

Review

NF- κ B and Its Regulation on the Immune System

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NF- κ B is a transcription factor of eukaryote, five members of whose family in mammals and three in drosophila. Transcription factors of the NF- κ B family are activated in response to signals that lead to cell growth, differentiation, apoptosis and other events. NF- κ B takes part in expression of numerous cytokines and adhesion molecules which are critical elements involved in the regulation of immune responses. In this review, we focus on our current understanding of NF- κ B signal pathway and its role in the innate and adaptive immune responses in which these transcription factors have a key regulatory function. Furthermore we review what is currently known about their effects associated with apoptosis. *Cellular & Molecular Immunology*. 2004; 1(5):343-350.

Key Words: NF- κ B, innate immunity, adaptive immunity, apoptosis

The NF- κ B family

Among numerous eukaryotic transcription factors, NF- κ B is an essential transcription factor which exists in virtually all cell types. It was first described in 1986 as a nuclear factor indispensable for immunoglobulin κ light chain transcription in B cells (1). Since it was first observed, NF- κ B has been found to play an active part in immune responses, apoptosis, and cellular growth, as well as being present in diseases such as cancer, arthritis, asthma, and others.

The NF- κ B family is composed of several members. In mammals, the NF- κ B family comprises five members: NF- κ B1 (p105/p50), NF- κ B2 (p100/p52), RelA (p65), RelB, and c-Rel. NF- κ B1 is synthesized as a large polypeptide, and after the posttranslational cleavage, the DNA binding subunit p50 is generated. Similarly, the p52 is the posttranslational product of NF- κ B2, which is also a large polypeptide like NF- κ B1 (2). In *Drosophila*, the NF- κ B family contains three members: Dorsal, Dif, and Relish. Structurally, each of the NF- κ B family proteins shares a highly conserved NH₂-terminal region, known as the Rel homology domain (RHD) (3); the RHD contains a nuclear localization sequence (NLS) and is involved in dimerization, sequence-specific DNA binding and

interaction with the inhibitory I κ B proteins. The NF- κ B proteins dimerize to form homo- and hetero-dimers, which are associated with specific biological responses that stem from their ability to regulate target gene transcription differently. The heterodimer of p50 and p65 subunits was the first described NF- κ B molecule. And this heterodimer constitutes the most common inducible NF- κ B binding activity in spite of the diversity of other members so far. Although most of the NF- κ B proteins are transcriptionally active, some homo- or hetero-dimers are thought to act as inactive or repressive complexes. The complexes of p50/p65, p50/c-rel, p65/p65, and p65/c-rel are all transcriptionally active, while p50 homodimer and p52 homodimer are transcriptionally repressive (1). RelB displays a greater regulatory flexibility, and can be both an activator and a repressor. RelB forms stable heterodimers with either p50 or p52 and does not homodimerize (4).

In unstimulated cells, NF- κ B/Rel dimers are bound to I κ Bs (inhibitors of NF- κ B) and retained in the cytoplasm in an inactive form. Like NF- κ B, I κ B is also the member of a multigene family containing several members. In mammals, the I κ B family proteins include I κ B α , I κ B β , I κ B γ , I κ B ϵ , Bcl-3, the precursor Rel-proteins, p100, and p105. In *Drosophila*, only one I κ B protein is identified, known as Cactus (3). Recently, Soh Yamazaki, et al. discovered a novel I κ B protein, I κ B ξ , which is thought to act in the Nuclei (5).

In the past, only one NF- κ B signaling pathway was recognized, known as the classical signaling pathway (Figure 1). In mammals, the activated NF- κ B signaling pathway is based on degradation of I κ B inhibitors. This degradation depends on activation of the I κ B kinase (IKK) complex. The most common form of this complex is comprised of the IKK α and IKK β catalytic subunits and the IKK γ regulatory subunit (also called NEMO-NF- κ B essential modulator). IKK α and IKK β undergo homo- and hetero-dimerization. Stimuli such as proinflammatory cytokines and pathogen-associated molecular patterns

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Received for publication Jul 11, 2004. Accepted for publication Aug 21, 2004.

