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## REVIEW

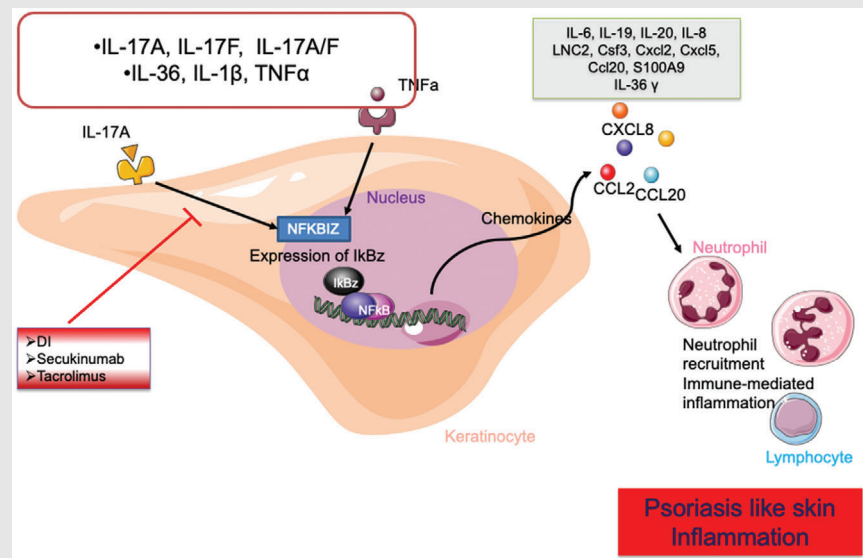
# Emerging role of $I\kappa B\zeta$ in inflammation: Emphasis on psoriasis

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**Graphical Abstract**

Expression of *NFKBIZ* is stimulated by cytokines such as IL-17, TNF $\alpha$ , IL-1 $\beta$  and IL-36. Increased expression of  $I\kappa B\zeta$  eventually activates NF- $\kappa$ B 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.

## REVIEW

# Emerging role of $I\kappa B\zeta$ in inflammation: Emphasis on psoriasis

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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. I $\kappa$ B-Zeta ( $I\kappa B\zeta$ ) is an atypical transcriptional factor of the I $\kappa$ B protein family since, contrary to the other family members, it positively regulates NF- $\kappa$ B pathway by being exclusively localized into the nucleus.  $I\kappa B\zeta$  deficiency reduces visible manifestations of experimental psoriasis by diminishing expression of psoriasis-associated genes. It is thus tempting to consider  $I\kappa B\zeta$  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  $I\kappa B\zeta$ , its downstream targets, its involvement in pathogenesis of multiple disorders with emphasis on psoriasis and evidences supporting that inhibition of  $I\kappa B\zeta$  may be a promising alternative to current therapeutic managements of psoriasis.

## KEYWORDS

psoriasis, ikappabZeta,  $I\kappa B\zeta$ , 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.<sup>1</sup> Even though its etiology still remains elusive,<sup>2</sup> the implication of the immune-immediate response engaging Th1, Th17,  $\gamma\delta$  T cells, dendritic cells and keratinocytes has been described to play a significant role in disease immunopathogenesis.<sup>3–5</sup>

In general, IL23 cytokine induces the secretion of IL17 by skin  $T\gamma\delta$  cells, mucosal-associated invariant T cells, innate lymphoid cells, and possibly by neutrophils leading to the induction of the inflammatory response.<sup>6</sup> Therapeutics targeting IL23 and IL17 have been clinically approved and found to significantly manage the disorder.<sup>7</sup> 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,<sup>8</sup> rheumatoid arthritis,<sup>9</sup> Crohn's disease,<sup>10</sup> and ulcerative colitis.<sup>11</sup>

The protein I $\kappa$ B-Zeta ( $I\kappa B\zeta$ ) was independently discovered by Kitamura et al., Shiina et al. and Haruta

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et al.<sup>12–14</sup> It was initially named as “molecule possessing ankyrin-repeats induced by lipopolysaccharide” (MAIL)<sup>12</sup> and “interleukin (IL)-1-inducible nuclear ankyrin-repeat protein” (INAP).<sup>14</sup> For sake of clarity, in the present manuscript, *NFKBIZ* (nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta) and  $I\kappa B\zeta$  are used hereafter to refer to gene/mRNA and protein, respectively.  $I\kappa B\zeta$  belongs to the nuclear  $I\kappa B$  family and carries ankyrin repeats-containing domains. In mice, stimulation of the NF- $\kappa$ B 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.<sup>12</sup> Moreover,  $I\kappa B\zeta$  was found to migrate promptly into the nucleus to regulate NF- $\kappa$ B activity,<sup>14,15</sup> a key inflammatory pathway involved in psoriasis onset. Interestingly, recent studies have highlighted the link between  $I\kappa B\zeta$  and psoriasis in both in vivo and in vitro psoriatic conditions.<sup>16–19</sup> With the aim to formalize the contribution of  $I\kappa B\zeta$  to psoriasis via NF- $\kappa$ B modulation, we reviewed the current knowledge on the *NFKBIZ* gene including its expression regulation, its genetic variations, its encoded protein  $I\kappa B\zeta$  and how this latter associate with NF- $\kappa$ B 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 $I\kappa B\zeta$

