 Emerging role of IκBζ in inflammation: Emphasis on psoriasis

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Graphical Abstract

Expression of NFκB1Z is stimulated by cytokines such as IL-17, TNFα, IL-1β and IL-36. Increased expression of IκBζ eventually activates NF-κB leading to increased expression of various proinflammatory cytokines, chemokines, as well as psoriasis-associated genes. This cascade of molecules causes recruitment of neutrophils and other immune-mediated inflammatory cells, which consequently leads to the development of psoriasis-like skin inflammation.
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Abstract
Psoriasis is a chronic inflammatory disorder affecting skin and joints that results from immunological dysfunction such as enhanced IL-23 induced Th-17 differentiation. IkappaB-Zeta (IκBζ) is an atypical transcriptional factor of the IκB protein family since, contrary to the other family members, it positively regulates NF-κB pathway by being exclusively localized into the nucleus. IκBζ deficiency reduces visible manifestations of experimental psoriasis by diminishing expression of psoriasis-associated genes. It is thus tempting to consider IκBζ as a potential therapeutic target for psoriasis as well as for other IL23/IL17-mediated inflammatory diseases. In this review, we will discuss the regulation of expression of NFKBIZ and its protein IκBζ, its downstream targets, its involvement in pathogenesis of multiple disorders with emphasis on psoriasis and evidences supporting that inhibition of IκBζ may be a promising alternative to current therapeutic managements of psoriasis.

KEYWORDS
psoriasis, ikappabZeta, IκBζ, inflammation, NFKBIZ

1 | INTRODUCTION

Psoriasis is a common chronic inflammatory disease characterized by relapsing cutaneous erythro-squamous patches (psoriasis vulgaris) and/or inflamed joints (psoriatic arthritis). Psoriasis affects millions of individuals worldwide with a prevalence ranging from 0.5% to 11% in adults and below 1.37% in children.1 Even though its etiology still remains elusive,2 the implication of the immune-immediate response engaging Th1, Th17, γδ T cells, dendritic cells and keratinocytes has been described to play a significant role in disease immunopathogenesis.3

In general, IL23 cytokine induces the secretion of IL17 by skin Tyδ cells, mucosal-associated invariant T cells, innate lymphoid cells, and possibly by neutrophils leading to the induction of the inflammatory response.6 Therapeutics targeting IL23 and IL17 have been clinically approved and found to significantly manage the disorder.7 In addition to psoriasis, IL23/IL17 axis is a global immune regulatory mechanism involved in the pathogenesis of multiple immune-mediated inflammatory disorders such as spondyloarthritis,8 rheumatoid arthritis,9 Crohn’s disease,10 and ulcerative colitis.11 The protein IkappaBZeta (IκBζ) was independently discovered by Kitamura et al., Shiina et al. and Haruta...
et al.12–14 It was initially named as “molecule possessing ankyrin-repeats induced by lipopolysaccharide” (MAIL)12
and “interleukin (IL)-1-inducible nuclear ankyrin-repeat protein” (INAP).14 For sake of clarity, in the present manuscript, NFKBIZ (nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta) and IxBζ were used hereafter to refer to gene/mRNA and protein, respectively. IxBζ belongs to the nuclear IxB family and carries ankyrin repeats-containing domains. In mice, stimulation of the NF-xB inflammatory response by intraperitoneal injection of lipopolysaccharide (LPS) rapidly induced expression of NFKBIZ mRNA in the spleen, lymph nodes and lungs which further potentiated interleukin-6 (IL-6) mRNA expression.12 Moreover, IxBζ was found to migrate promptly into the nucleus to regulate NF-xB activity,14,15 a key inflammatory pathway involved in psoriasis onset. Interestingly, recent studies have highlighted the link between IxBζ and psoriasis in both in vivo and in vitro psoriatic conditions.16–19 With the aim to formalize the contribution of IxBζ to psoriasis via NF-xB modulation, we reviewed the current knowledge on the NFKBIZ gene including its expression regulation, its genetic variations, its encoded protein IxBζ and how this latter associate with NF-xB to modulate multiple downstream targets. We also conclude on the recent advances highlighting its implications in immune homeostasis related to several pathologies such as psoriasis but also cancer and infections.

1.1 Generalities about the NFKBIZ gene and its protein IxBζ

By genomic mapping, Shiina et al.13 found that the Nfkzbiz gene is located on the chromosome (Chr) 16 C1.2-C1.3 and Chr 11q21.1 in mice and in rat, respectively. This gene is well conserved in human, chimpanzee, rhesus monkey, dog, cow, as well as in mouse, chicken, rat and zebrafish.20

The mice Nfkzbiz gene encodes for three isoforms of IxBζ protein, the longest isoform 1 composed of 728 amino acids (AA) named as IxBζ(L);12 the shorter isoform 2 of 629AA lacking the first 99AA named IxBζ(S);21 and the isoform 3 of 534AA lacking the AA 236–429 named as IxBζ(D).22

The human NFKBIZ gene is a single copy gene mapped on the chromosome 3 at the locus 3q12.3 (Gene ID: 64332) (Figure 1A). NFKBIZ gene encodes for IxBζ protein with three isoforms produced by alternative splicing; the longest isoform 1 composed of 718 amino acids (AA) (encoded by ensembl transcript variant: ENST00000354291.3; gene ID: NCBI Transcript ID: NM_0010005474.3) named IxBζ(L); the shorter isoform 2 of 618 AA lacking the first hundred AA (represented with black arrow, encoded by ensembl transcript variant ENST00000394054.6; gene ID: NCBI Transcript ID: NM_0010005474.3) named IxBζ(S); and the isoform 3 long to 596 AA lacking the AA 237 to 358 (represented with red arrow, encoded by ENST00000326151.9) named as IxBζ(D) (Figure 1A,C). The amino acid sequence from 359 to 718 is conserved between the three human isoforms of IxBζ. Seven ankyrin repeats located in the carboxyl terminal domain of the protein were identified to interact with the p50 subunit of NF-xB. Furthermore, several functional domains have been identified in the IxBζ(L) isoform: a nuclear localization signal (NLS) spanning 164–179 AA; an internal fragment between 321 and 394 AA with a transcriptional activity domain (TAD) (Figure 1B).20,22 As isoform IxBζ(D) carries deletion in the central region supporting transactivation activity, this isoform may lack transcriptional activity.