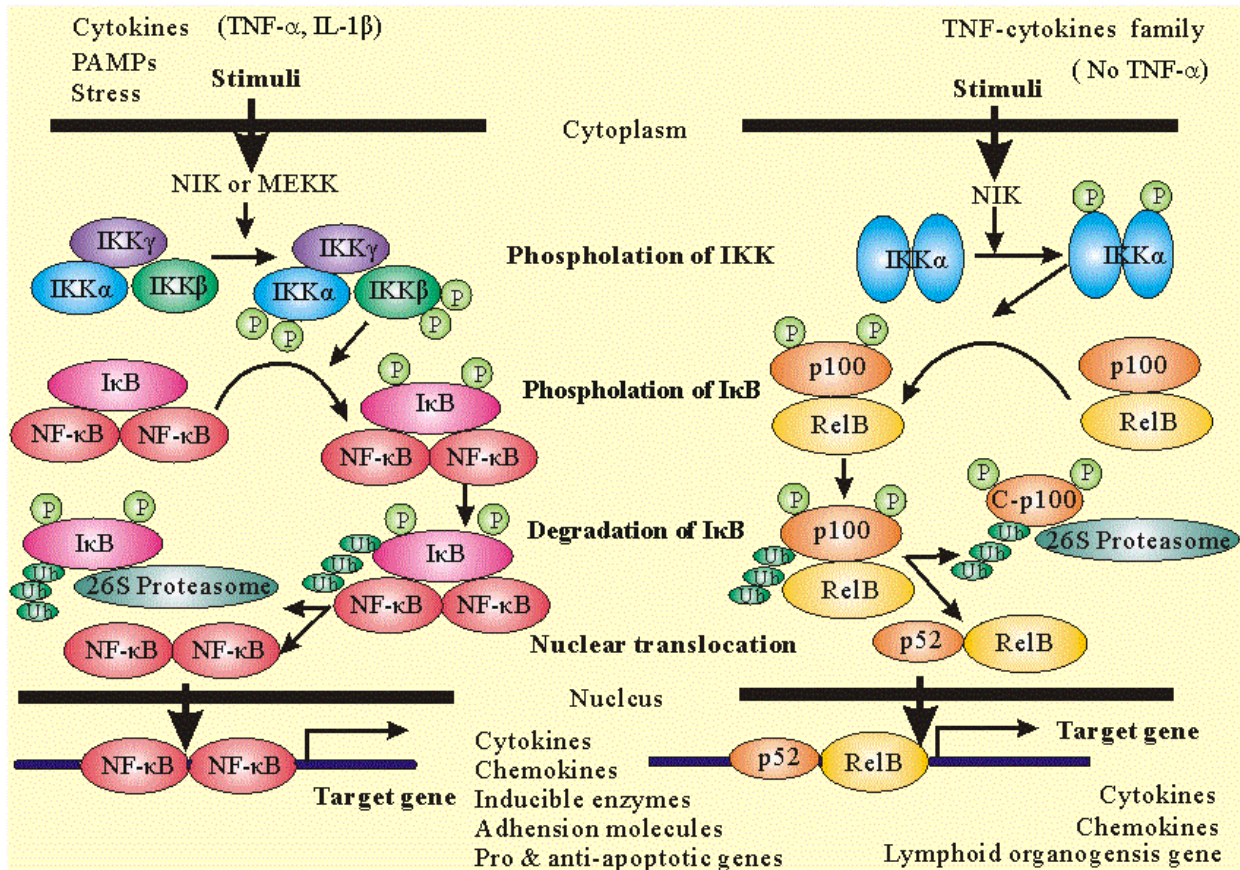


Figure 1. Classical and alternative NF-κB pathway. The left is a schematic illustration of the steps involved in the activation of the classical NF-κB pathway, and the right illustrates the alternative NF-κB pathway. NF-κB is activated by signals that activate IκB kinase (IKK), resulting in the phosphorylation of IκB, this targets IκB for degradation in the proteasome and frees the NF-κB dimer, which then translocates to the nucleus and binds to consensus κB sequences in the enhancers region of κB target genes. Most products of these genes are essential for the immune system (C-p100, the C-terminal region of p100).

