorylation of I- $\kappa$ B $\alpha$  is necessary. Phosphorylation of I- $\kappa$ B $\beta$  and the regulatory subunit of I- $\kappa$ B $\gamma$  are indispensable to activating the heterodimer of p50/p65. There are transient changes in NF- $\kappa$ B activity duo to reductions in I- $\kappa$ B- $\epsilon$ , which might contribute to long-term, persistent changes that accompany B cell differentiation<sup>11</sup>.

It is understandable that IKKs must be activated before I- $\kappa$ B complex phosphorylated. The noncatalytic IKK component IKK $\gamma$ /NEMO plays an essential role for NF- $\kappa$ B activation, and serves as an adaptor recruiting Tax to IKK catalytic subunits, I- $\kappa$ B $\alpha$  and I- $\kappa$ B $\beta$ . IKK $\beta$  phosphorylates I- $\kappa$ B and IKK $\alpha$  phosphorylates the NF- $\kappa$ B2/p100 precursor<sup>12</sup>. The ubiquitination of IKK $\gamma$ /NEMO may lead to the recruitment of an I- $\kappa$ B $\beta$  kinase, such as MEKK3 or  $\zeta$ PKC to the IKK complex, thereby resulting in I- $\kappa$ B $\beta$  phosphorylation and consequently IKK activation. Interestingly, the phosphorylated I- $\kappa$ B $\beta$  has the ability to phosphorylate IKK $\gamma$ , I- $\kappa$ B $\alpha$  is phosphorylated by IKK $\gamma$ /IKK $\beta$ -p complex<sup>13</sup>, finally, IKK takes the role in activating I- $\kappa$ B complex. However, the lymphotoxin  $\beta$  receptor (LT $\beta$ R) in stromal cells induces processing of p100 via an alternative pathway, which leads to the delayed and sustained liberation of p50-RelB and p52-RelB complex<sup>14</sup>. IKK $\alpha$  preferentially phosphorylates NF- $\kappa$ B2/p100, and this activity requires its phosphorylation by upstream kinase, one of which may be NIK<sup>12</sup>.

After NF- $\kappa$ B divorcing from NF- $\kappa$ B- I- $\kappa$ B complex, then translocating into nucleus and binding to the DNA reaction domains, consequently the transcription of cytokines, chemokines, and other molecules begin to come about. In brief, the general pathway of NF- $\kappa$ B observes IKK kinase/IKKs-p/ I- $\kappa$ Bs-p/ NF- $\kappa$ B/transcription processing. LPS, TNF- $\alpha$ , BCR and Bradykinin are four representative stimuli, which respectively activate the NF- $\kappa$ B signalling pathways.

### LPS ACTIVATING NF- $\kappa$ B SIGNALLING

Regardless of gram-negative or gram-positive bacteria, LPS's way could almost stand for the general signalling transduction. As one of the important endotoxins, LPS can lead to an array of signalling molecules activated, which phosphorylate I- $\kappa$ Bs and that of degradation.

LPS induces cellular responses by complexing with circulating LPS-binding protein (LBP) and subsequently binding to CD14. It is generally accepted that LPS signal transduction is mediated by toll-like receptor (TLR), especially TLR4. Latest study shows that a specific binding site for LPS on the human HSP60, region as aa 354-365<sup>15</sup>.