1.2 Genetic variations in NFKBIZ

Several genetic variants have been reported in NFKBIZ. The presence of a 23 bp indel variation (rs3217713) in the intron 10 region of NFKBIZ was directly associated with psoriasis23,24 and the patient’s response to anti-TNF drug adalimumab.25 In addition to psoriasis, the deletion allele of rs3217713 was also reported as an independent risk factor for the development of early-onset coronary artery disease.26 This common indel polymorphism is positioned 3’ to exon 10 and co-occurrence of alternative transcript lacking exon 10 predicts the possible impact of this genetic variant on pre-mRNA splicing. As exon 10 encodes the ankyrin repeats of the protein which is responsible for the binding of IxBζ to NF-xB/p50, this genetic variant might be considered as a potential marker for NF-xB-associated pathologies.23 Additionally, the rare genetic variant rs7152376 C in NFKBIZ was found to be more frequent in psoriatic arthritis patients in comparison to healthy controls.27 Chapman et al. and Sangil et al. also revealed association of multiple NFKBIZ genetic variants with invasive pneumococcal disease.28,29 Despite the prominent contribution of NFKBIZ in inflammatory disorders, detailed studies elucidating the functional impact of its genotypic variants are lacking.

1.3 NF-xB and IxBζ interaction

NF-xB plays a central role in inflammation, cell growth, survival and differentiation. In resting conditions, NF-xB is seized inside the cytoplasm by associating with IxB family proteins such as IxBz, IxBζ and IxBc. However, in the presence of stimulus such as bacterial LPS, cytoplasmic IxB
proteins undergo phosphorylation-induced degradation by the proteasome. The liberated NF-κB translocates into the nucleus and activates the expression of several pro-inflammatory cytokines, chemokines and anti-microbial peptides, thereby playing a crucial role in host defense. IκBζ is barely present in resting conditions, but in the presence of stimulating agents like LPS, IκBζ is induced and localized into the nucleus where it preferentially interacts with p50 but not p65 subunit of NF-κB. IκBζ has been initially described as a negative regulator of NF-κB, as IκBζ expression plasmid transfected into RAW264.7 cells was found to inhibit activity of NF-κB reporter plasmid (pELAM1-Luc) stimulated with LPS. This description of a negative activity of IκBζ on NF-κB transactivation appears controversial, since the same author and others claimed thereafter the occurrence of latent transcriptional activation led by IκBζ upon interaction with p50 subunit of NF-κB. Afterward, Trinh et al. highlighted the functional interaction between NF-κB and IκBζ. They demonstrated in cellulo, by pull-down approach, that IκBζ, p50 homodimer of NF-κB and DNA form a stable ternary complex, in which glycin-rich region at the C-terminal end of NF-κB p50 homodimer binds with IκBζ, to prevent the proteolytic degradation of the NF-κB subunit. This direct interaction between IκBζ and NF-κB was shown to be a prerequisite for the expression of the pro-inflammatory cytokine IL-6 in activated peritoneal macrophages. Lately, Kohda et al. described that Asp-451 in the N-terminus of the ankyrin repeat 1 of IκBζ was critical for its interaction with the p50 subunit of NF-κB, while the Lys-717 and Lys-719 in the C-terminal region of ankyrin repeat 7 is responsible for IκBζ binding to the promoter of the lipocalin 2 gene leading to its transcriptional activation.
1.4 | Tissue expression and transcriptional regulation of NFKBIZ

Northern-blot analysis revealed that Nfkbiz was barely expressed in unstimulated macrophages. However, upon proinflammatory challenge with LPS and IL-1β, expression of IxBζ was strongly induced. In mice, Nfkbiz mRNA level was significantly augmented in lung, liver, kidney, heart, testis, thymus, lymph node and spleen after intraperitoneal injection of LPS.12,21 The basal expression of IxBζ was also reported in unstimulated cells within connective tissues like keratinocytes, corneal epithelial cells, conjunctival epithelial cells, few subconjunctival cells, tracheal epithelium and small intestine (and https://www.proteinatlas.org/ENSG00000144802-NFKBIZ/tissue). Yamamoto et al. further demonstrated that in addition to IL-1β and LPS, expression of Nfkbiz mRNA was also induced by peptidoglycans via TLR2, bacterial lipoproteins via TLR1/TLR2, flagellin via TLR5, MALP-2 via TLR6/TLR2, R-848 via TLR7 and CpG DNA via TLR9. Surprisingly, no expression of IxBζ was reported when cells were stimulated with TNFα alone.37 Once the above-mentioned ligands bind to Toll/IL-1 receptors, several signalling pathways are activated via the adaptor protein MyD88 and TRAF6. Eventually, TRAF6 activation leads to the stimulation of the MAP3K7/TAK-1 complex which subsequently activates the NIK/IKK/IxB/NF-κB pathway.38,20 Then, NF-κB acts as a transcription factor for many inflammatory genes which interestingly includes IxBζ since inhibition of NF-κB’s activities or invalidation of the MyD88 gene led to a complete repression of IxBζ expression in fibroblast cells, for instance.37,39 Additionally, the sequence analysis of mouse Nfkbiz revealed a potential transcription factor binding site for NF-κB as well as the existence of a TATA box element located into the proximal promoter region. Moreover, under the stimulus of LPS, the upstream region of the mouse Nfkbiz promoter was capable of promoting gene expression.43

1.5 | Post-transcriptional regulation of NFKBIZ

Activation of IL-17, LPS and IL-1β signalling pathways induces not only the transcriptional activation of NFKBIZ but also the stabilization of its mRNA. MaruYama et al. elucidated the contribution of LPS/IL-1β-MyD88 pathway to the stabilization of IxBζ mRNA.40 They showed that in response to LPS/IL-1β stimulation, MyD88-deficient macrophages failed to express NFKBIZ due to lack of stability of its mRNA. Moreover, IL-17 also contributes to the stabilization of NFKBIZ mRNA.41 Mechanistically, IL-17 induces expression of the RNA-binding protein AT-rich interactive domain containing protein 5a (Arid5a), which is recruited to the NF-κB activator 1 (Act1) and TNF receptor-associated factor 2 (TRAF2) complex. Herein, Arid5a performs two post-transcriptional functions: first, it binds to 3’ UTR of NFKBIZ and counteracts the endonuclease Regnase 1-mediated degradation resulting in mRNA stability; second, Arid5a facilitates translation of NFKBIZ by coordinating with eukaryotic translation initiation complex.42 Regnase-1, also known as MCPIP1, degrades mRNA transcripts undergoing active translation following IL-17 response, including IL-6 and NFKBIZ.43 Interestingly, a recent study reported that Regnase-3, also known as MCPIP3, contributes to skin inflammation by directly degrading NFKBIZ mRNA.44