By genomic mapping, Shiina et al.<sup>13</sup> found that the *Nfkbiz* 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.<sup>20</sup>

The mice *Nfkbiz* gene encodes for three isoforms of  $I\kappa B\zeta$  protein, the longest isoform 1 composed of 728 amino acids (AA) named as  $I\kappa B\zeta(L)$ <sup>12</sup>; the shorter isoform 2 of 629AA lacking the first 99AA named  $I\kappa B\zeta(S)$ <sup>21</sup>; and the isoform 3 of 534AA lacking the AA 236–429 named as  $I\kappa B\zeta(D)$ .<sup>22</sup>

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  $I\kappa B\zeta$  protein with three isoforms produced by alternative splicing: the longest isoform 1 composed of 718 amino acids (AA) (encoded by ensembl transcript variant: ENST00000326172.9, NCBI Transcript ID: NM\_031419.4) named as  $I\kappa B\zeta(L)$ ; the shorter isoform 2 of 618 AA lacking the first hundred AA (represented

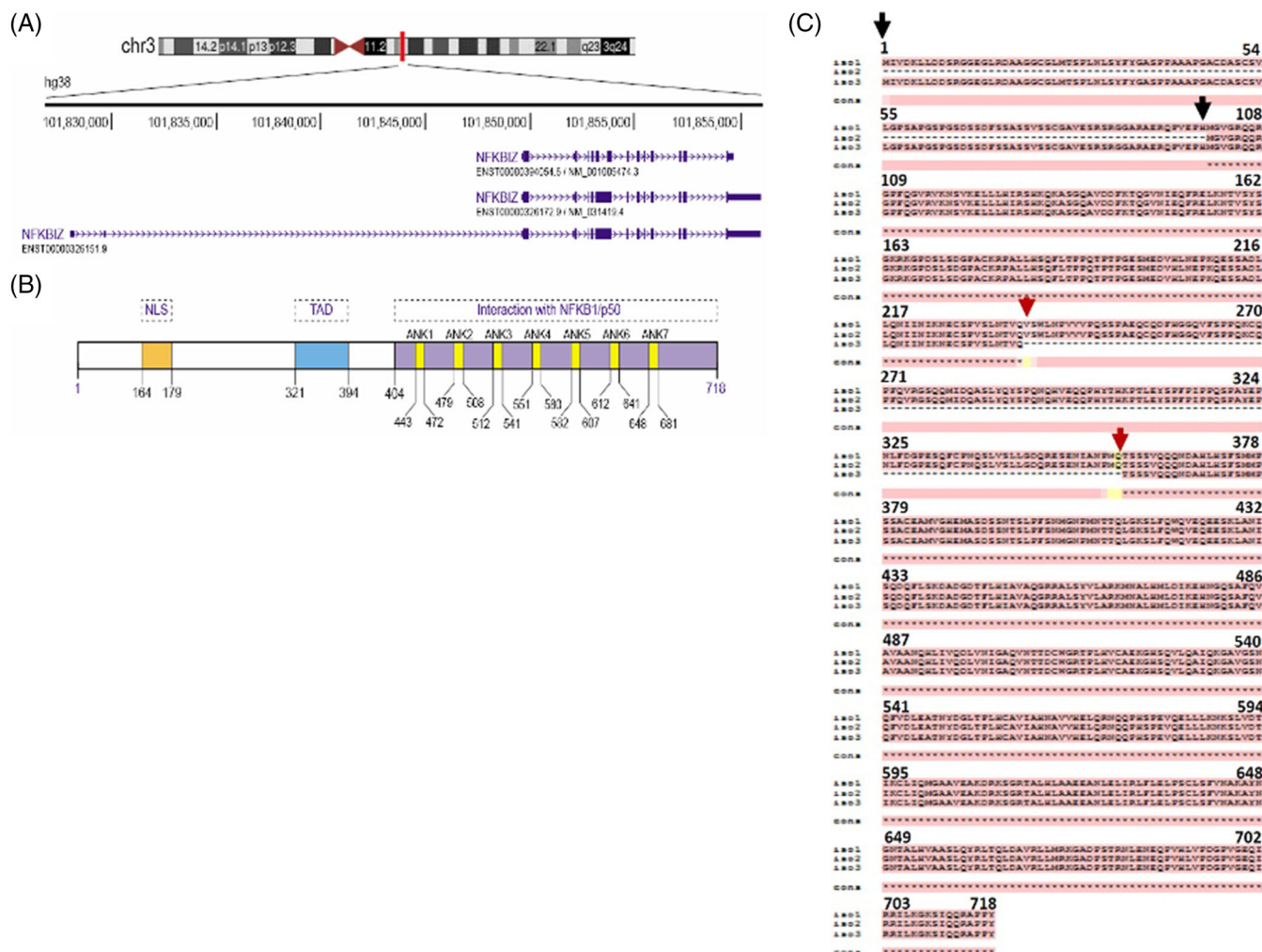
with black arrow, encoded by ensembl transcript variant ENST00000394054.6, NCBI Transcript ID: NM\_001005474.3) named  $I\kappa B\zeta(S)$ ; and the isoform 3 long to 596 AA lacking the AA 237 to 358 (represented with red arrow, encoded by ENST00000326151.9) named as  $I\kappa B\zeta(D)$  (Figure 1A,C). The amino acid sequence from 359 to 718 is conserved between the three human isoforms of  $I\kappa B\zeta$ . Seven ankyrin repeats located in the carboxyl terminal domain of the protein were identified to interact with the p50 subunit of NF- $\kappa$ B. Furthermore, several functional domains have been identified in the  $I\kappa B\zeta(L)$  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).<sup>20,22</sup> As isoform  $I\kappa B\zeta(D)$  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 psoriasis<sup>23,24</sup> and the patient’s response to anti-TNF drug adalimumab.<sup>25</sup> 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.<sup>26</sup> 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  $I\kappa B\zeta$  to NF- $\kappa$ B/p50, this genetic variant might be considered as a potential marker for NF- $\kappa$ B-associated pathologies.<sup>23</sup> Additionally, the rare genetic variant rs7152376 C in *NFKBIZ* was found to be more frequent in psoriatic arthritis patients in comparison to healthy controls.<sup>27</sup> Chapman et al. and Sangil et al. also revealed association of multiple *NFKBIZ* genetic variants with invasive pneumococcal disease.<sup>28,29</sup> Despite the prominent contribution of *NFKBIZ* in inflammatory disorders, detailed studies elucidating the functional impact of its genotypic variants are lacking.