(PAMPs) can activate the classical NF-κB signaling pathway, mainly acting through the phosphorylation of IκBs (at sites equivalent to Ser32 and Ser36 of IκBα) catalyzed by IKKβ in an IKKγ-dependent manner (4). Phospho-IκB is then recognized by the β-TrCP-containing SCF ubiquitin ligase complex, leading to its poly ubiquitination (at sites equivalent to Lys21 and Lys22 of IκBα). This modification subsequently targets IκB proteins for rapid degradation by the 26S proteasome. IKKβ but not IKKα is essential for inducible IκB phosphorylation and degradation. The degradation of IκB exposes the nuclear localization signal of the NF-κB family protein, leading to its nuclear translocation and binding to enhancers or promoters of target genes (6).

Three years ago, a second evolutionary conserved pathway leading to NF-κB activation, which is known as the alternative NF-κB activation pathway now (Figure 1), was discovered (7). This pathway is activated by certain members of the TNF cytokines family but not by TNF-α itself. The NF-κB activation in this pathway is strictly dependent on IKKα and independent of IKKβ and IKKγ. Therefore, the IKKα is an essential component of the alternative NF-κB activation pathway based on regulated NF-κB2 processing rather than IκB degradation. In this

pathway, IKKα phosphorylates NF-κB2 at two C-terminal sites, and this activity requires its phosphorylation by upstream kinases, one of which may be NF-κB-inducing kinase (NIK). Phosphorylation of these sites is essential for p100 processing to p52, while polyubiquitination and proteasomal degradation are also indispensable. The phosphorylation-dependent ubiquitination of p100 results in degradation of its inhibitory C-terminal half, which is different from the complete degradation of p100, as seen with IκBs. The N-terminal region of NF-κB: the p52 polypeptide that contains the RHD – is released soon after the C-terminal half is degraded. The activation of this alternative pathway then brings about nuclear translocation of p52-RelB dimers (4).

Recent results suggest that the classical pathway is mostly involved in innate immunity while the alternative pathways maybe involved in adaptive immunity. Uwe Senftleben, et al. (7) provide evidences that the alternative NF-κB activation is required for B cell maturation and formation of secondary lymphoid organs.

Regulation on innate immunity

The innate immune responses in mammals are the first line

of defense against invading microorganisms.

The main players in innate immunity are phagocytes such as macrophages, neutrophils, and dendritic cells (8). These cells recognize invading pathogens by germ-line-encoded pattern recognition receptors (PRRs) mainly depending on the family of Toll-like receptors (TLRs) (9), which are originally identified in *Drosophila* as essential receptors for the establishment of the dorso-ventral pattern in developing embryos. Subsequently, mammalian homologues of Toll receptor were identified one after another, and designated as Toll-like receptors (TLRs) (10), including TLR4, TLR2, TLR9, TLR5 and others (11). The cytoplasmic domains of the Toll family define a subclass of TIR (Toll/IL-1-receptor homologous region) domains (12). The engagement of TLRs with microbial products will activate and initiate several intracellular signal transduction pathways, while NF- κ B activation is the most prominent and best characterized.

TLR-induced NF- κ B activation is important in ancient innate host defense system, which is phylogenetically conserved in insects and mammals. Upon appropriate activation, TLRs most likely form homodimers and subsequent recruitment of adapter MyD88, maybe some other adapter molecules. MyD88 interacts with the TLR *via* a homotypic TIR connection. The death domain of MyD88 then recruits downstream kinase IRAK (IL-1 receptor-associated kinase) to the receptor complex. IRAK is then autophosphorylated and dissociated from the receptor complex and recruits TRAF6 (TNF receptor-associated factor 6) that in turn activate downstream kinases such as NIK and MEKK1 (mitogen-activated protein kinase/ERK kinase 1). Activated NIK or MEKK1 is individually capable of activating the IKK complex. Subsequently, I κ B is phosphorylated and degraded, leading to nuclear translocation of NF- κ B and initiation of target genes transcription.

