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Review Article

NFκB function and regulation in cutaneous T-cell lymphoma

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Abstract: The nuclear accumulation and transcriptional activity of NFκB are constitutively increased in cutaneous T-cell lymphoma (CTCL) cells, and are responsible for their increased survival and proliferation. However, in addition to the anti-apoptotic and pro-inflammatory genes, NFκB induces expression of immunosuppressive genes, such as IL-10 and TGFβ, which inhibit the immune responses and are characteristic for the advanced stages of CTCL. While the mechanisms regulating NFκB-dependent transcription of anti-apoptotic and pro-inflammatory genes have been studied extensively, very little is known about the NFκB regulation of immunosuppressive genes. The specificity of NFκB-regulated responses is determined by the subunit composition of NFκB complexes recruited to the individual promoters, post-translational modifications of NFκB proteins, as well as by their interactions with other transcriptional factors and regulators. In this review, we discuss the mechanisms regulating the transcription of NFκB-dependent anti-apoptotic, pro-inflammatory and immunosuppressive genes in CTCL cells, as potential targets for CTCL therapies.

Keywords: Apoptosis, bortezomib, cutaneous T cell lymphoma, IκBα, IL-10, immunosuppression, NFκB, proteasome inhibition, TGFβ

Introduction

Nuclear factor κB (NFκB) is a key transcriptional regulator of genes involved in immune and inflammatory responses, as well as genes regulating cell survival, differentiation, proliferation, angiogenesis and metastasis [1]. Since NFκB activity and transcription of NFκB-dependent genes are increased in many types of cancer and leukemia, inhibition of NFκB-dependent transcription thus represents an important therapeutic target [2-4]. NFκB activity is constitutively increased in cutaneous T-cell lymphoma (CTCL), where it plays a central mediator between malignant cell survival and inflammatory signaling. Recently, studies from our laboratory have indicated that the increased NFκB activity in CTCL is responsible for the increased resistance to apoptosis by up-regulating the anti-apoptotic genes cIAP1, cIAP2 and Bcl-2 [5]. However, in addition to the anti-apoptotic role of NFκB in CTCL, NFκB also regulates the expression of pro-inflammatory and anti-inflammatory genes.

Tumors and leukemia cells often avoid the immune surveillance by expressing anti-inflammatory genes that inhibit expression of pro-inflammatory genes, thus suppressing the immune responses [6]. Indeed, CTCL cells are characterized by the high expression of anti-inflammatory genes, IL-10 and TGFβ [7], which may be involved in the suppression of pro-inflammatory cytokines IL-1β, IL-8, TNFα and IL-17. Thus, NFκB seems to have a complex regulatory role in CTCL, where it regulates expression of anti-apoptotic, pro-inflammatory as well as immunosuppressive genes (**Figure 1**). However, while the NFκB regulation of anti-apoptotic and pro-inflammatory genes has been extensively studied and documented, relatively very little is known about the NFκB regulation of immunosuppressive genes. Thus, effective therapeutic targeting of NFκB in CTCL

should include the anti-apoptotic, pro-inflammatory as well as the immunosuppressive function of NFκB.

CTCL

Cutaneous T-cell lymphoma (CTCL) encompasses a group of lymphoproliferative disorders characterized by skin invasive neoplastic T cells [8, 9]. Mycosis fungoides (MF) and the leukemic variant Sézary syndrome (SS) are the most common clinical forms [10]. MF patients often present with patches and plaques on skin and experience skin symptoms without serious complications. In contrast, patients with SS exhibit a leukemic form of the disease, which is characterized by malignant T cells in the blood. Advanced stages of MF and SS are associated with aggressive course and poor prognosis [11-14].

SS is an erythrodermic leukemic variant of CTCL that is characterized by a high level of constitutive NFκB activity, which is responsible for the increased expression of NFκB-dependent anti-apoptotic genes and resistance to apoptosis [15-17]. Patients with SS have high levels of malignant CD4+ T cells expressing IL-4, IL-10 and TGFβ that suppress the immune system and diminish the antitumor responses [18-23]. However, despite the recent advances in elucidating the immune mechanisms responsible for pathogenesis of CTCL, there is no effective strategy to prolong survival in the advanced stages.