## 1.3 | NF- $\kappa$ B and $I\kappa B\zeta$ interaction

NF- $\kappa$ B plays a central role in inflammation, cell growth, survival and differentiation. In resting conditions, NF- $\kappa$ B is seized inside the cytoplasm by associating with  $I\kappa B$  family proteins such as  $I\kappa B\alpha$ ,  $I\kappa B\beta$  and  $I\kappa B\epsilon$ . However, in the presence of stimulus such as bacterial LPS, cytoplasmic  $I\kappa B$



**FIGURE 1** Schematic representation of the chromosomal localization and transcript variants (demonstrated using <https://genome.ucsc.edu/>) (A), protein structure of human  $I\kappa B\text{-}\zeta$  (B), sequence alignment of three human isoforms (performed with <https://www.ebi.ac.uk/Tools/msa/tcoffee/>) (C). NLS, nuclear localizing signal; TAD, transactivating domain; ANK, ankyrin-repeat; NF- $\kappa$ B/p50, nuclear factor of  $\kappa$ B; NFKBIZ, nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, Zeta

proteins undergo phosphorylation-induced degradation by the proteasome. The liberated NF- $\kappa$ B 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.  $I\kappa B\zeta$  is barely present in resting conditions, but in the presence of stimulating agents like LPS,  $I\kappa B\zeta$  is induced and localized into the nucleus where it preferentially interacts with p50 but not p65 subunit of NF- $\kappa$ B.<sup>30,31</sup>

$I\kappa B\zeta$  has been initially described as a negative regulator of NF- $\kappa$ B, as  $I\kappa B\zeta$  expression plasmid transfected into RAW264.7 cells was found to inhibit activity of NF- $\kappa$ B reporter plasmid (pELAM1-Luc) stimulated with LPS.<sup>21</sup> This description of a negative activity of  $I\kappa B\zeta$  on NF- $\kappa$ B transactivation appears controversial, since the same author and others claimed thereafter the occurrence of latent transcriptional activation led by  $I\kappa B\zeta$  upon

interaction with p50 subunit of NF- $\kappa$ B.<sup>22,32</sup> Afterward, Trinh et al. highlighted the functional interaction between NF- $\kappa$ B and  $I\kappa B\zeta$ .<sup>33</sup> They demonstrated in cellulo, by pull-down approach, that  $I\kappa B\zeta$ , p50 homodimer of NF- $\kappa$ B and DNA form a stable ternary complex, in which glycine-rich region at the C-terminal end of NF- $\kappa$ B p50 homodimer binds with  $I\kappa B\zeta$ , to prevent the proteolytic degradation of the NF- $\kappa$ B subunit. This direct interaction between  $I\kappa B\zeta$  and NF- $\kappa$ B was shown to be a prerequisite for the expression of the pro-inflammatory cytokine IL-6 in activated peritoneal macrophages.<sup>33</sup> Lately, Kohda et al. described that Asp-451 in the N-terminus of the ankyrin repeat 1 of  $I\kappa B\zeta$  was critical for its interaction with the p50 subunit of NF- $\kappa$ B, while the Lys-717 and Lys-719 in the C-terminal region of ankyrin repeat 7 is responsible for  $I\kappa B\zeta$  binding to the promoter of the lipocalin 2 gene leading to its transcriptional activation.<sup>34</sup>