In the innate immune responses, the host immediately secretes cytokines and other mediators to defend it from microbial pathogens. It has been noted that the phylogenetically conserved cellular signaling mechanisms in innate immunity provide an immediate reaction to utilize the NF- κ B system at the heart of this first-line defense (13).

NF- κ B regulates the expression of a wide variety of genes that play critical roles in innate immune responses. These NF- κ B target genes include those encoding cytokines (e.g., IL-1, IL-2, IL-6, IL-12, TNF- α , LT α , LT β , and GM-CSF), adhesion molecules (e.g., intercellular adhesion molecule, vascular cell adhesion molecule, and endothelial leukocyte adhesion molecule), chemokines (e.g., IL-8), acute phase proteins (e.g., SAA), and inducible enzymes (e.g., iNOS and COX-2) (1, 2, 14). Additionally, it has been demonstrated recently that NF- κ B can also regulate several evolutionarily conserved antimicrobial peptides, β -defensins for example (15). These molecules are important components of the innate immune response to invading microorganisms and are required for migration of inflammatory and phagocytic cells to tissues where NF- κ B has been activated in response to infection or injury. It has been demonstrated that NF- κ B activation is the underlying molecular mechanism for constitutive expression

of E-selectin, VCAM-1 (Vascular Cell Adhesion Molecule-1), and ICAM-1 (Intercellular Cell Adhesion Molecule-1) on human B lymphocytes and plasma cells. These molecules are essential for the recruitment of leukocytes to the site of infection or tissue injury, which is integral to innate immunity (16). In macrophages, NF- κ B in cooperation with other transcription factors coordinates the expression of genes encoding iNOS (inducible nitric oxide synthase), COX-2 (Cyclooxygenase-2), TNF- α (17, 18) and other proteins. Studies showed that inhibitory effects on LPS-induced NO production and expression of iNOs are through down-regulation of I κ B kinase (19) or inhibition of I κ B α degradation and NF- κ B activation (20). Recent studies strongly suggested that the age-associated and ceramide-induced increase in COX-2 transcription was mediated through higher NF- κ B activation, which is, in turn, because of a greater I κ B degradation in old macrophages (18). Complement factor B (Bf) is a serine protease which plays an important role in activating the alternative complement pathway. The inflammatory cytokines, in particular TNF- α and IFN- γ , are critical in the regulation of Bf gene expression in macrophages. Yong Huang, et al. (21) found that a NF- κ B cis-binding site between -433 and -423 bp was required for TNF- α responsiveness and for TNF- α - and IFN- γ -stimulated synergistic responsiveness of the Bf gene. And they also demonstrated that TNF- α signaling to Bf induction was an I κ B phosphorylation dependent process. The results of Hyeon G Yoo, et al. (22) suggest that the activation of NF- κ B is required for the IL-1 β -induced expression of MMP-9, one of the MMPs (matrix metalloproteinase) which allow macrophages to penetrate through the basement membrane into the tissue stroma.

LPS and various cytokines including TNF- α , IFN- γ , IL-1 β , IL-2, and IL-15 rapidly induce TLR2 gene expression in macrophages (23). Studies showed the 5' upstream region of the mouse TLR2 (mTLR2) gene contains two NF- κ B consensus sequences. In mouse macrophage cell lines, deletion of both NF- κ B sites caused the complete loss of mTLR2 promoter responsiveness to TNF- α (24). Besides, it has been demonstrated that LPS stimulation could upregulate gene expression of TLR9 *via* NF- κ B, ERK, and p38 MAPK signal pathways in macrophages, indicating that macrophages with increased TLR9 expression, which might play important role in controlling the overall responses of immune cells to bacteria, responds to invading bacteria more effectively (25).