1.6 | Downstream targets of IxBζ

In the last two decades, IxBζ has emerged as a critical regulator of NF-κB-mediated genes associated with inflammatory disorders. As stated earlier, IxBζ acts as a transcriptional regulator for various genes involved in cell survival, apoptosis and senescence. Interestingly, IxBζ itself lacks DNA binding site and rather assists other transcription factors in doing so.20 Some reports also hint that IxBζ negatively regulates STAT3 transcriptional activity (signal transducer and activator of transcription 3), thereby, influencing cellular growth and apoptosis.45 Furthermore, p38 mitogen-activated protein kinase (MAPK), Act1 and Jun NH2-terminal kinase (JNK) were also demonstrated as key signalling pathways in NFKBIZ/IxBζ regulation (Table 1).46 Numerous studies have highlighted that IxBζ binds to NF-κB and upregulates the transcription of several secondary response genes such as IL12, IL12, LCN2, IFNG and defensin beta 4 (DEFB4). DEFB4A gene encodes for protein human beta-defensin 2 (hBD-2) which is primarily produced by epithelial cells after exposure to gram-negative bacteria, viruses and pro-inflammatory cytokines such as IL-1β and TNFα.47 A study carried out by Kao et al.48 demonstrated that IL-17A-induced up-regulation of IxBζ increases expression of DEFB4, since IxBζ knockdown reduced DEFB4 expression in normal human bronchial epithelial cells. Neutrophil gelatinase-associated lipocalin (NGAL) another epithelial cells associated protein, is encoded by the LCN2 gene and is induced by IL-1β during inflammation in lungs and colon, in a NF-κB-dependent manner.49,50 Karlsten et al. indicated that co-stimulation of epithelial cells with TNFα and IL-17 led to IxBζ accumulation, which in turn bound to NF-κB on the LCN2 promoter, stimulating the expression of NGAL gene.51 Moreover, in lung epithelial A549 cell line,
TABLE 1  Downstream targets of Ixβζ with the respective stimulus

| Target genes/proteins                          | Stimuli                        | Cells                        | Refs       |
|-----------------------------------------------|--------------------------------|------------------------------|------------|
| IL-6                                          | LPS; pneumococcal strain D39   | Swiss 3T3 cells; human monocytes; peritoneal macrophages | 6,45,46    |
| LCN2/NGAL                                     | IL-1γζ; TNFα and IL-17 co-stimulation | Epithelial cells; lung epithelial A549 cell line | 40,41,42  |
| IFNG                                          | IL-18 and IL-1γ acting in synergy with TNFα IL-12/IL-18 | KGI cell line; Human NK cells | 43,44     |
| DEFB4/hBD-2                                   | IL-17A                         | Normal human bronchial epithelial cells | 39        |
| IL-36γ                                        | IL-17A                         | Psoriatic keratinocytes      | 47        |
| CCL2 (MCP-1)                                  | LPS or bacterial peptidoglycan | In vivo zymosan peritonitis model | 48        |
| IL-8                                          | γ-irradiation                  | Glioma cells                 | 49        |
| CXCL1                                         | γ-irradiation                  | Glioma cells                 | 49        |
| IL-19                                         | IL-17A and TNFα                | Human keratinocytes          | 53        |
| IL-20                                         | IL-17A and TNFα                | Human keratinocytes          | 53        |
| IL-33 dependent cytokines and chemokines such as IL-6, IL-13, CCL2, CCL3, and TNFα | IL-33 | Bone marrow-derived mast cells | 54        |

CCL, chemokine (C-C motif) ligand; Cxcl, chemokine (C-X-C motif) ligand; DEFB4, defensin beta 4; hBD-2, human beta-defensin 2; IFNG, interferon gamma; IL, interleukin; LCN2, lipocalin 2; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; NGAL, neutrophil gelatinase-associated lipocalin; TNFα, tumour necrosis factor-alpha.

IL-1γζ stimulation, but not TNFα, led to the transcriptional activation of NGAL which was also mediated by the binding of Ixβζ to NF-xB. Additionally, Ixβζ also up-regulates IFN-γ in a NF-xB-dependent manner in human NK cells and KGI cell line. Thus, IL-18 and IL-1γ acting in synergy with TNFα were found to stimulate Ixβζ-mediated IFN-γ expression in KGI cells, and stimulation with IL-12/IL-18 was found to be sufficient to induce Ixβζ which further results in secretion of IFN-γ in human NK cells. Pioneer studies carried out by Kitamura et al. revealed that upon LPS stimulation, Ixβζ amplifies expression and secretion of IL-6 in Swiss 3T3 cells. Mechanistically, TLR and NOD-like receptor activation by several ligands (like LPS) is followed by the binding of Ixβζ to p50 subunit of NF-xB which results in remarkable production of IL-6 in human monocytes. Sundaram et al. also demonstrated that under exposure to pneumococcal strain D39, Ixβζ was induced in a concentration-dependent manner in human monocytes but not in bronchial epithelial cells, consequently accounting for the increased expression of IL-6 and GMCSF. Ixβζ was also reported to regulate the production of IL-36γ in psoriatic keratinocytes. Moreover, the role of Ixβζ in the production of chemokines such as CCL2 (also known as MCP-1), which is responsible for the migration of blood monocytes to the site of inflammation, was also shown. It was demonstrated that Ixβζ-deficient macrophages had an impaired secretion of CCL2 when challenged with LPS or bacterial peptidoglycan, whereas Ixβζ-deficient mice displayed a reduced CCL2 secretion and monocytes infiltration in the zymosan peritonitis model. Upon γ-irradiation of glioma cells, expression of Ixβζ was elevated which eventually led to enhanced transcription of tumour-promoting cytokines such as IL-6, IL-8 and chemokine (C-X-C motif) ligand 1 (CXCL1). IL-19 and IL-20, members of the IL-10 family, were found to be associated with psoriasis-like skin abnormalities and upregulate psoriasis-related cytokines. The knowledge on Ixβζ regulation of inflammatory cytokines and chemokines was further extended in a study demonstrating that in human keratinocytes, synergistic induction of IL-17A and TNFα regulates IL-19 and IL-20 mRNA and protein expression, by Ixβζ-mediated p38 MAPK, NF-xB and JNK1/2-dependent signalling pathway. In a recent study, NF-xB-mediated induction of Ixβζ was found to boost the expression of IL-33-dependent cytokines and chemokines such as IL-6, IL-13, CCL2, CCL3 and TNFα in bone marrow-derived mast cells. Overall, numerous evidences show that Ixβζ in association with NF-xB upregulates production and secretion of various pro-inflammatory cytokines and chemokines in immune cells, epithelial cells and human keratinocytes. Thus, positioning Ixβζ as a consistent player in the pathogenesis of skin inflammatory disorders such as psoriasis appears to be a particularly relevant hypothesis.
1.7 | IxBζ in psoriasis