## 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-1 $\beta$ , expression of I $\kappa$ B $\zeta$  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.<sup>12,21</sup> The basal expression of I $\kappa$ B $\zeta$  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-1 $\beta$  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 I $\kappa$ B $\zeta$  was reported when cells were stimulated with TNF $\alpha$  alone.<sup>37</sup> 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/I $\kappa$ B/NF- $\kappa$ B pathway.<sup>38,20</sup> Then, NF- $\kappa$ B acts as a transcription factor for many inflammatory genes which interestingly includes I $\kappa$ B $\zeta$  since inhibition of NF- $\kappa$ B's activities or invalidation of the MyD88 gene led to a complete repression of I $\kappa$ B $\zeta$  expression in fibroblast cells, for instance.<sup>37,39</sup> Additionally, the sequence analysis of mouse *Nfkbiz* revealed a potential transcription factor binding site for NF- $\kappa$ B 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.<sup>13</sup>

## 1.5 | Post-transcriptional regulation of *NFKBIZ*

Activation of IL-17, LPS and IL-1 $\beta$  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-1 $\beta$ -MyD88 pathway to the stabilization of I $\kappa$ B $\zeta$  mRNA.<sup>40</sup> They showed that in response to LPS/IL-1 $\beta$  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.<sup>41</sup> Mechanistically,

IL-17 induces expression of the RNA-binding protein AT-rich interactive domain containing protein 5a (Arid5a), which is recruited to the NF- $\kappa$ B 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.<sup>42</sup> Regnase-1, also known as MCPIP1, degrades mRNA transcripts undergoing active translation following IL-17 response, including *IL-6* and *NFKBIZ*.<sup>43</sup> Interestingly, a recent study reported that Regnase-3, also known as MCPIP3, contributes to skin inflammation by directly degrading *NFKBIZ* mRNA.<sup>44</sup>

## 1.6 | Downstream targets of I $\kappa$ B $\zeta$

In the last two decades, I $\kappa$ B $\zeta$  has emerged as a critical regulator of NF- $\kappa$ B-mediated genes associated with inflammatory disorders. As stated earlier, I $\kappa$ B $\zeta$  acts as a transcriptional regulator for various genes involved in cell survival, apoptosis and senescence. Interestingly, I $\kappa$ B $\zeta$  itself lacks DNA binding site and rather assists other transcription factors in doing so.<sup>20</sup> Some reports also hint that I $\kappa$ B $\zeta$  negatively regulates STAT3 transcriptional activity (signal transducer and activator of transcription 3), thereby, influencing cellular growth and apoptosis.<sup>45</sup> Furthermore, p38 mitogen-activated protein kinase (MAPK), Act1 and Jun NH2-terminal kinase (JNK) were also demonstrated as key signalling pathways in *NFKBIZ*/I $\kappa$ B $\zeta$  regulation (Table 1).<sup>46</sup>

Numerous studies have highlighted that I $\kappa$ B $\zeta$  binds to NF- $\kappa$ B and upregulates the transcription of several secondary response genes such as *IL6*, *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-1 $\beta$  and TNF $\alpha$ .<sup>47</sup> A study carried out by Kao et al.<sup>48</sup> demonstrated that IL-17A-induced up-regulation of I $\kappa$ B $\zeta$  increases expression of *DEFB4*, since I $\kappa$ B $\zeta$  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-1 $\beta$  during inflammation in lungs and colon, in a NF- $\kappa$ B-dependent manner.<sup>49,50</sup> Karlsen et al. indicated that co-stimulation of epithelial cells with TNF $\alpha$  and IL-17 led to I $\kappa$ B $\zeta$  accumulation, which in turn bound to NF- $\kappa$ B on the *LCN2* promoter, stimulating the expression of *NGAL* gene.<sup>51</sup> Moreover, in lung epithelial A549 cell line,

**TABLE 1** Downstream targets of  $\text{I}\kappa\text{B}\zeta$  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-1 $\beta$ ; TNF $\alpha$ and IL-17 costimulation	Epithelial cells; lung epithelial A549 cell line	40,41,42
IFNG	IL-18 and IL-1 $\beta$ acting in synergy with TNF $\alpha$ IL-12/IL-18	KG1 cell line Human NK cells	43,44
DEFB4/ hBD-2	IL-17A	Normal human bronchial epithelial cells	39
IL-36 $\gamma$	IL-17A	Psoriatic keratinocytes	47
CCL2 (MCP-1)	LPS or bacterial peptidoglycan	In vivo zymosan peritonitis model	48
IL-8	$\gamma$ -irradiation	Glioma cells	49
CXCL1	$\gamma$ -irradiation	Glioma cells	49
IL-19	IL-17A and TNF $\alpha$	Human keratinocytes	53
IL-20	IL-17A and TNF $\alpha$	Human keratinocytes	53
IL-33 dependent cytokines and chemokines such as IL-6, IL-13, CCL2, CCL3, and TNF $\alpha$	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; TNF $\alpha$ , tumour necrosis factor-alpha.