TLR4 trigger a common intracellular signalling pathway that includes myeloid differentiation factor 88 (MyD88) or Toll/IL-1 receptor domain-containing adaptor protein (TIRAP)/MyD88-adaptor-like (MAL)<sup>16</sup>. Then interleukin-1 receptor-associated kinase-1 and -2 (IRAK1, IRAK2) is recruited to the receptor through MyD88, becomes phosphorylated and is rapidly degraded<sup>17</sup>. Interacting with TNF receptor-activated factor 6 (TRAF6)<sup>18</sup> relay the signal downstream. Downstream of TRAF6, mitogen-activated protein kinase (MAPK) is activated and I- $\kappa$ Bs degraded, finally, activator protein-1 (AP-1) and NF- $\kappa$ B are activated<sup>19</sup>. TRAF6 bridges IRAK-1 and IRAK-2 to transforming-growth factor- $\beta$ -activated and NIK<sup>20</sup>, NIK activates IKK complex. However, several molecules, including TAK1/TAB1, are capable of activating the MAPKKs, MKK3/6 and MKK4, which in turn activate p38 and JNK, respectively<sup>21</sup>. MEKK1 also activates the JNK pathway by phosphorylating MKK4<sup>22</sup>. Moreover, LPS activates a c-Src-Ras-MEK1/2-MAPK-PP90rsk signalling pathway that leads to activation of NF- $\kappa$ B (p50/p65). One MyD88-independent signalling pathway by TLR4 has showed that overexpression of TRAM, along with TRIF, caused IRF3 to translocate to the nucleus and take the role with p65 together<sup>23</sup>.

So far, ten human Toll-related proteins are characterized, Toll-like receptors (TLRs) 1 to 10, with human called TLR4<sup>24</sup>, which is LPS's receptor. Upon repeated LPS stimulation, there is an upregulation of p50 and little production of TNF mRNA and protein, i.e., the cells are tolerant to LPS. (**Figure 1**)

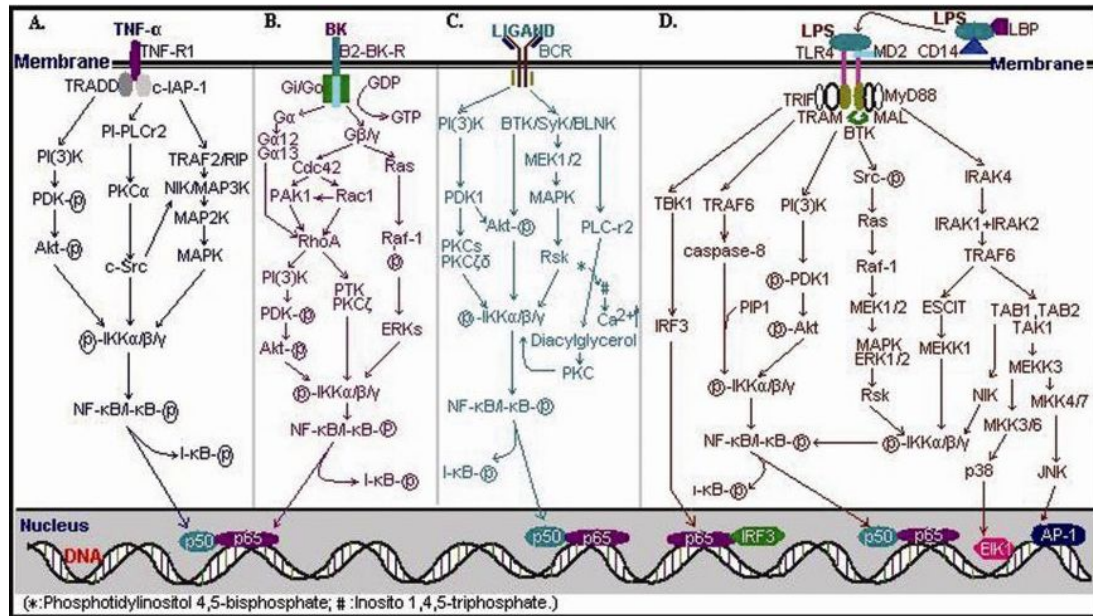
### TNF-A ACTIVATING NF- $\kappa$ B SIGNALLING

TNF- $\alpha$  and IL-1 are two major cytokines that induce an almost identical proinflammatory response; here we merely elucidate TNF- $\alpha$  signalling transduction.