Innate immunity is thought to provide the host with a defense system capable of effectively dealing with the continuous challenge by a wide array of microbes at surface epithelia. Ruxana T. Sasikot, et al. (26) have shown that airway epithelial cells can be stimulated to activate NF- κ B and produce cytokines and chemokines that are important for directing innate immune responses in the lungs. Selective expression of I κ B kinases in airway epithelium results in NF- κ B activation, inflammatory mediator production, and neutrophilic lung inflammation. Moreover, X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID), a human primary immunodeficiency associated with impaired

NF- κ B signaling was recently described. It is caused by hypomorphic mutations in the gene encoding NEMO/IKK γ , the regulatory subunit of the I κ B-kinase (IKK) complex (27).

Regulation on adaptive immunity

In addition to its well-known role in innate immunity, NF- κ B has important functions in adaptive immunity. NF- κ B plays a critical role in the activation of immune cells by upregulating the expression of many cytokines essential to the immune response. In particular, NF- κ B stimulates the production of IL-1, IL-6, TNF- α , lymphotoxin, and IFN- γ . Furthermore, some of these cytokines, e.g., IL-1 and TNF- α , activate NF- κ B themselves, thus initiate an autoregulatory feedback loop.

NF- κ B and T cell

Since its original discovery in B cells, NF- κ B has been widely implicated in the transcriptional control of genes involved in T cell activation and growth. The expression of most of the NF- κ B members in T cells indicates that they are likely to be involved in T cell functions and are essential for the establishment of normal T cell subsets.

The role of NF- κ B in T cell development

The thymic phase of T cell development involves an orderly progression from double-negative to double-positive thymocytes. Many studies have shown the importance for NF- κ B in T cells development that is specifically involved in adaptive immunity.

Immunohistochemical and immunofluorescence analyses of human thymocytes and thymic sections revealed a higher density of prototypical NF- κ B and c-Rel/p50 proteins in the medullary thymocytes, but the prototypical NF- κ B was also detected in nuclei of some cortical thymocytes (28). These results suggested a role for NF- κ B in the complex maturation process that takes place in the thymus.

Recent study has shown that there are several new lines of evidence for the involvement of NF- κ B in T cell development. For example, Gao X, et al. (29) suggested that Curcumin most likely inhibits the development of cytotoxic T lymphocytes and the production of cytokines by T lymphocytes by inhibiting NF- κ B target genes involved in induction of these immune responses. To circumvent the technical problems that these gene disruption experiments are complicated by the potential for functional redundancy and, as shown for RelA, can lead to early embryonic lethality (30), the researchers targeted to the T lineage a truncated form of I κ B α that constitutively represses the nuclear expression of multiple NF- κ B dimers. The study of neuroimmunology provides new evidences that estriol significantly inhibited T cell transmigration at a concentration range typical of pregnancy and the regulatory effect of estriol is through its interaction with the NF- κ B signal pathway (31).

Requirement for RelA and c-Rel in IL-2 responsive

proliferation

The development of an adaptive T-cell response is balanced by the proliferation and expansion of antigen-specific T cells during the initiation of the response and the loss of excess T cells as a response resolves.

NF- κ B regulates IL-2 production, which increases the proliferation and differentiation of T lymphocytes. Gene disruption experiments have demonstrated that c-Rel-deficient T cells exhibit a defect in IL-2 production, which led to a diminished proliferative response (32). In these prior studies, exogenous IL-2 restored T cell proliferation, indicated that the IL-2 signaling pathway is intact in c-Rel-deficient lymphocytes. Direct evidence for the effects of NF- κ B in T cell proliferation from murine models is provided by studies of transgenic mice that express the degradation-deficient I κ B transgene, which acts as a global inhibitor of NF- κ B activity. According to former researchers, the T cells from these mice have severely impaired proliferative responses (33). Additional evidences show that mice lacking the polypeptide p105 precursor of NF- κ B1 have impaired proliferative responses. (2). It is still controversial in understanding the basis of this mechanism. It has been recently illustrated that T cell which express the Δ I κ B transgene have a defect in their ability to activate the transcription factor STAT5a, which is required for T cell proliferation mediated through IL-2 and IL-4 (34).