IL-1 $\beta$  stimulation, but not TNF $\alpha$ , led to the transcriptional activation of NGAL which was also mediated by the binding of  $\text{I}\kappa\text{B}\zeta$  to NF- $\kappa$ B.<sup>50</sup> Additionally,  $\text{I}\kappa\text{B}\zeta$  also up-regulates IFN- $\gamma$  in a NF- $\kappa$ B-dependent manner in human NK cells and KG1 cell line. Thus, IL-18 and IL-1 $\beta$  acting in synergy with TNF $\alpha$  were found to stimulate  $\text{I}\kappa\text{B}\zeta$ -mediated IFN- $\gamma$  expression in KG1 cells, and stimulation with IL-12/IL-18 was found to be sufficient to induce  $\text{I}\kappa\text{B}\zeta$  which further results in secretion of IFN- $\gamma$  in human NK cells.<sup>52,53</sup> Pioneer studies carried out by Kitamura et al. revealed that upon LPS stimulation,  $\text{I}\kappa\text{B}\zeta$  amplifies expression and secretion of IL-6 in Swiss 3T3 cells.<sup>12</sup> Mechanistically, TLR and NOD-like receptor activation by several ligands (like LPS) is followed by the binding of  $\text{I}\kappa\text{B}\zeta$  to p50 subunit of NF- $\kappa$ B which results in remarkable production of IL-6 in human monocytes.<sup>54</sup> Sundaram et al. also demonstrated that under exposure to pneumococcal strain D39,  $\text{I}\kappa\text{B}\zeta$  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 GM-CSF.<sup>55</sup>  $\text{I}\kappa\text{B}\zeta$  was also reported to regulate the production of IL-36 $\gamma$  in psoriatic keratinocytes.<sup>56</sup> Moreover, the role of  $\text{I}\kappa\text{B}\zeta$  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  $\text{I}\kappa\text{B}\zeta$ -deficient macrophages had an impaired secretion of CCL2 when

challenged with LPS or bacterial peptidoglycan, whereas  $\text{I}\kappa\text{B}\zeta$ -deficient mice displayed a reduced CCL2 secretion and monocytes infiltration in the zymosan peritonitis model.<sup>57</sup> Upon  $\gamma$ -irradiation of glioma cells, expression of  $\text{I}\kappa\text{B}\zeta$  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).<sup>58</sup> 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.<sup>59–61</sup> The knowledge on  $\text{I}\kappa\text{B}\zeta$  regulation of inflammatory cytokines and chemokines was further extended in a study demonstrating that in human keratinocytes, synergistic induction of IL-17A and TNF $\alpha$  regulates IL-19 and IL-20 mRNA and protein expression, by  $\text{I}\kappa\text{B}\zeta$ -mediated p38 MAPK, NF- $\kappa$ B and JNK1/2-dependent signalling pathway.<sup>62</sup> In a recent study, NF- $\kappa$ B-mediated induction of  $\text{I}\kappa\text{B}\zeta$  was found to boost the expression of IL-33-dependent cytokines and chemokines such as IL-6, IL-13, CCL2, CCL3 and TNF $\alpha$  in bone marrow-derived mast cells.<sup>63</sup> Overall, numerous evidences show that  $\text{I}\kappa\text{B}\zeta$  in association with NF- $\kappa$ B upregulates production and secretion of various pro-inflammatory cytokines and chemokines in immune cells, epithelial cells and human keratinocytes. Thus, positioning  $\text{I}\kappa\text{B}\zeta$  as a consistent player in the pathogenesis of skin inflammatory disorders such as psoriasis appears to be a particularly relevant hypothesis.