TNF- $\alpha$  interaction with TNF-R1 results in receptor trimerization and subsequent association with the adaptor TRADD via the death domains of both proteins. TRADD then recruits TRAF2, RIP and other molecules, leading to the formation of the TNF-R1 signalling complex, downstream of NIK activation, NIK then phosphorylates IKK $\alpha$ . In addition to activating the NIK-IKK $\alpha$ / $\beta$  pathway, TNF- $\alpha$  activates the PKC-dependent c-Src pathway, these two pathways cross-link between c-Src and NIK, and converge at IKK $\alpha$ / $\beta$ <sup>25</sup>, and go on to activate NF- $\kappa$ B, via serine phosphorylation and degradation of I- $\kappa$ B $\alpha$ . TNF- $\alpha$  activates phosphatidylinositol-3-OH kinase (PI-3K) and its downstream target Akt (protein kinase B) are necessary for TNF activation of NF- $\kappa$ B<sup>26</sup>. The role for NF- $\kappa$ B in growth factor signalling, an anti-apoptosis pathway of Ras/PI3K/Akt/IKK/NF- $\kappa$ B, is

linking anti-apoptotic signalling with transcription machinery. Yin L et al. verified that NIK acts in a receptor-selective manner, and its function is limited in the case of the Lymphotoxin- $\beta$  receptor (LT $\beta$ R) to promoting the transcriptional action of the NF- $\kappa$ B complex<sup>27</sup>. So, the function of NIK in LT $\beta$ R signalling may be similar to that of glycogen

synthase kinase-3 $\beta$  or the T2K/TBK1/NAK kinase, which functions in TNF and IL-1 signalling to induce NF- $\kappa$ B activation without altering I- $\kappa$ B degradation or NF- $\kappa$ B nuclear translocation<sup>28</sup>. NIK and IKK $\alpha$  are essential for the induction of NF- $\kappa$ B through LT $\beta$ R, whereas the NIK-IKK $\alpha$  pathway is dispensable in TNF-R1 signalling<sup>29</sup>. (Figure 1)



**Figure 1: The schematic of NF- $\kappa$ B activation signalling transduction pathways:** Cells are exposed to TNF- $\alpha$ , Bradykinin, BCR ligands, and LPS as A, B, C, D showed respectively, as a consequence, the degradation of I- $\kappa$ B and translocation of NF- $\kappa$ B are followed, NF- $\kappa$ B then interacts with DNA to control transcription.

### BCR LIGANDS ACTIVATING NF- $\kappa$ B SIGNALLING

B cell receptor (BCR) engagement directs B cell biological responses by initiating biochemical signalling cascades<sup>30</sup>, which firstly needs the BCR binding ligands are in existence. Bruton's tyrosine kinase (BTK) transmits signals from the B cell antigen receptor to transcription factor NF- $\kappa$ B. BTK, in concert with the protein tyrosine kinase Syk and the adaptor protein BLNK, has recently been demonstrated to phosphorylate and activate phospholipase C-r2 (PLC-r2). PLC-r2 catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate, generating inositol 1,4,5-trisphosphate and diacylglycerol. Inositol 1,4,5-trisphosphate induces the release of Ca<sup>2+</sup> from intracellular stores, and diacylglycerol facilitates the activation of PKC. BTK and PLC-r2 play substantial role in the transmission of BCR signals to activate NF- $\kappa$ B, especially, PLC-r2 mediates BCR-responsive activation of IKK, phosphorylation of I- $\kappa$ B $\alpha$ <sup>31</sup>. However, BTK activates a distinct set of signal transduces to initiate downstream signalling events, of these, Akt, MAPK can activate IKKs<sup>32</sup>. NF- $\kappa$ B signalling is required for cyclin D<sub>2</sub> induction via the BCR, MEK1/2-p42/44ERK and

NF- $\kappa$ B pathways link PI-3K activity to Ag receptor-mediated cyclin D<sub>2</sub> induction in B cells<sup>33</sup>. PI-3K family members to cyclin D<sub>2</sub> induction are linked by components of NF- $\kappa$ B pathway. PI-3K and Akt have been reported to directly interact with and phosphorylate IKK<sup>26</sup>. Alternatively, PI-3K might initiate NF- $\kappa$ B activation via PDK-1, which phosphorylates and activates conventional PKCs and PKC- $\zeta$  and - $\delta$ <sup>34</sup>, finally, phosphorylation of IKKs and activation of NF- $\kappa$ B. (Figure 1)