Psoriasis is characterized as a chronic immune-mediated skin disease primarily provoked by increased expression of the pro-inflammatory cytokines IL-23, TNF-α and IL-17.64 Precisely, TNFα and IL-17A have been considered as major players in the pathogenesis of psoriasis, since Chiricozzi et al. identified that costimulation of keratinocytes with TNFα and IL-17A leads to synergistic upregulation of hundreds of genes, including a group of genes with the highest level of expression in psoriatic skin, such as IL-8, IL-17C, IL-19, CCL20 and DEFB4.65 Although the underlying molecular mechanism is still not fully comprehended, these data highlight the potential relevance of the anti-psoriasis therapeutics based on TNFα or IL-17 antagonists. In this line, a significant step ahead was provided by an enhanced meta-analysis and replication studies which allowed to discover a new psoriasis susceptibility locus. Herein, the NFκBIZ gene was reported as a downstream target of IL-17 signalling in human skin keratinocytes.17 Several mouse models as well as clinical studies were subsequently conducted, emphasizing the implication of the proinflammatory cytokine IL-17 in the pathogenesis of psoriasis and showing the advantageous usage of IL-17 antagonist or of its receptor blockade on clinical symptoms of psoriasis.66 Furthermore, Nfkbiz-encoded protein IxBζ contributes to the development of Th17 cells in mice.67 Previousthat it was believed that IL-6 and transforming growth factor-β (TGF-β) with the help of nuclear receptors RORγt and RORα were responsible for the development of Th17 cells.68 In 2010, Okamoto et al. demonstrated that the combined ectopic expression of IxBζ with RORγt or RORα in naive CD4+ T cells also led to remarkable induction of Th17 cells even in the absence of IL-6 and TGF-β.69 Moreover, Nfkbiz knockout mice were resistant to experimental autoimmune encephalomyelitis (a classical Th17-dependent disorder).69 Overall, the data support that IxBζ is critically involved in IL-17 mediated development of Th17 cells in multiple autoimmune disorders including psoriasis. Despite the existence of data obtained in synovial fibroblast during rheumatoid arthritis, it is noteworthy that Nfkbiz expression has not yet been studied in psoriatic arthritis, a frequent extra-skin manifestation of psoriasis.

1.7.1 | Inducers of NFκBIZ in psoriasis

Numerous detailed studies were subsequently published, further pinning down the potential involvement of IxBζ in psoriasis and elaborating its mechanism of action. The cornerstone in this direction was the study by Johansen et al., in 2015, describing that IxBζ is a master regulator of psoriasis-associated proteins such as CCL20, DEFB4, SI00A7, IL-8, IL-19 and LCN2 in cultured human keratinocytes.18 The study provided evidence that IL-17A is a strong inducer of NFκBIZ expression while TNFα has an insignificant impact on its expression. Lesioned psoriatic skin was found to express high level of IxBζ. Moreover, systemic and local deletion of IxBζ using siRNA results in either absence or reduction of psoriasis-like skin lesions along with diminished expression of psoriasis-related genes. This study delineated that IxBζ may be a better target than TNFα or IL-17A to manage psoriasis, as psoriasis-like skin inflammation was still occurring in the absence of TNFα and IL-17A, whereas it was completely missing in the absence of IxBζ.18 Next, the impact of NFκBIZ knockdown was further demonstrated in human keratinocyte cell line, HaCaT. NFκBIZ-deficient cells had a reduced expression of IL-17A-induced DEFB4A, IL19 and CSF3 genes even after co-stimulation with TNFα. This finding emphasized that NFκBIZ is crucial for IL-17A target genes.19 Reminiscent of IL-17A, IL-17F was also found to be associated with IxBζ-mediated regulation of psoriasis-associated genes in cultured human keratinocytes.70 Therefore, IxBζ has emerged as a key regulator of both IL-17A and IL-17F-pathway accountable for IxBζ-mediated downstream regulation of psoriasis-associated genes.18 It is noteworthy that IL-17A and TNFα were primarily considered as stimulants of IxBζ-executed psoriasis-like skin lesions; however, the search for additional IxBζ inducers was pursued. A possible rationale for this continuous search was the observation of elevated IxBζ mRNA levels in inflamed skin areas despite the global knockout of IL-17A and TNFα in mice. These findings eventually underline the existence of IL-17A/TNFα-independent pathway accountable for IxBζ-mediated downstream regulation of psoriasis-associated genes.18

Taking forward this search, IL-36α and IL-36γ appeared to be also potent stimulators of IxBζ expression in both in vivo and in vitro studies. Thus, IL-36-induced IxBζ expression was demonstrated to be mainly supported by MyD88, NF-κB and STAT3 activation. IxBζ-deficient primary human keratinocytes and IxBζ knockout mice were also found to be prevented from IL-36-inducible psoriasis-associated gene expression and psoriasis-like dermatitis, respectively.72 These observations further validate the interest of modulating IxBζ for psoriasis therapy. Moreover, dsRNAs released from necrotic cells in skin and IL-17A synergistically co-stimulated IL-36γ expression as well as other proinflammatory mediators. In this
mechanism, IxBζ also accumulated and it was observed that IL-17A and dsRNAs elevated IL-36γ production through a p38 MAPK, NF-xB and IxBζ-dependent mechanism. Herein, a positive feedback loop is operated by NF-xB-induced IxBζ, which subsequently improves the NF-xB binding to the IL-36γ promoter. The studies by Müller et al. and Liu et al. highlighted the potential involvement of IL-36γ in NF-xB-mediated IxBζ pathway in human keratinocytes. Based on these studies, IL-36γ might be positioned in a positive feedback loop with IxBζ, the latter being able to further up-regulate IL-36γ. In psoriasis patients receiving anti-IL-17A treatment, expression of NFKBIZ and IL36G are positively correlated. Furthermore, combined TNFα and IL-17A stimulation led to an elevation in the expression of IL-36γ which was found to be regulated by IxBζ. The downstream targets of IL-17A- and IL-36-induced IxBζ such as Cxcl2, Cxcl5 and Csf3, were diminished after keratinocyte-specific depletion of IxBζ. This abrogation did not alter T cell infiltration into the site of inflammation but was sufficient to suppress the recruitment of neutrophils and monocytes.

Since IL36 has emerged as an important regulator of NF-κB/GAUTAM et al. 2021

1.8 Inhibitors of IxBζ pathway

Considering that IxBζ plays an imperative role in the pathogenesis of psoriasis, the search for potent therapeutic agents inhibiting IxBζ is emerging. LPS and IL-17 were considered as major inducers of IxBζ in psoriasis, and it was observed that dimethyl itaconate administration in psoriasis mice model suppressed LPS- and IL-17-induced IxBζ expression. Recently, tacrolimus, a T cell-targeted immunosuppressant was examined on cultured human keratinocytes co-stimulated with TNFα/IL-17A. This study reported that tacrolimus was successfully able to abrogate downstream targets of TNFα/IL-17A-induced IxBζ such as psoriasis-associated genes IL-36γ, CCL-20, IL-1β and S100-A9. In addition to tacrolimus, dimethyl fumarate and secukinumab (an anti-IL17A antibody) were also found to be protective in psoriasis by compromising IL-17-mediated induction of IxBζ.