## 1.7 | $\text{I}\kappa\text{B}\zeta$ 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- $\alpha$  and IL-17.<sup>64</sup> Precisely, TNF $\alpha$  and IL-17A have been considered as major players in the pathogenesis of psoriasis, since Chiricozzi et al. identified that costimulation of keratinocytes with TNF $\alpha$  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*.<sup>65</sup> Although the underlying molecular mechanism is still not fully comprehended, these data highlight the potential relevance of the anti-psoriasis therapeutics based on TNF $\alpha$  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 *NFKBIZ* gene was reported as a downstream target of IL-17 signalling in human skin keratinocytes.<sup>17</sup> 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.<sup>66</sup> Furthermore, *Nfkbiz*-encoded protein  $\text{I}\kappa\text{B}\zeta$  contributes to the development of Th17 cells in mice.<sup>67</sup> Previously, it was believed that IL-6 and transforming growth factor- $\beta$  (TGF- $\beta$ ) with the help of nuclear receptors ROR $\gamma$ t and ROR $\alpha$  were responsible for the development of Th17 cells.<sup>68</sup> In 2010, Okamoto et al. demonstrated that the combined ectopic expression of  $\text{I}\kappa\text{B}\zeta$  with ROR $\gamma$ t or ROR $\alpha$  in naive CD4<sup>+</sup> T cells also led to remarkable induction of Th17 cells even in the absence of IL-6 and TGF- $\beta$ .<sup>67</sup> Moreover, *Nfkbiz* knockout mice were resistant to experimental autoimmune encephalomyelitis (a classical Th17-dependent disorder).<sup>69</sup> Overall, the data support that  $\text{I}\kappa\text{B}\zeta$  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 *NFKBIZ* in psoriasis

Numerous detailed studies were subsequently published, further pinning down the potential involvement of  $\text{I}\kappa\text{B}\zeta$  in psoriasis and elaborating its mechanism of action. The cornerstone in this direction was the study by Johansen

et al., in 2015, describing that  $\text{I}\kappa\text{B}\zeta$  is a master regulator of psoriasis-associated proteins such as CCL20, DEFB4, S100A7, IL-8, IL-19 and LCN2 in cultured human keratinocytes.<sup>18</sup> The study provided evidence that IL-17A is a strong inducer of *NFKBIZ* expression while TNF $\alpha$  has an insignificant impact on its expression. Lesioned psoriatic skin was found to express high level of  $\text{I}\kappa\text{B}\zeta$ . Moreover, systemic and local deletion of  $\text{I}\kappa\text{B}\zeta$  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  $\text{I}\kappa\text{B}\zeta$  may be a better target than TNF $\alpha$  or IL-17A to manage psoriasis, as psoriasis-like skin inflammation was still occurring in the absence of TNF $\alpha$  and IL-17A, whereas it was completely missing in the absence of  $\text{I}\kappa\text{B}\zeta$ .<sup>18</sup> Next, the impact of *NFKBIZ* knockdown was further demonstrated in human keratinocyte cell line, HaCaT. *NFKBIZ*-deficient cells had a reduced expression of IL-17A-induced *DEFB4A*, *IL19* and *CSF3* genes even after co-stimulation with TNF $\alpha$ . This finding emphasized that *NFKBIZ* is crucial for IL-17A target genes.<sup>19</sup> Reminiscent of IL-17A, IL-17F was also found to be associated with  $\text{I}\kappa\text{B}\zeta$ -mediated regulation of psoriasis-associated genes in cultured human keratinocytes.<sup>70</sup> Therefore,  $\text{I}\kappa\text{B}\zeta$  has emerged as a key regulator of both IL-17A and IL-17F-inducible psoriasis-associated genes. Apart from the aforementioned inflammatory mediators, IL-17A/F heterodimer which was recently identified to mimic both IL-17A and IL-17F was also found to regulate  $\text{I}\kappa\text{B}\zeta$ -mediated psoriasis associated genes.<sup>71</sup> It is noteworthy that IL-17A and TNF $\alpha$  were primarily considered as stimulants of  $\text{I}\kappa\text{B}\zeta$ -executed psoriasis-like skin lesions; however, the search for additional  $\text{I}\kappa\text{B}\zeta$  inducers was pursued. A possible rationale for this continuous search was the observation of elevated  $\text{I}\kappa\text{B}\zeta$  mRNA levels in inflamed skin areas despite the global knockout of IL-17A and TNF $\alpha$  in mice. These findings eventually underline the existence of IL-17A/TNF $\alpha$ -independent pathway accountable for  $\text{I}\kappa\text{B}\zeta$ -mediated downstream regulation of psoriasis-associated genes.<sup>18</sup>

Taking forward this search, IL-36 $\alpha$  and IL-36 $\gamma$  appeared to be also potent stimulators of  $\text{I}\kappa\text{B}\zeta$  expression in both in vivo and in vitro studies. Thus, IL-36-induced  $\text{I}\kappa\text{B}\zeta$  expression was demonstrated to be mainly supported by MyD88, NF- $\kappa$ B and STAT3 activation.  $\text{I}\kappa\text{B}\zeta$ -deficient primary human keratinocytes and  $\text{I}\kappa\text{B}\zeta$  knockout mice were also found to be prevented from IL-36-inducible psoriasis-associated gene expression and psoriasis-like dermatitis, respectively.<sup>72</sup> These observations further validate the interest of modulating  $\text{I}\kappa\text{B}\zeta$  for psoriasis therapy. Moreover, dsRNAs released from necrotic cells in skin and IL-17A synergistically co-stimulated IL-36 $\gamma$  expression as well as other proinflammatory mediators. In this