NFκB

The NFκB family consists of five distinct transcription factors: p65 (RelA), RelB, c-Rel, p50 (p105/NFκB1) and p52 (p100/NFκB2) [24]. These transcription factors share the N-terminal Rel-homology domain (RHD) that is responsible for dimerization, DNA binding and nuclear translocation [25, 26]. The individual NFκB proteins can form homo- and heterodimers, which can bind to promoter κB sites and modulate transcription of NFκB-dependent genes [27-29].

The Rel proteins, including RelA, RelB and c-Rel, contain transcription activation domain (TAD), while p105/50 and p100/52 contain C-terminal ankyrin-repeat domain (ANK), but no TAD. Thus, while p105/p50 and p100/p52 can bind to DNA, they cannot activate transcription. The precursor proteins p105 and p100 can function as IκB proteins, and inhibit nuclear localization and transcriptional activity of NFκB dimers. Removal of the ANK domains produces p50 and p52 subunits that can form homodimers, which can repress transcription by displacing the transcriptionally active heterodimers from κB binding sites [30, 31].

Signaling pathways

The signaling pathways that mediate NFκB activation can be broadly classified into canonical and non-canonical pathways [32, 33]. The canonical pathway is engaged by ligands for antigen and cytokine receptors, and leads to the nuclear translocation of p50/RelA and p50/c-Rel dimers. The non-canonical pathway is initiated by stimulation of different signaling molecules, and leads to the activation of the p52/RelB dimers [34-36].

In most unstimulated cells, NFκB proteins are bound to the inhibitory IκB proteins, which retain them in an inactive form in the cytoplasm. Upon activation with different stimuli including pro-inflammatory cytokines, oxidative stress and lipopolysaccharide, IκB is phosphorylated by the enzymes of IκB kinase (IKK) complex, ubiquitinated and subsequently degraded by the 26S proteasome. The released NFκB proteins then translocate to the nucleus and bind to the promoter regions of target genes to stimulate their transcription [37, 38].

While the cytoplasmic pathways leading to nuclear translocation and activation of NFκB have been studied extensively [28-34], much less is known about the nuclear events regulating NFκB-dependent transcription. This nuclear regulation involves post-translational modifications of NFκB subunits, variations in the DNA sequence of the NFκB binding site, and binding of other transcription factors or coactivators [28-34].

Regulation of NFκB activity

The primary mechanism for regulating NFκB activity is through the inhibitory IκB proteins, which include IκBα, IκBβ, IκBε, IκBζ, Bcl-3, p100, and p105 [39-47]. Phosphorylation of IκB proteins is mediated by the enzymes of IKK complex that include IKKα, IKKβ, and the regu-