1.9 IxBζ in cancer and other-related pathologies

In addition to psoriasis, numerous studies have investigated the role of IxBζ in various types of cancers. For instance, IxBζ was found to be overexpressed in lymphoid cancers and activated B-cell-like subtype of diffuse large B-cell lymphoma. Increased transcription of NFKBIZ was also correlated with the occurrence of primary testicular and primary central nervous system lymphomas. Furthermore, the role of IxBζ in cancer was strongly validated when IxBζ was found to inhibit the transcriptional activity of Bcl3. In addition to Bcl3, IxBζ was also observed to inhibit the transcriptional activity of STAT3. A study by Totzke et al. appraised the involvement of IxBζ in apoptosis and demonstrated that IxBζ repression induces resistance to apoptosis while its overexpression leads to cell death in human fibrosarcoma cells and breast carcinoma cells. The role of IxBζ was also shown in age-related inflammatory disorders in both human and mouse.

The role of IxBζ in inflammatory disorders was further extended to osteoarthritis (OA); as in mice chondrocytes, IxBζ is overexpressed in response to IL-1β. Furthermore, this overexpression caused upregulation in the levels of matrix-degrading enzymes, thereby, associating IxBζ with cartilage destruction in OA. In addition to this, IxBζ was also found to be overexpressed in human OA cartilage as compared to undamaged cartilage. Similar observations were recorded in the experimental mice model for OA. Interestingly, IxBζ was also found to be involved in regulating IL17A and TNF-induced transcription factor, ELF3 in synovial fibroblasts collected from rheumatoid arthritis (RA) and OA patients. In line with this, a recent study also supports that IxB-ζ is involved in inflammation, senescence and oxidative stress in OA-associated chondrocytes. The same group previously also described IxB-ζ as a redox-sensitive protein which partially contributes to the inflammation encouraged/favoured by LDHA-induced ROS in OA-associated chondrocytes. Additionally, the deletion of IxB-ζ or STAT3 genes in murine epithelial cells was found to enhance apoptosis and early lymphocyte filtration which eventually leads to development of the Sjögren’s syndrome-like inflammation. In aged rat kidneys, up-regulation of Nfk biz was associated with increased macrophage infiltration. Furthermore, LPS-treated aged rats were manifested with oxidative stress in the kidneys, whereas TGF-β-induced activation of kidney fibroblasts was found to be driven...
by Nfkbiiz-associated cytokines. These findings validate Nfkbiiz involvement in age-associated progressive renal fibrosis. Besides, IxBζ engages NF-xB in fibroblasts and contributes to the production of chemoattractants in response to IL-17, which are further responsible for the recruitment of neutrophils and monocytes to the site of inflammation. Interestingly, exposure toward the possible involvement of IxBζ in lymphoid follicles and the absolute number of lymphocytes as well as the absence of Iκκ expression in bacterial infections and influences protective fibrosis. Besides, Iκκ involvement in age-associated progressive renal Nfkbiz. Furthermore, exposure of two gut commensals of significance in maintaining the plasticity and stability of mast cells. The critical role of Iκκ was also involved in initiating IL-33-dependent cytokine production in bone marrow-derived mast cells. The critical role of Iκκ in the pathogenesis of house dust mite–induced asthma was elucidated by Sundaram et al. This group described that IxBζ is involved in regulating inflammatory response in lung epithelium. Altogether, the abovementioned studies strongly suggest that IxBζ is critically involved in tumour expansion, apoptosis, recruitment of various inflammatory cells and secretion of both inflammatory cytokines and chemokines.

1.10  | IxBζ in immune homeostasis and infections

Since IxBζ can positively alter the NF-xB pathway and manipulate differentiation and recruitment of various immune cells, we speculate that IxBζ may be differentially expressed in bacterial infections and influences protective immune response. A recent study demonstrated that in the absence of IxBζ, the number of isolated lymphoid follicles and the absolute number of lymphocytes as well as their percentage fraction was significantly increased in the colonic lamina propria of mice. These observations hint toward the possible involvement of IxBζ in maintaining immune homeostasis in the gut. Interestingly, exposure of human blood monocytes to pneumococcal strain D39 successfully induces expression of IxBζ and downstream targets involved in host defense. Moreover, overexpression of IxBζ elevates the expression of IL-6 and GMCSF in HEK293 cells while its knockdown diminishes mRNA expression of pneumococcus-induced IL-6 and GMCSF in monocytes. This study also demonstrated that expression of IxBζ is stimulated by TLR1/TLR2-mediated p38 MAP kinase and NF-xB. The immunoregulatory role of IxBζ was also exposed in T-lymphocytes because IxBζ-deficient T cells contribute to increase in peripheral effector/memory CD4+ cells and IFN-γ-producing CD4+ T cells. Furthermore, removal of IxBζ also revealed its significance in maintaining the plasticity and stability of Tregs. Furthermore, exposure of two gut commensals of low and high immunogenicity, Bacteroides vulgates and Escherichia coli, respectively, to bone marrow-derived dendritic cells (BMDCs) leads to differential regulation of IxBζ expression. Of interest, secretion of IL-6 and IL-10 in response to infection was found to be dependent on IxBζ in BMDCs. This study also showed that the commensals stimulate TLR4 signalling which in response stimulates the secretion of Th17-inducing cytokines in BMDCs. Moreover, IxBζ also upregulates Nlrp3 gene in bone marrow-derived macrophages, thereby, playing crucial role in the activation of NLRP3 inflammasome. Interestingly, the potential regulatory role of Nfkbiiz in the skin immunity was exposed when Nfkbiiz-deficient mice was found to spontaneously develop dermatitis along with expansion of Staphylococcus xylosus in the skin. Additionally, in Salmonella infection, IxBζ also emerged as an important preventive component by stimulating IgG secretion and Th1 differentiation. Ishiguro-Oonuma et al. also observed that Nfkbiiz-deficient mice develop atopic dermatitis-like lesions, and keratinocytes in these mice were less proliferative. Considering the significant contribution of IxBζ in the abovementioned inflammation-mediated immune response, IxBζ seems to consequently be well suited to also fine tune the protective immune response under bacterial infections.