mechanism,  $I\kappa B\zeta$  also accumulated and it was observed that IL-17A and dsRNAs elevated IL-36 $\gamma$  production through a p38 MAPK, NF- $\kappa$ B and  $I\kappa B\zeta$ -dependent mechanism. Herein, a positive feedback loop is operated by NF- $\kappa$ B-induced  $I\kappa B\zeta$ , which subsequently improves the NF- $\kappa$ B binding to the IL-36 $\gamma$  promoter.<sup>56</sup> The studies by Müller et al. and Liu et al. highlighted the potential involvement of IL-36 $\gamma$  in NF- $\kappa$ B-mediated  $I\kappa B\zeta$  pathway in human keratinocytes.<sup>56,72</sup> Based on these studies, IL-36 $\gamma$  might be positioned in a positive feedback loop with  $I\kappa B\zeta$ , the latter being able to further up-regulate IL-36 $\gamma$ . In psoriasis patients receiving anti-IL-17A treatment, expression of *NFKBIZ* and *IL36G* are positively correlated. Furthermore, combined TNF $\alpha$  and IL-17A stimulation led to an elevation in the expression of IL-36 $\gamma$  which was found to be regulated by  $I\kappa B\zeta$ .<sup>73</sup> The downstream targets of IL-17A- and IL-36-induced  $I\kappa B\zeta$ , such as *Cxcl2*, *Cxcl5* and *Csf3*, were diminished after keratinocyte-specific depletion of  $I\kappa B\zeta$ . This abrogation did not alter T cell infiltration into the site of inflammation but was sufficient to suppress the recruitment of neutrophils and monocytes.<sup>74</sup> Since IL36 has emerged as an important regulator of NF- $\kappa$ B/ $I\kappa B\zeta$  pathway in the pathogenesis of psoriasis but also in pustular psoriasis, a role for NF- $\kappa$ B/ $I\kappa B\zeta$  is highly probable in pustular psoriasis. These observations strongly suggest that  $I\kappa B\zeta$  is abnormally expressed in psoriasis-related cells and tissues. As its expression is regulated by several pro-inflammatory mediators,  $I\kappa B\zeta$  has emerged as a central modulator of NF- $\kappa$ B-mediated inflammatory response in psoriasis. Therefore, it is noteworthy that  $I\kappa B\zeta$  inhibition has the potential therapeutic relevance to manage psoriasis symptoms, as illustrated by several in vivo and in vitro  $I\kappa B\zeta$  knockout models. The graphical abstract provides an overview of the role of  $I\kappa B\zeta$  in triggering inflammatory conditions under the influence of proinflammatory stimulus in psoriasis.

## 1.8 | Inhibitors of $I\kappa B\zeta$ pathway

Considering that  $I\kappa B\zeta$  plays an imperative role in the pathogenesis of psoriasis, the search for potent therapeutic agents inhibiting  $I\kappa B\zeta$  is emerging. LPS and IL-17 were considered as major inducers of  $I\kappa B\zeta$  in psoriasis, and it was observed that dimethyl itaconate administration in psoriasis mice model suppressed LPS- and IL-17-induced  $I\kappa B\zeta$  expression.<sup>75</sup> Recently, tacrolimus, a T cell-targeted immunosuppressant was examined on cultured human keratinocytes co-stimulated with TNF $\alpha$ /IL-17A. This study reported that tacrolimus was successfully able to abrogate downstream targets of TNF $\alpha$ /IL-17A-induced  $I\kappa B\zeta$  such as psoriasis-associated genes *IL-36 $\gamma$* , *CCL-20*, *IL-1 $\beta$*  and *S100-A9*.<sup>76</sup> 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  $I\kappa B\zeta$ .<sup>46,77</sup>

## 1.9 | $I\kappa B\zeta$ in cancer and other related-pathologies

In addition to psoriasis, numerous studies have investigated the role of  $I\kappa B\zeta$  in various types of cancers. For instance,  $I\kappa B\zeta$  was found to be overexpressed in lymphoid cancers and activated B-cell-like subtype of diffuse large B-cell lymphoma.<sup>78,79</sup> Increased transcription of *NFKBIZ* was also correlated with the occurrence of primary testicular and primary central nervous system lymphomas.<sup>80</sup> Furthermore, the role of  $I\kappa B\zeta$  in cancer was strongly validated when  $I\kappa B\zeta$  was found to inhibit the transcriptional activity of Bcl3. In addition to Bcl3,  $I\kappa B\zeta$  was also observed to inhibit the transcriptional activity of STAT3.<sup>45,81</sup> A study by Totzke et al. appraised the involvement of  $I\kappa B\zeta$  in apoptosis and demonstrated that  $I\kappa B\zeta$  repression induces resistance to apoptosis while its overexpression leads to cell death in human fibrosarcoma cells and breast carcinoma cells.<sup>15</sup> The role of  $I\kappa B\zeta$  was also shown in age-related inflammatory disorders in both human and mouse.