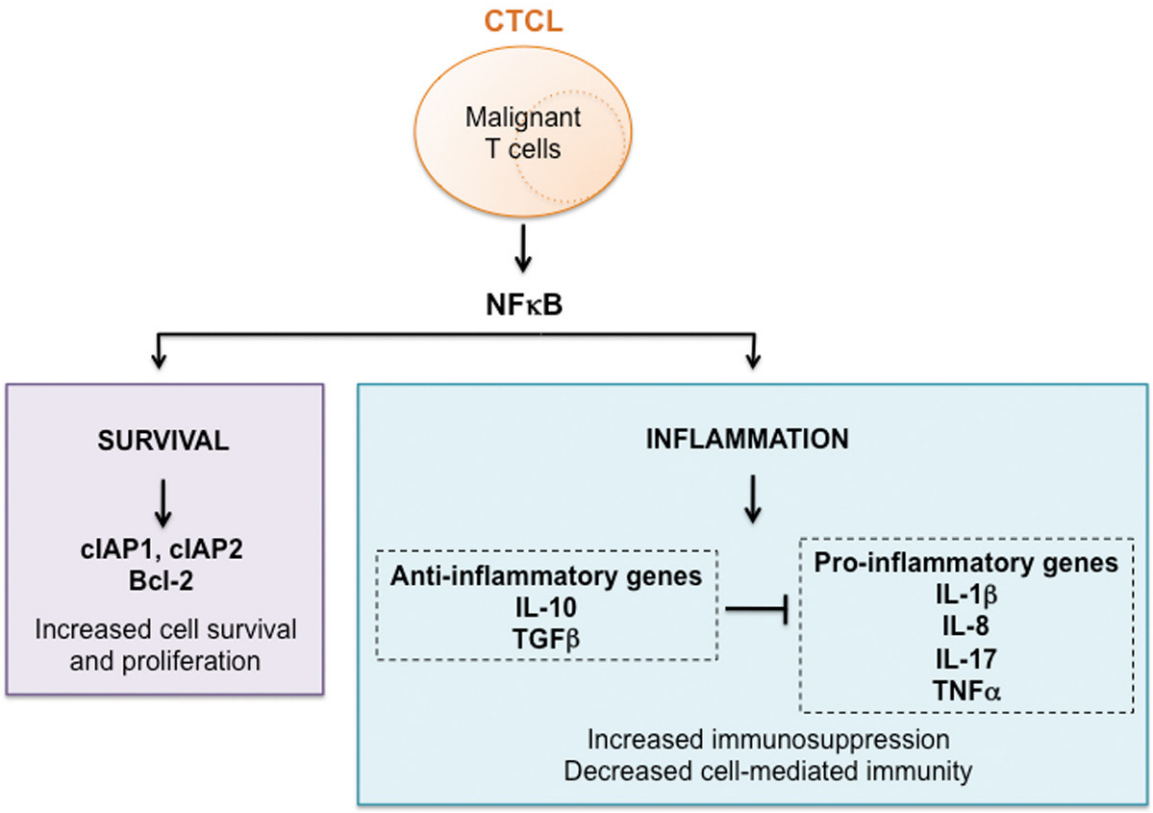

Figure 1. Schematic representation of the NFκB-regulated genes in CTCL. The increased activity of NFκB induces expression of anti-apoptotic genes cIAP1, cIAP2 and Bcl-2 in CTCL cells, resulting in their increased survival. In addition, NFκB also induces expression of pro-inflammatory genes IL-1, IL-8, TNFα and IL-17, and anti-inflammatory genes IL-10 and TGFβ. The increased expression of anti-inflammatory genes in CTCL inhibits expression of pro-inflammatory genes, resulting in the characteristic immuno-suppressory nature of CTCL.

latory subunit IKKγ (NEMO) [48, 49]. While the cytoplasmic degradation of IκB, resulting in the nuclear translocation of NFκB subunits, represents a general step in NFκB activation, the specificity of NFκB-regulated responses is mediated by the subunit composition of NFκB dimers and their post-translational modifications [49-54].

The repertoire of pro-inflammatory genes expressed upon NFκB activation includes pro-inflammatory cytokines IL-1β, IL-17 and TNFα, chemokines IL-8, CCL2 and CXCL5, as well as adhesion molecules. In addition, NFκB activates expression of many anti-apoptotic genes that include the cellular inhibitor of apoptosis (cIAP), the TNF receptor-associated factors (TRAF-1 and TRAF-2), and the family of Bcl-2 proteins, A-1/Bfl-1, Bcl-2 and Bcl-xL. By increasing expression of these anti-apoptotic proteins, NFκB activation decreases apoptosis and increases survival of leukemia and cancer cells [1-6]. Accordingly, inhibition of NFκB activity decreases the expression of pro-inflammatory and anti-apoptotic genes, and induces apoptosis.

In majority of human cancers and leukemia, NFκB is constitutively activated due to the increased degradation of IκBα and increased nuclear levels of NFκB subunits. Since the suppression of NFκB activity inhibits pro-inflammatory and anti-apoptotic gene expression, NFκB appears to be one of the most promising targets in the treatment of many inflammatory disorders as well as different types of cancer and leukemia. However, one of the main concerns regarding the NFκB inhibitors is their specificity, since many steps leading to NFκB activation are important for other cellular functions as well. Thus, a better understanding of the mechanisms regulating the specificity of NFκB-regulated responses will ultimately lead to the development of more specific anti-cancer and anti-inflammatory therapies.