The proliferative deficiency of the transgenic T cells was associated with an increased apoptosis. Therefore, NF- κ B is critical for apoptotic protection of T cells. The details will be discussed below.

Taken together, these findings demonstrate that NF- κ B is indispensable in the development and homeostatic control of mature T cells.

The control of Rel/NF- κ B during T cell activation

The abilities of accessory cells to present antigens, provide costimulation, and produce cytokines in response to infection are critical to the subsequent adaptive immune response. Some studies have shown the functions of NF- κ B in other accessory cell functions are specifically involved in adaptive immunity. For example, RelA is required for the ability of embryonic fibroblasts to express optimal levels of major histocompatibility complex class I and CD40, molecules required for the development of CD8⁺ T-cell responses (35). Furthermore, T cells acquire CD83 expression, which is expressed on the surface of mature dendritic cells that present processed antigens to T lymphocytes, following mitogenic stimulation *in vitro*. According to previous studies, there are definite evidences demonstrating that this inducible lymphocyte response is genetically programmed by transcription factor NF- κ B and contingent upon proteolytic breakdown of its cytoplasmic inhibitor I κ B α (36). NF- κ B is also involved in regulating gene expressions during T cell activation where it is induced by signaling through the TCR/CD3 complex and the costimulatory molecule CD28 (37). A recent research which used a mouse with a homozygous-Rel deletion supports a unique and non-redundant role for c-Rel in dendritic cell costimulatory capacity. As we all know, the maturation state of the dendritic cell determines the

quantity and quality (Th1, Th2) of the subsequent T cell response (38).

Besides, the maintenance of long-term memory cells is the hallmark of adaptive immunity, and NF- κ B has been implicated in the signals that allow memory to develop. Recent findings have demonstrated the effect of NF- κ B transcription factors in determining the number of memory-phenotype CD8 cells. (39)

B cell activation and effector function

NF- κ B/Rel transcription factor family is expressed constitutively during B cell development and is further induced by mitogen activation. Mice harboring germline disruptions in individual NF- κ B subunits exhibit distinct defects in B lymphocyte activation and survival.

NF- κ B/Rel family of polypeptides is a primary regulator of growth responses and gene expression programs in activated B lymphocytes (40). Members of the NF- κ B transcription factor family, including c-Rel, are regulated by many TNF family members and their receptors and are essential for mitogens induced proliferation of B cells. C-Rel-deficient B cells proliferate poorly and have survival defects after stimulation (41). C-Rel is also required for cell cycle progression of B cells (42). The importance of NF- κ B in the control of B-cell functions was confirmed by recent experimental observations which also support that NF- κ B/Rel factors are important mediators of B cell development and survival. For example, dual repression of the RelA and c-Rel transactivating subunits severely impair Ig κ gene assembly in precursor (pre-) B lymphocytes (43). Alina Patke, et al. proposed that the B-cell activating factor of the TNF family receptor (BAFF-R) signaling, which contributes to the survival of mature resting B cells in the periphery, enhances the expression of survival genes through direct chromatin modifications in NF- κ B target gene promoters (44). Activation of NF- κ B resulted in a resistance to TGF- β -mediated suppression of IL-4 signaling, which was associated with induction of the ϵ isotype switch (45).

To assess the cell intrinsic roles of NF- κ B during B lymphocyte development and homeostasis, expression of a trans-dominant inhibitor form of I κ B α was targeted to the B lineage in mice. Expression of the inhibitor protein, I κ B Δ N, specially inhibits NF- κ B/Rel signaling and cellular proliferation in response to BCR ligation. These biochemical defects were manifest *in vivo* as a dramatic depletion of the long-lived mature B cell subset residing in the bone marrow (46). Using conditional gene targeting to evaluate the role of these proteins in B cells in adult mice, researchers found that B lineage-specific disruption of either IKK signaling by deletion of NEMO, or of IKK2-specific signals by ablation of IKK2 activity led to the disappearance of mature B lymphocytes (47). As a result, the maintenance of mature B cells depends on IKK-mediated activation of NF- κ B.