1.11  | Future prospectives

Over the last decade, remarkable progress has been made for the management of psoriasis with neutralizing antibodies that target specific cytokines and immune cells. However, these therapies have difficult application routes as well as impose an economic burden for society considering their high cost. Also, the systemic utilization of neutralizing antibodies grounds for side effects such as upper respiratory tract infections, and can lead to progressive loss of efficacy owing to the development of anti-drug antibodies. As a consequence, there is a need for the complementary development of a localized effective new therapy for psoriasis. Moreover, Johansen et al. demonstrated that IxBζ inhibition is associated with reduced expression of psoriasis-related genes and eventually provides protection against manifestations of psoriasis in both in vivo and in vitro models. Also, Mandal et al. successfully inhibited NFKBIIZ by delivering small interfering RNA in skin with the help of ionic liquids and observed subsequent suppression of psoriasis-related genes and signal. Hence, one can assume that IxBζ is a potential therapeutic target in IL-17-related inflammatory pathologies, including psoriasis. However, clinical inhibition of IxBζ is complicated as IxBζ lacks enzymatic activity making difficult the development of direct IxBζ inhibitors. Small molecule inhibitors or siRNA blocking the stimulation of IxBζ or hindering its downstream
activity could be an alternative seducing pharmacological approach for psoriasis.

2 | CONCLUDING REMARKS

The critical involvement of IκBζ pathway in inflammation and cell survival suggests its relevance to be used as a marker of psoriasis pathogenesis but also in other inflammatory disorders. Furthermore such observations indicate that therapeutically targeting IκBζ/NF-κB pathway could be of interest in the management of these disorders.

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REFERENCES
1. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol. 2017;31:205–212. https://doi.org/10.1111/jdv.13854
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. New Engl J Med. 2009;361:496–509. https://doi.org/10.1056/nejmra0804595
3. Perera GK, Meglio PD, Nestle FO. Psoriasis. Annu Rev Pathol. Mech Dis 2012;7:385–422. https://doi.org/10.1146/annurev-pathol-011811-132448
4. Otsuka M, Egawa G, Kabashima K. Uncovering the mysteries of Langerhans cells, inflammatory dendritic epidermal cells, and monocyte-derived Langerhans Cell-like cells in the epidermis. Front Immunol. 2018;9:1768. https://doi.org/10.3389/fimmu.2018.01768
5. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of Psoriasis. Immunology. 2014;32:227–255. https://doi.org/10.1146/annurev-immunol-032713-120225
6. Bugaut H, Aractingi S. Major Role of the IL17/23 axis in psoriasis supports the development of new targeted therapies. Front Immunol. 2021;12:621956. https://doi.org/10.3389/fimmu.2021.621956
7. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021;397:754–766. https://doi.org/10.1016/s0140-6736(21)00184-7
8. Tsukazaki H, Kaito T. The role of the IL-23/IL-17 axis in the pathogenesis of spondyloarthritis. Int J Mol Sci. 2020;21:6401. https://doi.org/10.3390/ijms21176401
9. Lubberts E. The IL-23–IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol. 2015;11:415–429. https://doi.org/10.1038/nrrheum.2015.53
10. Fragoulis GE, Siebert S, Mclnnes IB. Therapeutic targeting of IL-17 and IL-23 cytokines in immune-mediated diseases. Annu Rev Med. 2016;67:337–353. https://doi.org/10.1146/annurev-med-051914-021944
11. Noviolo D, Mager R, Roda G, et al. The IL23-IL17 immune axis in the treatment of ulcerative colitis: successes, defeats, and ongoing challenges. Front Immunol. 2021;12:611256. https://doi.org/10.3389/fimmu.2021.611256
12. Kitamura H, Kanehira K, Okita K, et al. MAIL, a novel nuclear IκB protein that potentiates LPS-induced IL-6 production. Febs Lett. 2000;485:53–56. https://doi.org/10.1016/s0014-5793(00)02185-2
13. Shiina T, Morimatsu M, Kitamura H, et al. Genomic organization, chromosomal localization, and promoter analysis of the mouse gene Mail. Immunogenetics. 2001;53:649–655. https://doi.org/10.1007/s00251-001-0376-x
14. Haruta H, Kato A, Todokoro K. Isolation of a Novel interleukin-1-inducible nuclear protein bearing ankyrin-repeat motifs*. J Biol Chem. 2001;276:12485–12488. https://doi.org/10.1074/jbc.c100075200
15. Totzke G, Essmann F, Pohlmann S, et al. A novel member of the IκB family, human IκBζ, inhibits transactivation of p65 and its DNA binding*. J Biol Chem. 2006;281:12645–12654. https://doi.org/10.1074/jbc.m511956200
16. Johansen C, Flindt E, Kragballe K, et al. Inverse regulation of the nuclear factor-xB binding to the p53 and interleukin-8 xB response elements in lesional psoriatic skin. J Invest Dermatol. 2005;124:1284–1292. https://doi.org/10.1097/0jidd.01326497
17. Tsol LC, Spain SL, Ellingham E, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. Nat Commun. 2015;6:7001. https://doi.org/10.1038/ncomms8001
18. Johansen C, Mose M, Ommen P, et al. IκBζ is a key driver in the development of psoriasis. Proc National Acad Sci. 2015;112:E5825–E5833. https://doi.org/10.1073/pnas.1509971112
19. Muromoto R, Hirao T, Tawa K, et al. IL-17A plays a central role in the expression of psoriasis signature genes through the induction of IκBζ in keratinocytes. Int Immunol. 2016;28:443–452. https://doi.org/10.1093/intimm/dxw011
20. Willems M, Dubois N, Musumeci L, et al. IκBζ an emerging player in cancer. Oncotarget. 2016;7:66310–66322. https://doi.org/10.18632/oncotarget.11624
21. Yamazaki S, Muta T, Takeshige K. A Novel IκB Protein, IκBζ. Induced by Proinflammatory Stimuli, Negatively Regulates Nuclear Factor-xB in the Nuclei*. J Biol Chem 2001;276:27657–27662. https://doi.org/10.1074/jbc.m103426200
22. Motoyama M, Yamazaki S, Eto-Kimura A, et al. Positive and negative regulation of nuclear factor-xB-mediated transcription by IκBζ, an inducible nuclear protein*. J Biol Chem. 2005;280:7444–7451. https://doi.org/10.1074/jbc.m41278200
23. Coto-Segura P, González-Lara L, Gómez J, et al. NFκBι in psoriasis: assessing the association with gene polymorphisms and report of a new transcript variant. Hum Immunol. 2017;78:435–440. https://doi.org/10.1016/j.humimm.2017.02.008
24. Queiro R, Coto P, González-Lara L, Coto E. Genetic variants of the NF-κB pathway: unraveling the genetic architecture of psoriatic disease. Int J Mol Sci. 2021;22:13004. https://doi.org/10.3390/ijms222313004
25. Coto-Segura P, González-Lara L, Batalla A, et al. NFKBι and CW6 in adalimumab response among psoriasis patients: genetic association and alternative transcript analysis. Mol Diagn Ther. 2019;23:627–633. https://doi.org/10.1007/s40291-019-00409-x
26. Coto E, Reguero JR, Avanzas P, et al. Gene variants in the NF-kB pathway (NFKB1, NFKBIA, NFKBIZ) and risk for early-onset coronary artery disease. Immunol Lett. 2019;208:39–43. https://doi.org/10.1016/j.imlet.2019.02.007
27. Coto-Segura P, Coto E, González-Lara L, et al. Gene variant in the NF-κB pathway inhibitor NFKBIA distinguishes...
patients with psoriatic arthritis within the spectrum of psoriatic disease. *Biomed Res Int.* 2019;2019:1–6. https://doi.org/10.1155/2019/1030256