Dimerization of NFκB

Dimerization is required for the NFκB binding to promoter regions of target genes [55]. More than 12 different combinations of NFκB homo- and heterodimers have been described [56]. Different dimer combinations have different transcriptional activity and regulate different sets of target genes [57, 58]. In addition, the dimer-specific functions are controlled by interactions with other co-regulatory proteins or transcription factors. Thus, depending on these interactions, NFκB dimers can function as activators or repressors. For example, even though p50 homodimers function mainly as transcriptional repressors, since they lack the transactivation domain, their association with Bcl-3 in T cell lymphoma cells increases transcriptional activation [59].

NFκB in CTCL

Increased activation of NFκB promotes cell survival, proliferation, tumorigenesis, angiogenesis and metastasis [60-75]. CTCL cells express all five members of the NFκB family; however, only p65, p50, p52 and Rel-B have been found in patients with MF or SS [76, 77]. The increased activity of NFκB induces expression of anti-apoptotic and pro-inflammatory genes in CTCL cells, resulting in their increased proliferation and survival. However, NFκB also induces expression of anti-inflammatory genes, thus contributing to the immunosuppressive nature of CTCL. Therefore, NFκB plays a central regulatory role in the pathogenesis of CTCL, by regulating expression of anti-apoptotic, pro-inflammatory and anti-inflammatory genes (**Figure 1**).

NFκB rearrangement

Chromosomal amplification, over-expression and rearrangement of genes coding for NFκB subunits have been described in many human hematopoietic and solid tumors [78]. Rearrangements of RelA, c-Rel and NFκB1 genes have been found in human lymphoid tumors, but not in CTCL [79-81]. However, NFκB2 rearrangements have occurred in some cases of CTCL, B-cell chronic lymphocytic leukemia, multiple myeloma and B-cell lymphoma [82], and have been associated with poor prognosis in CTCL [83-87].

Anti-apoptotic role of NFκB

High resistance to apoptosis is a characteristic feature of CTCL. This high resistance to apoptosis is mediated by the high constitutive activity of NFκB, both in CTCL cell lines and in tumor cells from patients with SS [15, 88-90]. CTCL cells express constitutive NFκB, c-myc and STAT5 activities that regulate the transcription of anti-apoptotic genes cIAP1, cIAP2 and Bcl-2 [91]. NFκB has been suggested to regulate the apoptotic sensitivity in CTCL through Fas pathway [92]. In addition, the deregulation of Notch1 signaling might be linked to the development of CTCL and several solid malignancies based on the NFκB-mediated cell survival [93].

Several pharmacological agents have been shown to inhibit NFκB activity and induce apoptosis in CTCL. Arsenic trioxide (As_2O_3) is effective against CTCL by reducing the DNA-binding activity of NFκB and inducing apoptosis [94]. PBOXs (pyrrolo-1,5-benzoxazepines) induces apoptosis in several CTCL cell lines through the NFκB-mediated activation of caspase-3 like proteases, and has the potential use as a novel anticancer drug [95]. The nitric oxide generating compound, sodium nitroprusside (SNP), can induce apoptosis in CTCL Hut-78 cell line by suppressing NFκB activity, and thereby Bcl-xL expression [96]. Non-steroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, sodium salicylate, and diclofenac, which have been widely used in the treatment of chronic inflammatory disorders, induce apoptosis in CTCL cells [97]. AraC (cytosine arabinoside) inhibits NFκB activity by dephosphorylating the p65 subunit, resulting in the increased apoptosis in CTCL Hut-78 cells [98].

Curcumin (diferuloylmethane) is the active compound in turmeric, a dietary spice that has been widely consumed for centuries. Curcumin has been found to have anti-proliferative and pro-apoptotic effects in a number of tumor cell lines. In CTCL cells, curcumin induces apoptosis by inhibiting phosphorylation of IκBα and DNA binding activity of NFκB [99]. Curcumin also has an oxidative effect by generating reactive oxygen species (ROS) and inhibiting the constitutive activity of NFκB in CTCL Hut-78 cells [100]. Inhibition of the nuclear accumulation of NFκB p65 and p50 by IKKβ (IKK2) inhibitor (AS6028668) induces a potent apoptotic response in CTCL cell lines and patients with