The basis for the defects in humoral immunity in the NF- κ B-deficient mice is not well understood and may be intrinsic to the B-cell compartment or due to compromised accessory cell or T-cell functions. For example, NF- κ B2

has functions in cells of the hemopoietic and non hemopoietic lineages that regulate splenic micro architecture (48), and as a consequence of the disrupted splenic architecture and lack of germinal centers, mice harboring germline disruptions in individual NF- κ B subunits exhibit distinct defects in B lymphocyte activation and survival.

All of these findings indicate that the NF- κ B proteins are important regulatory factors that control the ability of B cells to survive, progress through the cell cycle, and mediate their effector functions.

NF- κ B and apoptosis

Apoptosis is a physiological process critical for organ development, development and selection of T and B lymphocytes, and tissue homeostasis. Apoptosis can be initiated by a wide variety of stimuli. The activation of NF- κ B is strongly linked to the regulation of apoptosis.

Pro- and anti-apoptotic functions of NF- κ B

In diverse cell types, NF- κ B transcription factors act as the critical factors in regulating the apoptotic program. Commonly, they are blockers of apoptosis, but sometime, they are essential for the induction of apoptosis (49).

At first, NF- κ B was considered as a pro-apoptotic factor. This is because of its rapid activation in cells in response to apoptotic signals and its involvement in the expression of some apoptotic genes, such as TNF- α , c-myc, and FasL (50). Previous studies illustrated that NF- κ B directly bound to the NF- κ B side on the promoter of FasL and upregulate the FasL gene expression (51). Overexpression of RelA induced a better activation of the FasL promoter and increases the expression of FasL (52). Similarly, Kasibhatla S, et al. (53) have suggested that activation of NF- κ B contributes to stress-induced apoptosis *via* the expression of FasL. As well, inhibition of NF- κ B by decoy oligodeoxynucleotides was shown to prevent apoptosis of endothelial cells after exposure to ischemia/reperfusion (54). A latest report has showed that the NF- κ B plays an essential part in activation of wild-type p53 tumor suppressor to initiate proapoptotic signaling in response to over-generation of superoxide (55).

However, more recent work revealed an anti-apoptotic effect of NF- κ B in response to a variety of apoptotic stimuli. The direct evidence for the anti-apoptotic effects of NF- κ B is supported by knocking out the genes encoding either members of NF- κ B family proteins or upstream kinases (56). RelA-deficient mice died at embryonic day 15-16 with massive liver cell apoptosis (57). Likewise, IKK- β gene knockout mice and IKK- β /IKK- α double-knockout mice died as embryos and showed extensive apoptosis in the liver (56). Moreover, numerous studies have indicated that NF- κ B activation is required to protect cells from the apoptotic cascade induced by TNF and other stimuli (58). In cardiomyocytes, activation of NF- κ B prevents TNF- α -induced apoptosis by regulating the expression of anti-apoptotic proteins (54). Likewise, NF- κ B protects pancreatic β -cells from TNF- α mediated apoptosis (59). Ruddier Gone, et al. (60) found that

inhibition of NF- κ B significantly enhanced TRAIL (TNF-related apoptosis-inducing ligand)-induced apoptosis, which suggests NF- κ B inhibits TRAIL-induced apoptosis.

The anti-apoptotic functions of NF- κ B are likely due to its ability to regulate expression of anti-apoptotic genes, including the cellular inhibitors of apoptosis (c-IAP1, c-IAP2, and XIAP), the TNF receptor-associated factors (TRAF1 and TRAF2), the Bcl-2 homologue A1/Bfl-1, Bcl-XL and IEX-IL (61). These proteins function at different levels in the caspase cascade to block apoptosis. Early in 1999, there was evidence that the prosurvival Bcl-2 homolog Bfl-1/A1 is a direct transcriptional target of NF- κ B that blocks TNF- α -induced apoptosis (62).