### BRADYKININ ACTIVATING NF- $\kappa$ B SIGNALLING

Bradykinin (BK) is known for its proinflammatory functions in both tissue injury and allergic inflammation of the airway mucosa. A correlation between BK-stimulated NF- $\kappa$ B activation and IL-1 $\beta$  production in the WI-38 fibroblasts exists. A constitutively active RhoA directly stimulated NF- $\kappa$ B binding activity, BK-mediated IL-1 $\beta$  synthesis results from RhoA-dependent NF- $\kappa$ B activation. After BK binding to G protein coupled receptor (GPCR), the heterotrimeric G proteins undergo GDP-GTP exchange, then dissociates into  $\alpha$ - and  $\beta\gamma$ - subunits, constitutively activate G $\alpha_{12}$  and G $\alpha_{13}$  subunits.  $\beta\gamma$ - subunits activate Cdc42 Rac, and

Rho. PAK1 is the primary kinase activated by both Cdc42 and Rac1 but not by RhoA. RhoA may also activate protein tyrosine kinases (PTKs) and protein kinase C- $\zeta$  (PKC- $\zeta$ ). PI-3K is a novel signal transducer for BK-induced NF- $\kappa$ B activation. Moreover, BK, acting through B<sub>2</sub>-BK receptor, induces activation of the Ras/Raf-1/ERK pathway, which in turn phosphorylates IKK  $\alpha\beta\gamma$  and then activates NF- $\kappa$ B<sup>35</sup>. (Figure 1)

## NF- $\kappa$ B AND RELATED DRUG DISCOVERING NF- $\kappa$ B-RELATED ACTIVATING DRUGS

Here we summarize the drugs that induce both NF- $\kappa$ B nuclear translocation and activation of target genes. Cisplatin leads to NF- $\kappa$ B activation through MEKK-1-mediated JUN activation. Daunorubicin, doxorubicin, vinblastine, and vincristine exert anticancer roles by phosphorylating I- $\kappa$ B via increasing activity of protein kinase C (PKC). Paclitaxel and gemcitabine stimulate the activation of NF- $\kappa$ B and increase the activation of Bcl-2 promoter, which can be blocked by inhibition of AKT signalling<sup>36</sup>. Sodium butyrate and trichostatin A stimulate NF- $\kappa$ B through AKT-dependent phosphorylation of p300, recruitment of p300 to chromatin, and prolongation of TNF-induced IKK complex activity<sup>37</sup>. Irinotecan and SN38 mobilize and stimulate the IKK complex, and phosphorylation of ser-32 and -36 is not essential for I- $\kappa$ B degradation, but the DNA double-strand breaking are necessary for this protein synthesis independent NF- $\kappa$ B activation. Other activators of NF- $\kappa$ B or associated activation signalling proteins are yet to be defined.

## NF- $\kappa$ B-ASSOCIATED INHIBITORY DRUGS

Proteasome inhibitors were originally considered as therapies for their potential protein targets through inhibiting I- $\kappa$ B degradation and leading to the maintenance of NF- $\kappa$ B in the cytoplasm<sup>38</sup>. Inhibitor BAY 11-7082 [(E)-3-(4-methylphenylsulphonyl)-2-propenenitrile] has been shown to inhibit I- $\kappa$ B $\alpha$  degradation, this drug show promise for the future in combination with conventional therapeutic agents. A TNF- $\alpha$  antagonist could also function as a NF- $\kappa$ B inhibitor, though further studies are needed to clarify the interrelationship between TNF- $\alpha$  antagonism and NF- $\kappa$ B inhibition. The most commonly accepted theory to account for the inhibitory effects of these facets on the inflammatory response arises from the thought that inhibition of COX<sub>2</sub> activity by non-steroidal anti-inflammatory drugs (NSAIDs) prevents prostaglandin synthesis. Salicylates, sulindac, and sulfasalazine inhibit NF- $\kappa$ B activation by blocking IKK activity. Vegetable products such as genistein, a natural isoflavonoid found in soybean products,

have been shown to inhibit NF- $\kappa$ B and induce apoptosis of tumor cells through partly mediating AKT pathway<sup>39</sup>.