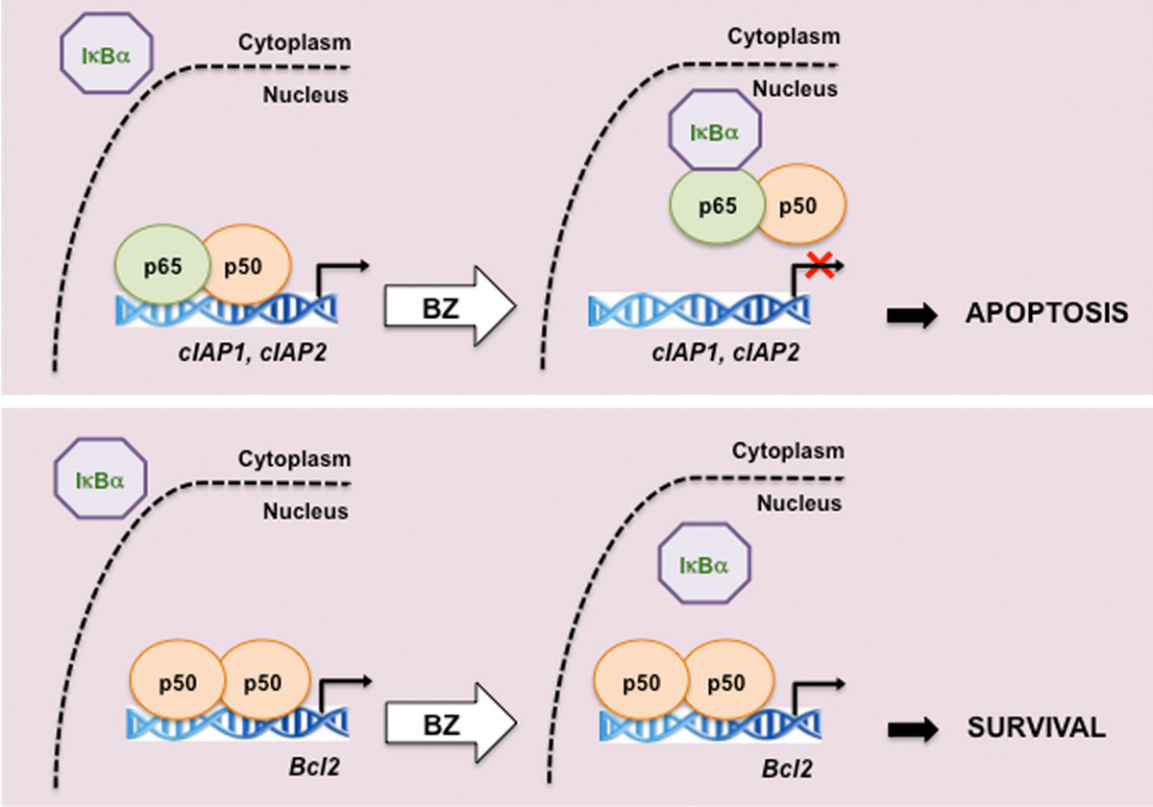

Figure 2. Proposed model of the gene specific regulation of NFκB-dependent anti-apoptotic genes by proteasome inhibition in CTCL cells. In CTCL Hut-78 cells, proteasome inhibition by BZ induces nuclear translocation and accumulation of IκBα. The BZ-induced nuclear IκBα removes NFκB p65/p50 heterodimers from the promoters of cIAP1 and cIAP2 genes, resulting in their suppression. However, the nuclear IκBα does not remove p50/50 homodimers from Bcl-2 promoter; consequently, Bcl-2 expression is not inhibited by BZ [5].

SS [16]. In malignant T-cell lines established from patients with CTCL, the high constitutive activity of NFκB induces expression of the oncogenic B-lymphoid kinase (Blk) that promotes proliferation of malignant CTCL cells [101].

The 26S proteasome inhibitor bortezomib (BZ; Velcade), which has been approved by the FDA for treatment of multiple myeloma and mantel cell lymphoma, acts by targeting the catalytic 20S core of the proteasome and induces apoptosis in cancer cells. One of the mechanisms consists of inhibiting the cytoplasmic degradation of IκBα, resulting in the suppression of NFκB DNA binding activity and decreased expression of NFκB-dependent anti-apoptotic genes. BZ has been also evaluated in CTCL and exhibited promising anti-tumor activity [102-104]. Sors et al. have demonstrated that in CTCL cells, proteasome inhibition by BZ inhibits the *in vitro* DNA binding activity of NFκB [15]. Interestingly however, a recent study has indicated that in CTCL cell lines, proteasome inhibition actually increases NFκB activity [105].