28. Chapman SJ, Khor CC, Vannberg FO, et al. NFκBIZ polymorphisms and susceptibility to pneumococcal disease in European and African populations. *Genes Immun.* 2010;11:319–325. https://doi.org/10.1038/gene.2009.76

29. Sangil A, Arranz MJ, Güerri-Fernández R, et al. Genetic susceptibility to invasive pneumococcal disease. *Infect Genet Evol.* 2018;59:126–131. https://doi.org/10.1016/j.meegid.2018.01.024

30. MaruYama T, Sayama A, Ishii KJ, Muta T. Screening of post-κ29. Sangil A, Arranz MJ, Güerri-Fernández R, et al. Genetic susceptibility to invasive pneumococcal disease. *Infect Genet Evol.* 2018;59:126–131. https://doi.org/10.1016/j.meegid.2018.01.024

31. O'Dea E, Hoffmann A. The regulatory logic of the NF-κB signaling system. *Csh Perspect Biol.* 2010;2:a000216. https://doi.org/10.1101/cshperspect.a000216

32. Yamazaki S, Muta T, Matsuo S, Takeshige K. Stimulus-specific stabilization. *J Biol Chem.* 2004;280:1678–87

33. Trinh DV, Zhu N, Farhang G, et al. The nuclear IκB protein IκBζ specifically binds NF-κB p50 homodimers and forms a ternary complex on NFκB binding sites and IκBζ is a key player in the antipsoriatic effects of seucakinumab. *J Allergy Clin Immun.* 2020;145:379–390. https://doi.org/10.1016/j.jaci.2019.09.029

34. Kohda A, Yamazaki S, Sumimoto H. The nuclear protein IκBζ forms a transcriptionally active complex with nuclear factor-xB (NF-xB) p50 and the Lcn2 promoter via the N- and C-terminal ankyrin repeat motifs*. *J Biol Chem.* 2016;291:20739–20752. https://doi.org/10.1074/jbc.m116.719302

35. Shiina T, Konno A, Oonuma T, et al. Targeted disruption of MAIβ, a nuclear IκB protein, leads to severe atopic dermatitis-like disease*. *J Biol Chem.* 2004;279:55493–55498. https://doi.org/10.1074/jbc.m409770200

36. Ueta M, Hamuro J, Yamamoto M, et al. Spontaneous ocular surface inflammation and goblet cell disappearance in IκBζ gene-disrupted mice. *Invest Ophth Vis Sci.* 2005;46:579–588. https://doi.org/10.1097/01.IOS.0000101946.40134.31

37. Yamamoto M, Yamazaki S, Uematsu S, et al. Regulation of Toll/IL-1-receptor-mediated gene expression by the inducible nuclear protein IκBζ*. *Nature.* 2004;430:218–222. https://doi.org/10.1038/nature02738

38. Manavalan B, Basith S, Choi S. *Encyclopedia of Signaling Molecules*. Springer: 2016:1–9. https://doi.org/10.1007/978-1-4614-6438-9_43_1

39. Eto A, Muta T, Yamazaki S, Takeshige K. Essential roles for NF-xB and a Toll/IL-1 receptor domain-specific signal(s) in the induction of IκBζ. *Biochem Bioph Res Co.* 2003;301:495–501. https://doi.org/10.1006/0006-291x(02)00382-6

40. MaruYama T, Sayama A, Ishii KJ, Muta T. Screening of post-transcriptional regulatory molecules of IκBζ. *Biochem Bioph Res Co* 2016;469:711–715. https://doi.org/10.1016/j.bbrc.2015.12.068

41. Muromoto R, Tawa K, Ohgakiuchi Y, et al. IκBζ expression requires both TYK2/STAT3 activity and IL-17-regulated mRNA stabilization. *Immunohorizons.* 2019;3:172–185. https://doi.org/10.4049/immunohorizons.1900023

42. Amatya N, Childs EE, Cruz JA, et al. IL-17 integrates multiple self-reinforcing, feed-forward mechanisms through the RNA binding protein Arid5a. *Sci Signal.* 2018;11:eaat4617. https://doi.org/10.1126/scisignal.aat4617

43. Garg AV, Amatya N, Chen K, et al. MCPIP1 endoribonuclease activity negatively regulates interleukin-17-mediated signaling and inflammation. *Immunity.* 2015;43:475–487. https://doi.org/10.1016/j.immuni.2015.07.021

44. Liu B, Huang J, Ashraf A, et al. The RNase MCPIP3 promotes skin inflammation by orchestrating myeloid cytokine response. *Nat Commun.* 2021;12:4105. https://doi.org/10.1038/s41467-021-24352-w

45. Wu Z, Zhang X, Yang J, et al. Nuclear protein IκBζ inhibits the activity of STAT3. *Biochim Bioph Res Co.* 2009;387:348–352. https://doi.org/10.1016/j.bbrc.2009.07.023

46. Bertelsen T, Ljungberg C, Litman T, et al. IκBζ is a key player in the antipsoriatic effects of seucakinumab. *J Allergy Clin Immun.* 2020;145:379–390. https://doi.org/10.1016/j.jaci.2019.09.029

47. Machado LR, Ottoñi B. An evolutionary history of defensins: a role for copy number variation in maximizing host innate and adaptive immune responses. *Front Immunol.* 2015;6:115. https://doi.org/10.3389/fimmu.2015.00115

48. Kao C-Y, Kim C, Huang F, Wu R. Requirements for two proximal NFκB binding sites and IκBζ in IL-17A-induced human β-defensin 2 expression by conducting airway epithelium*. *J Biol Chem.* 2008;283:15309–15318. https://doi.org/10.1074/jbc.m708289200

