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Roles of TRAFs in NF-κB signaling pathways mediated by BAFF

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ABSTRACT

B cell activating factor (BAFF) is an important cytokine for the maintenance of B cell development, survival and homeostasis. BAFF/BAFF-R could directly activate nuclear factor kappa B (NF-κB) pathway. Tumour necrosis factor receptor-associated factors (TRAFs) are key regulatory proteins in NF-κB signaling pathways. TRAF1 enhances the activation of tumor necrosis factor receptor 2 (TNF-R2) induced by NF-κB. TRAF2 and TRAF3 signal adapters act cooperatively to control the maturation and survival signals mediated by BAFF receptor. TRAF5 is most homologous to TRAF3, as well as most functionally similar to TRAF2. TRAF6 is also required for the BAFF-mediated activation of NF-κB signal pathway. TRAF7 is involved in signal transduction pathways that lead either to activation or repression of NF-κB transcription factor. In this article, we reviewed the roles of TRAFs in NF-κB signaling pathway mediated by BAFF.

1. Introduction

B cell activating factor (BAFF), one of the members of tumor necrosis factor (TNF) family, represents the main survival signals for immature, naive and activated B cells. BAFF/BAFF-R signaling pathway is essential for B cell maturation [1]. The requirement for BAFF and BAFF-R in normal human and mouse B cells is well studied, but there is also significant evidence to suggest that BAFF plays an important role in malignant B cell proliferation and survival. There is also increasing genetic evidence, suggesting an association between the development of human disease with genetic variation in genes encoding BAFF and its receptors [2].

BAFF/BAFF-R not only activate anti-apoptotic signal pathway by inducing the expression of nuclear factor kappa B (NF-κB) and Bcl-2, but also induce the expression of CD21 and CD23, promoting the survival of mature B cell [3,4]. The transcription factor NF-κB is a central mediator of immune and inflammatory responses [5]. The NF-κB family is composed of five members: RelA, RelB, c-Rel, NF-κB1, and NF-κB2, which function as various dimeric complexes that transactivate specific target genes [6]. Tumour necrosis factor receptor-associated factors (TRAFs) are key regulatory proteins in the NF-κB signaling pathways. Acting as a positive regulator of the NF-κB2 pathway, TRAF1 enhances TNF-R2 induced NF-κB activation and interacts with the cytoplasmic domain of BAFF receptor [7]. The adapter proteins of TRAF2 and TRAF3 act cooperatively to control maturation and survival signals mediated by BAFF receptor. TRAF5 plays an important role in regulating NF-κB signaling pathway. TRAF6 is also required for the BAFF-mediated activation of NF-κB signal pathway [2]. TRAF7 is involved in the activation or repression of NF-κB transcription factor. In this article, we reviewed the roles of TRAFs in NF-κB signaling pathway mediated by BAFF.

2. BAFF is critical for maintenance of B cell development and homeostasis

BAFF, which is also called BLyS, THANK, TALL-1, or zTNF4, is a critical TNF family member (TNFSF13B) for maintenance of B cell development and homeostasis. As a potent cell-survival factor expressed in many hematopoietic cells, BAFF involves in B cell survival and maturation. Excessive BAFF production can destroy B cell self tolerance status, which maybe result in systemic autoimmune disease. BAFF increases humoral immune response, which induces B cell proliferation, differentiation and immunoglobulin production [8]. BAFF exerts its biologic functions by binding to three TNF receptors: B cell maturation antigen (BCMA; TNFRSF17), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI; TNFRSF13B), and BAFF-R (also called BR3 or TNFRSF13C) [9]. BCMA and BAFF-R are predominantly expressed on B lymphocytes, whereas TACI can be found on B cells and activated T cells [10]. Initial studies of the effects of BAFF on B cell physiology demonstrate that BAFF co-stimulates B cell proliferation and immunoglobulin secretion. BAFF/BAFF-R not only activates anti-apoptotic signal pathway by inducing the expression of anti-apoptotic protein, but also induces the expressions of CD21 and CD23, as well as promotes the survival of mature B cell [11]. BAFF/BAFF-R

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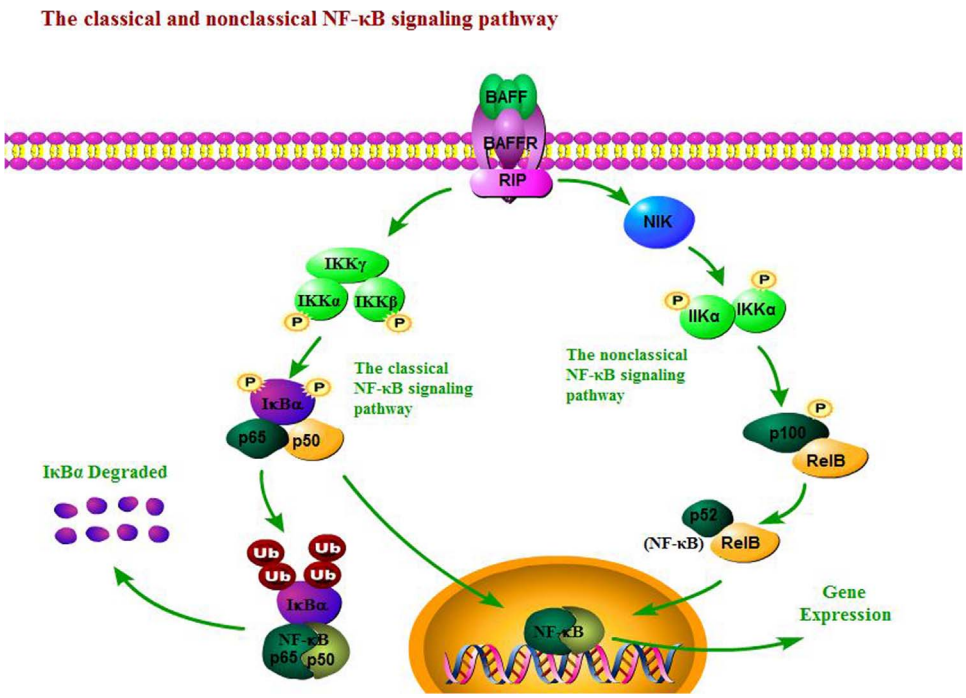