This seeming discrepancy can be explained by our previous study demonstrating that proteasome inhibition by BZ has a gene specific effect on the regulation of NFκB-dependent anti-apoptotic genes in CTCL Hut-78 cells [5]. Our results have shown that proteasome inhibition suppresses NFκB activity and induces apoptosis by a novel mechanism that consists of the increased nuclear translocation and accumulation of IκBα [5, 106, 107]. Promoters of the anti-apoptotic genes cIAP1 and cIAP2 are occupied by NFκB p65/50 heterodimers, and the BZ-induced nuclear IκBα inhibits this occupancy, resulting in the decreased cIAP1 and cIAP2 expression. In contrast, Bcl-2 promoter is occupied predominantly by p50/50 homodimers, and this occupancy and Bcl-2 expression are not suppressed by the BZ-induced nuclear IκBα

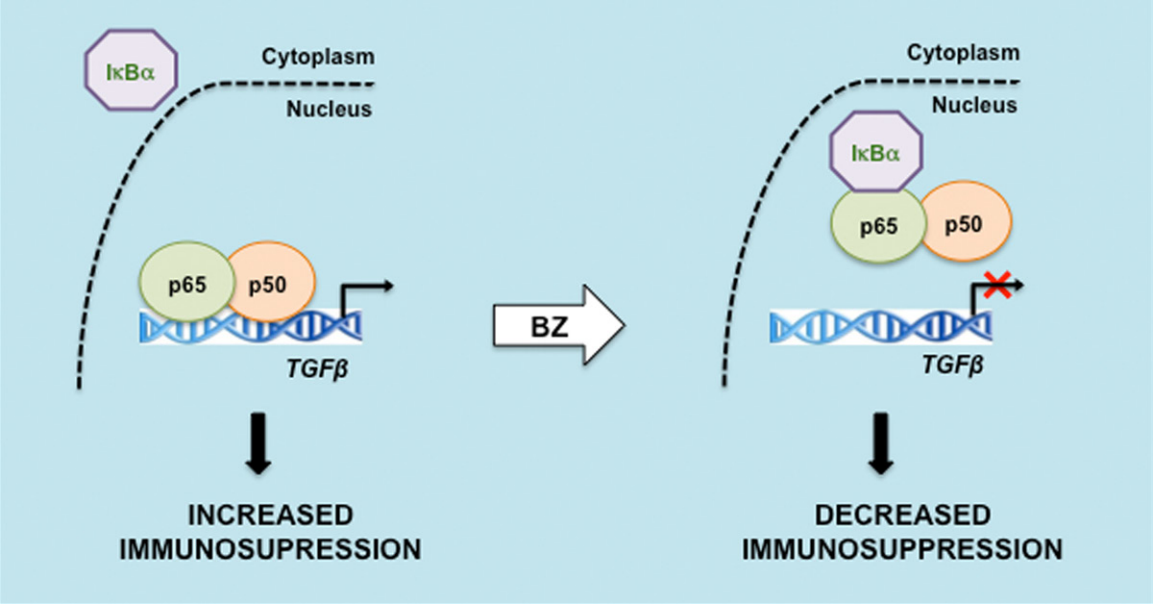

Figure 3. Proposed model of TGFβ regulation by NFκB and proteasome inhibition in CTCL cells. In CTCL Hut-78 cells, the promoter of TGFβ is occupied predominantly by NFκB p65/p50 homodimers. Proteasome inhibition induces the nuclear accumulation of IκBα, resulting in p65/p50 removal from TGFβ promoter, and inhibition of the TGFβ expression [Chang et al, manuscript in preparation].

(**Figure 2**). These data suggest that the regulation of anti-apoptotic genes by NFκB is gene specific, and depends on the subunit composition of NFκB proteins recruited to the promoters.