49. Cowland JB, Sørensen OE, Sehested M, Borregaard N. Neutrophil gelatinase-associated lipocalin is up-regulated in human epithelial cells by IL-1β, but Not by TNF-α. *J Immunol.* 2003;171:6630–6639. https://doi.org/10.4049/jimmunol.171.12.6630

50. Cowland JB, Muta T, Borregaard N. IL-1β-specific Up-regulation of neutrophil gelatinase-associated lipocalin is controlled by IκBζ. *J Immunol.* 2006;176:5559–5566. https://doi.org/10.4049/jimmunol.176.9.5559

51. Karlsen JR, Borregaard N, Cowland JB. Induction of neutrophil gelatinase-associated lipocalin expression by co-stimulation with interleukin-17 and tumor necrosis factor-α is controlled by IκBζ but neither by C/EBP-β nor C/EBP-δ*. *J Biol Chem.* 2010;285:14088–14100. https://doi.org/10.1074/jbc.m109.017129

52. Raices RM, Kannan Y, Bellamkonda-Athmaram V, et al. A novel role for IκBζ in the regulation of IFNγ production. *PLoS One.* 2009;4:e6776. https://doi.org/10.1371/journal.pone.0006776

53. Kannan Y, Yu J, Raices RM, et al. IκBζ augments IL-12- and IL-18-mediated IFNγ production in human NK cells. *Blood.* 2011;117:2855-2863. https://doi.org/10.1182/blood-2010-07-294702

54. Seshadri S, Kannan Y, Mitra S, et al. MAIβ regulates human monocyte IL-6 production. *J Immunol.* 2009;183:5358–5368. https://doi.org/10.4049/jimmunol.0802736

55. Sundaram K, Rahman Mohd A, Mitra S, et al. IκBζ regulates human monocyte pro-inflammatory responses induced by *Streptococcus pneumoniae*. *PLoS One.* 2016;11:e0161931. https://doi.org/10.1371/journal.pone.0161931

56. Liu S, Wu F, Wu Z, et al. IL-17A synergistically enhances TLR3-mediated IL-36γ production by keratinocytes: a potential role in injury-amplified psoriatic inflammation. *Exp Dermatol.* 2019;28:233–239. https://doi.org/10.1111/exd.13871

57. Hildebrand DG, Alexander E, Hörber S, et al. IκBζ is a transcriptional key regulator of CCL2/MCP-1. *J Immunol.* 2013;190:4812–4820. https://doi.org/10.4049/jimmunol.1300089
86. Okuma A, Hoshino K, Ohba T, et al. Enhanced apoptosis by disruption of the STAT3-IkB-ζ signaling pathway in epithelial cells induces Sjögren’s syndrome-like autoimmune disease. *Immunity*. 2013;38:450-460. https://doi.org/10.1016/j.immuni.2012.11.016

87. Chung KW, Jeong HO, Lee B, et al. Involvement of NF-κBIZ and related cytokines in age-associated renal fibrosis. *Onco-target*. 2014;5:7315-7327. https://doi.org/10.18632/oncotarget.14614

88. Slowikowski K, Nguyen HN, Noss EH, et al. CUX1 and IkBζ (NFKBIZ) mediate the synergistic inflammatory response to TNF and IL-17A in stromal fibroblasts. *Proc National Acad Sci*. 2020;117:5532-5541. https://doi.org/10.1073/pnas.1912702117

89. Casas A, Hawisher D, Guzman CBD, et al. Regulation of the Nfkbiz gene and its protein product IkBζ in animal models of sepsis and endotoxic shock. *Infect Immun*. 2021;89:e00674. https://doi.org/10.1128/iai.00674-20

90. Sundaram K, Mitra S, Gavrilin MA, Wewers MD. House dust mite allergens and the induction of monocyte interleukin 17 production that triggers an IkBζ-dependent granulocyte macrophage colony-stimulating factor release from human lung epithelial cells. *Am J Resp Cell Mol*. 2015;53:400-411. https://doi.org/10.1165/rcmb.2014-0370oc

91. Sasaki T, Nagashima H, Okuma A, et al. Functional analysis of the transcriptional regulator IkB-ζ in intestinal homeostasis. *Digest Dis Sci*. 2021;1-8. https://doi.org/10.1007/s10620-021-06958-8

92. MaruYama T, Kobayashi S, Ogasawara K, et al. Control of IFN-γ production and regulatory function by the inducible nuclear protein IkB-ζ in T cells. *J Leukocyte Biol*. 2015;98:385-393. https://doi.org/10.1189/jlb.2015.01.084

93. Michaelis L, Treß M, Löw H-C, et al. Gut commensal-induced IkBζ expression in dendritic cells influences the Th17 response. *Front Immunol*. 2021;11:61236. https://doi.org/10.3389/fimmu.2020.61236

94. Kim J, Ahn H, Yu S, et al. IkBζ controls NLRP3 inflammasome activation via upregulation of the Nlrp3 gene. *Cytokine*. 2020;127:154983. https://doi.org/10.1016/j.cyto.2019.154983

95. Kim Y, Lee Y-S, Yang J-Y, et al. The resident pathobiont Staphylococcus xylosus in Nkbiz-deficient skin accelerates spontaneous skin inflammation. *Sci Rep-uk* 2017;7:6348. https://doi.org/10.1038/s41598-017-05740-z

96. Ahn J-H, Cho J, Kwon B-E, et al. IkBζ facilitates protective immunity against Salmonella infection via Th1 differentiation and IgG production. *Sci Rep-uk* 2019;9:8397. https://doi.org/10.1038/s41598-019-44019-3

97. Ishiguro-Oonuma T, Ochiai K, Hashizume K, et al. Nkbiz regulates the proliferation and differentiation of keratinocytes. *Jpn J Vet Res* 2015;63:107-114. https://doi.org/10.14943/jvjr.63.3.107

98. Wasilewska A, Winiarska M, Olszewska M, Rudnicka L. Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. *Adv Dermatology Allergology Postępy Dermatologii Alergologii* 2016;33:247-252. https://doi.org/10.5114/ada.2016.61599

99. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapies used in psoriasis: the science behind the scenes. *J Invest Dermatol*. 2015;135:31-38. https://doi.org/10.1038/jid.2014.295

100. Mandal A, Kumhojkar N, Reilly C, et al. Treatment of psoriasis with NFKBIZ siRNA using topical ionic liquid formulations. *Sci Adv*. 2020;6:eabb6049. https://doi.org/10.1126/sciadv.abb6049

101. Annemann M, Plaza-Sirvent C, Schuster M, et al. Atypical IkB proteins in immune cell differentiation and function. *Immunol Lett*. 2016;171:26-35. https://doi.org/10.1016/j.imlet.2016.01.006

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