Fig. 1. BAFF/BAFF-R participates in cell survival by activating classical and nonclassical NF-κB pathways. In the classical NF-κB pathways, the combination of ligands and receptors leads to the recruitment and activation of IKK complex. The IKK complex further phosphorylated IκB, and then IκB is degraded by proteases. IKKβ is mainly responsible for the IκB phosphorylation, followed by the rapid ubiquitination and degradation of NF-κB. Then NF-κB is translocated to nucleus and activates the target gene expression.The activation of nonclassical NF-κB is followed by the transfer of RelB and p52 heterodimer aggregates to the nucleus and activation of target gene expression.

participates in antibodies production in B cells of collagen induced arthritis (CIA) rats. In CIA rat, the level of BAFF in serum increase, BAFF might promote B cells proliferation through PI3K/Akt/mTOR signal mediated by BAFF/BAFF-R [4]. The level of BAFF increases in cases of autoimmune disease and is correlated with disease activity. Elevated levels of BAFF in serum were found in autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjo'gren's syndrome [12]. As an innate cytokine mediator, BAFF affects the immune response of synovial micro environment [13]. Transgenic over expression of BAFF in mice results in the elevated level of Bcl-2 and prolonged the survival of B cells. Transgenic mice overexpressing BAFF develop autoimmune disorders characterized by B cell hyperplasia and autoantibody production including anti-DNA and rheumatoid factor. Eventually, the animals succumb to an immune complex-mediated, lupus-like nephritis [2].

3. NF-κB signaling pathways mediated by BAFF involve in B cell survival

NF-κB is found in nearly all animal cell types. It is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL and microbial antigens, and has been shown to regulate the expression of many genes including bcl-2, bcl-xl, cIAP, suvivin, TRAF, COX-2, MMP-9, iNOS and cell cycle-regulatory components. Many carcinogens, inflammatory agents and tumor promoters have been shown to activate NF-κB, resulting in tumors development. NF-κB is necessary for the correct development and growth of immune system [27]. The abnormal regulation of NF-κB has been linked to inflammatory and autoimmune diseases, septic shock, viral infection and improper immune development. Aberrant NF-κB activation is frequently observed in autoimmune disease, cancer development and progression as well as in drug resistance. Inhibitors of NF-κB have potentially the effects of antitumor and greater sensitivity to antitumor agents.

Five members of NF-κB family are normally sequestered in the cytoplasm by a family of inhibitors, including IκBα and other related ankyrin repeat-containing proteins. NF-κB1 and NF-κB2 are translated as precursor proteins, p105 and p100, which contain an IκB-like C-terminal portion and function as NF-κB inhibitors. Proteasome-mediated processing of p105 and p100 not only produces the mature NF-κB1 (p65) and NF-κB2 (p52), but also results in disruption of the IκB-like function of these precursor proteins [6].

There are two main NF-κB pathways: classical and nonclassical NF-κB pathways. The classical NF-κB pathway activates IκB kinase (IKK) complex that controls the inducible degradation of most IκB family members (IκBa, IκBb, IκBe and p105). The nonclassical NF-κB pathway induces p100 processing and p52 generation through the activation of two kinases at least, which are NF-κB inducing kinase (NIK) and IκB kinase (IKKa) [15]. In the classical NF-κB pathways, the combination of ligands and receptors leads to the recruitment and activation of IKK complex. The IKK complex further phosphorylated IκB, and then IκB is degraded by proteases. IKKβ is mainly responsible for the IκB phosphorylation, followed by the rapid ubiquitination and degradation of NF-κB. Then NF-κB is translocated to nucleus and activates the target gene expression [22,23]. Conditional deletion of IKKβ results in the rapid loss of B cells, indicating that the classical NF-κB activation pathway mediated by IKKβ is probably required for the differentiation and homeostasis of B cells [22,23]. The activation of nonclassical NF-κB is followed by the transfer of RelB and p52 heterodimer aggregates to the nucleus and activation of target gene expression [24,25]. Mature B cell numbers are reduced in irradiated mice reconstituted with IKKa-deficient lymphocytes, indicating the important role of nonclassical NF-κB activation pathway mediated by BAFF-R in B cell survival [26].

BAFF/BAFF-R participates in cell survival by activating classical and nonclassical NF-κB pathways. NF-κB is involved in regulating BAFF-R expression through one NF-κB binding site in the BAFF-R promoter, suggesting that inhibiting NF-κB could decrease the expression of BAFF-R mRNA and protein, and promote the activity of BAFF-R gene. The NF-κB-binding site of BAFF-R may be a new therapeutic target in autoimmune diseases [16,17] (Fig. 1.).

4. The regulatary functions of TRAFs in NF-κB signaling pathways

TRAFs is a family of adaptor proteins that are involved in signaling by the TNF receptor family and toll/interleukin-1 receptor (TIR) family members [7,28,29]. The TRAF proteins are characterized by the presence of a conserved carboxy-terminal homology TRAF domain of about 180 amino acids. TRAF domain is involved in homo-heterodimerization