Pro-inflammatory role of NFκB

Inflammatory response is a critical part of innate immunity and involves signaling pathways that regulate both pro-inflammatory and anti-inflammatory genes [108]. Transcription of many of the pro-inflammatory genes is regulated by NFκB [109-112]. In the early stages of CTCL, activation of NFκB and cellular proliferation are induced by the autocrine production of TNFα, resulting in the increased activation of NFκB and resistance to apoptosis [113-116]. In addition to TNFα, epidermis of patients with CTCL displays increased levels of NFκB-dependent cytokines IL-1β and IL-8, suggesting a role of these cytokines in the pathogenesis of CTCL [117-119]. Recent studies have shown that malignant T cells and skin lesions from CTCL patients produce the pro-inflammatory cytokine IL-17 [120-122] that is also regulated by NFκB [123].

Zinc is an essential trace element and plays an important role in the activation of many enzymes involved in normal development and function of the immune system; therefore, zinc deficiency can cause growth retardation and decrease many cellular immune responses [124]. Zinc deficiency decreases Th1 cytokines, resulting in the shift from Th1 to Th2, and causing a severe cell-mediated dysfunction [125, 126]. Zinc-deficient CTCL Hut-78 cells displayed decreased phosphorylation of IKK and IκB, resulting in the reduced DNA binding of NFκB [127-129].

Anti-inflammatory role of NFκB

Although the role of NFκB in the transcriptional regulation of pro-inflammatory genes has been well established, recent studies have indicated that NFκB has an important anti-inflammatory function as well [130, 131]. In the later stages of CTCL, there is a gradual increase in malignant CD4 cells releasing the immunosuppressive cytokines IL-4, IL-10 and TGFβ [132-134]. Increased expression of these cytokines correlates with disease progression, immunosuppression, and susceptibility to infection [134-138].

Regulation of expression of IL-4, IL-10 and TGFβ is complex, and is controlled by several transcription factors and regulators, including NFκB