CHS828 [N-(6-(p-chlorophenoxy)-hexyl)-N'-cyano-N''-4-pyridylguanidine] is a potassium-channel opener, which correlates with its IKK inhibition<sup>40</sup>. Dehydroxymethylepoxyquinomicin (DHMEQ) a 5-dehydroxymethyl derivative of epoxyquinomicin C can inhibit TNF- $\alpha$  induced activation of NF- $\kappa$ B<sup>41</sup>. Flavopiridol, a synthetic flavone, has been found to inhibit cyclin-dependent kinases, suppress inflammation, modulate immune response, induce apoptosis, and inhibit IKK activity and p65 phosphorylation<sup>42</sup>. The development of specific NF- $\kappa$ B inhibitors would reduce side effects associated with drugs such as NSAIDs and glucocorticoids and provide important potential for the treatment of an array of human diseases.

Although several NF- $\kappa$ B-associated drugs have been found, an entirely effective drug is still to be warranted. Many distinct questions exist and need to be addressed if NF- $\kappa$ B inhibitors or activators are to be used at their full potential in the clinic.

## CONCLUDING REMARKS

Researches done upon the NF- $\kappa$ B activation pathways cannot be totally reviewed here, yet certain conclusion still can be made regarding NF- $\kappa$ B's role in several signalling transduction. In multicellular organisms, the NF- $\kappa$ B family is activated by several stimuli in a cell dependent manner and certain isoforms can either directly or indirectly target proteins to control transcription. The LPS, TNF- $\alpha$ , BCR and BK are four major trigger points in activating NF- $\kappa$ B that can significantly regulate gene expression via various signalling activation stimuli and transduction paradigms. NF- $\kappa$ B signalling associated effective and economical drug discovering should be focused on and might be useful to associated diseases therapy.

## ACKNOWLEDGEMENT

This work was support in part by the grant of National Scientific Foundation of China (NSFC, 30901397) and Science & Technology Development of Nanjing Medical University (07NMUM065, 08NMUZ033) in China. We also thank Dr. YuFeng Wang for her help in performing literature searches.

## LIST OF ABBREVIATIONS

Nuclear factor-kappa B (NF- $\kappa$ B); Lipopolysaccharide (LPS); Tumor necrosis factor-alpha (TNF- $\alpha$ ); B cell receptor (BCR), Bradykinin (BK); I- $\kappa$ B kinase (IKK); NF- $\kappa$ B essential modifier (NEMO); Helix-Loop-Helix (HLH); Lymphotoxin

$\beta$  receptor (LT $\beta$ R); Myeloid differentiation factor 88 (MyD88); Interleukin-1 receptor-associated kinase (IRAK); TNF receptor-activated factor (TRAF); Mitogen-activated protein kinase (MAPK); Activator protein-1 (AP-1); Toll-like receptor (TLR); Phosphatidylinositol-3-OH kinase (PI-3K); Lymphotoxin- $\beta$  receptor (LT $\beta$ R); Bruton's tyrosine kinase (BTK); Phospholipase C-r2 (PLC-r2); Protein kinase C (PKC); Protein tyrosine kinase (PTK); Non-steroidal anti-inflammatory drugs (NSAIDs); Dehydroxymethylepoxyquinomicin (DHMEQ) NF- $\kappa$ B-inducing kinase (NIK); LPS-binding protein (LBP); MyD88-adaptor-like (MAL); Toll/IL-1 receptor domain-containing adaptor protein (TIRAP); G protein coupled receptor (GPCR)

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