Previous studies have indicated that the NF- κ B functionally antagonizes p53 transcriptional activity. Recently, Archontoula Stoffel, et al. have shown that activation of NF- κ B by the API2/MALT1 fusions inhibited p53 dependent induced apoptosis (63). Conversely, as discussed before, p53 may in some case act through NF- κ B to induce apoptosis.

It seems that the NF- κ B has dual function in the apoptotic process. One possibility is that whether NF- κ B promotes or inhibits apoptosis appears to depend on the specific cell type and the type of inducer. The second possible explanation is that the dual function of NF- κ B depends on the relative levels of different NF- κ B family subunits, such as RelA and c-Rel. For example, overexpression of RelA or a transcriptional-deficient mutant of c-Rel inhibits TRAIL-induced apoptosis; depletion of RelA in mouse embryonic fibroblasts increases cytokine-induced apoptosis, whereas depletion of c-Rel blocks this process (64).

NF- κ B regulation of lymphocytes apoptosis

During the development and selection of T and B lymphocytes, NF- κ B pathway plays an essential role in the apoptotic process.

Studies showed that NF- κ B activation was required for protecting T and B cell from apoptosis induction by various stimuli. Early in 1997, VN Ivanov, et al. (65) had suggested that NF- κ B could regulate Fas-dependent activation-induced T cell apoptosis. Later in 1999, E Dudley, et al. (66) further indicated that NF- κ B protected T lymphocytes from Fas/APO-1/CD95- and TCR-mediated apoptosis. NF- κ B can also protect transformed T cells from TNF- α -induced apoptosis (67). Recently, there are new evidences for the anti-apoptosis function of NF- κ B in T cells. Protecting T cells from apoptosis induced by mitogens and an agonistic anti-Fas antibody requires the activation of NF- κ B (68). Increased CD8⁺ T cell apoptosis in scleroderma is associated with low levels of NF- κ B (69). This anti-apoptosis function of NF- κ B is likely to be an important regulator of T cell homeostasis and tolerance.

Apart from T lymphocyte, NF- κ B can protect B cell from apoptosis either. Prior studies showed that TGF- β 1 inhibited NF- κ B activity, inducing apoptosis of B cells (70). Recent studies further confirmed that NF- κ B was a survival factor for B cell development. NF- κ B down-regulation with inhibitors induced BU-11 (an early pre B cell line) cell apoptosis, indicating the default apoptosis

pathway is blocked by NF- κ B (71). The fact that NF- κ B is essential in inhibiting apoptotic cell death is demonstrated by a recent research in which Mohamed Abdouh, et al. found that 5-HT, as well as the selective 5-HT1A receptor agonist R-DPAT treatment increased intranuclear levels of the p50 and p65 subunits of NF- κ B. Thus, 5-HT1A-mediated promotion of mitogen-activated T and B cell survival and proliferation is associated with increased translocation of NF- κ B to the nucleus (72).

Although most studies link NF- κ B with prevention of apoptosis, NF- κ B has also been associated with proapoptotic functions for lymphocytes. For example, NF- κ B plays an essential role in promoting double positive thymocyte apoptosis (73).

The pathways triggered by stimuli as part of the innate immune response to activate NF- κ B converge with those induced by cytokines at the level of intracellular signal mediators and large multicomponent receptor and kinase complexes. NF- κ B controls the expression of multiple genes essential for the immunogenic response. It has been clearly established that sustained survival, mature and recirculating of lymphocytes as well as T and B cell-mediated immune responses require these pathways. In addition, excessive NF- κ B activation presumably leads to increased cell survival which favors lymphomagenesis. Numerous studies have illustrated that the NF- κ B family was required for the regulation of immune system. However, the different regulations and effector functions of the specific NF- κ B members are vague. And the detailed molecular mechanisms by which NF- κ B transcription factors contribute to immune responses and apoptotic control remain to be further determined. Therefore, A comprehensive understanding of the role of NF- κ B transcription factors in controlling immune responses and apoptosis can lead to the development of therapeutics for a wide variety of human diseases, including immunodeficiency, inflammation, arthritis, cancer, etc.

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