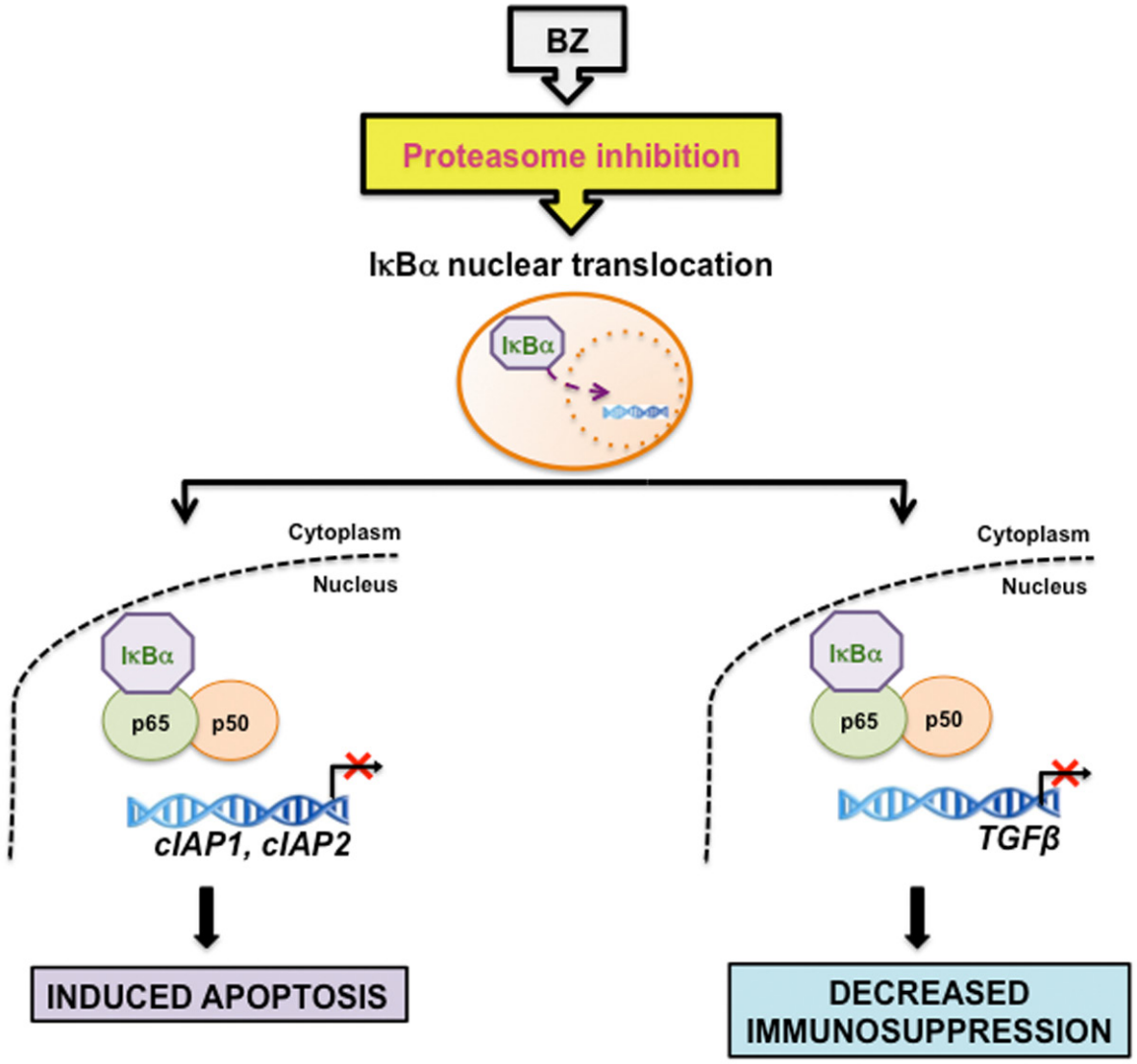

Figure 4. Proposed model of the regulation of NFκB-dependent genes by proteasome inhibition in CTCL cells. Proteasome inhibition by BZ induces the nuclear translocation and accumulation of IκBα, which inhibits expression of NFκB p65/p50-regulated anti-apoptotic genes cIAP1 and cIAP2, resulting in the increased apoptosis of CTCL cells. In addition, the BZ-induced nuclear IκBα inhibits expression of TGFβ, which may decrease the immunosuppressive phenotype associated with advanced stages of CTCL.

[139-143]. *In vitro* study in CTCL Hut-78 cells has indicated that the proximal NFκB binding site in IL-10 promoter is regulated predominantly by p50/50 homodimers that activate IL-10 transcription [141]. The IL-10 regulation by p50/50 homodimers was later confirmed by analysis of NFκB proteins recruited to the IL-10 promoter in murine macrophages [142]. This study showed that p50/50 homodimers activate IL-10 transcription, together with the transcriptional co-activator CREB-binding protein [142]. These data suggest that the p50/p50 homodimers might exert their immuno-suppressory function either by inhibiting transcription of NFκB-dependent pro-inflammatory genes, or by stimulating transcription of anti-inflammatory genes, such as IL-10.

Recent studies from our laboratory have indicated that the human TGFβ promoter is occupied predominantly by p65/p50 heterodimers in Hut-78 cells (**Figure 3**). In addition, the nuclear IκBα that is induced by proteasome inhibition by BZ significantly decreases this occupancy, resulting in the inhibition of TGFβ expression (**Figure 3**). These results indicate that proteasome inhibition has two beneficial effects in CTCL cells (**Figure 4**). It induces nuclear

accumulation of IκBα, which inhibits expression of NFκB p65/p50-regulated anti-apoptotic genes, resulting in the increased apoptosis of CTCL cells [5]. In addition, the BZ-induced nuclear IκBα inhibits expression of TGFβ, which may decrease the immunosuppressive phenotype associated with the advanced stages of CTCL (**Figure 4**).

Conclusion

The high constitutive NFκB activity in CTCL cells is responsible for their increased survival and proliferation, as well as for the increased expression of NFκB-dependent pro-inflammatory and anti-inflammatory cytokines. However, while the mechanisms regulating NFκB-dependent transcription of anti-apoptotic and pro-inflammatory genes have been studies extensively, the mechanisms of how NFκB regulates transcription of immuno-suppressory genes remain largely elusive. The specificity of NFκB binding to the individual promoters is determined by the subunit composition of NFκB complexes, their post-translational modifications, and interactions with other transcriptional factors and regulators. Understanding the mechanisms responsible for the NFκB regulation of immunosuppressive genes may provide new strategy for the treatment of CTCL and other disorders characterized by high levels of NFκB activity and immunosuppressive gene expression.

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