The role of  $I\kappa B\zeta$  in inflammatory disorders was further extended to osteoarthritis (OA); as in mice chondrocytes,  $I\kappa B\zeta$  is overexpressed in response to IL-1 $\beta$ . Furthermore, this overexpression caused upregulation in the levels of matrix-degrading enzymes, thereby, associating  $I\kappa B\zeta$  with cartilage destruction in OA. In addition to this,  $I\kappa B\zeta$  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.<sup>82</sup> Interestingly,  $I\kappa B\zeta$  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.<sup>83</sup> In line with this, a recent study also supports that  $I\kappa B\zeta$  is involved in inflammation, senescence and oxidative stress in OA-associated chondrocytes.<sup>84</sup> The same group previously also described  $I\kappa B\zeta$  as a redox-sensitive protein which partially contributes to the inflammation encouraged/favoured by LDHA-induced ROS in OA-associated chondrocytes.<sup>85</sup> Additionally, the deletion of  $I\kappa B\zeta$  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.<sup>86</sup> 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- $\beta$ -induced activation of kidney fibroblasts was found to be driven

by *Nfkbiz*-associated cytokines. These findings validate *Nfkbiz* involvement in age-associated progressive renal fibrosis.<sup>87</sup> Besides,  $I\kappa B\zeta$  engages NF- $\kappa B$  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.<sup>88</sup>  $I\kappa B\zeta$  was observed to play a crucial role in sepsis by elevating the expression of *Lcn2* which was also considered as predictor of mortality in septic patients.<sup>89</sup> Moreover, NF- $\kappa B$ -mediated  $I\kappa B\zeta$  signalling was also involved in initiating IL-33-dependent cytokine and chemokine production in bone marrow-derived mast cells.<sup>63</sup> The critical role of  $I\kappa B\zeta$  in the pathogenesis of house dust mite-induced asthma was elucidated by Sundaram et al. This group described that  $I\kappa B\zeta$  is involved in regulating inflammatory response in lung epithelium.<sup>90</sup> Altogether, the abovementioned studies strongly suggest that  $I\kappa B\zeta$  is critically involved in tumour expansion, apoptosis, recruitment of various inflammatory cells and secretion of both inflammatory cytokines and chemokines.

### 1.10 | $I\kappa B\zeta$ in immune homeostasis and infections

Since  $I\kappa B\zeta$  can positively alter the NF- $\kappa B$  pathway and manipulate differentiation and recruitment of various immune cells, we speculate that  $I\kappa B\zeta$  may be differentially expressed in bacterial infections and influences protective immune response. A recent study demonstrated that in the absence of  $I\kappa B\zeta$ , 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  $I\kappa B\zeta$  in maintaining immune homeostasis in the gut.<sup>91</sup> Interestingly, exposure of human blood monocytes to pneumococcal strain D39 successfully induces expression of  $I\kappa B\zeta$  and downstream targets involved in host defense.<sup>55</sup> Moreover, overexpression of  $I\kappa B\zeta$  elevates the expression of IL-6 and GM-CSF in HEK293 cells while its knockdown diminishes mRNA expression of pneumococcus-induced IL-6 and GM-CSF in monocytes. This study also demonstrated that expression of  $I\kappa B\zeta$  is stimulated by TLR1/TLR2-mediated p38 MAP kinase and NF- $\kappa B$ .<sup>55</sup> The immunoregulatory role of  $I\kappa B\zeta$  was also exposed in T-lymphocytes because  $I\kappa B\zeta$ -deficient T cells contribute to increment in peripheral effector/memory CD4+ cells and IFN- $\gamma$ -producing CD4+ T cells. Furthermore, removal of  $I\kappa B\zeta$  also revealed its significance in maintaining the plasticity and stability of Tregs.<sup>92</sup> Furthermore, exposure of two gut commensals of low and high immunogenicity, *Bacteroides vulgatus* and *Escherichia coli*, respectively, to bone marrow-derived den-

dritic cells (BMDCs) leads to differential regulation of  $I\kappa B\zeta$  expression. Of interest, secretion of IL-6 and IL-10 in response to infection was found to be dependent on  $I\kappa B\zeta$  in BMDCs. This study also showed that the commensals stimulate TLR4 signalling which in response stimulates the secretion of Th-17-inducing cytokines in BMDCs.<sup>93</sup> Moreover,  $I\kappa B\zeta$  also upregulates *Nlrp3* gene in bone marrow-derived macrophages, thereby, playing crucial role in the activation of NLRP3 inflammasome.<sup>94</sup> Interestingly, the potential regulatory role of *Nfkbiz* in the skin immunity was exposed when *Nfkbiz*-deficient mice was found to spontaneously develop dermatitis along with expansion of *Staphylococcus xylosus* in the skin.<sup>95</sup> Additionally, in Salmonella infection,  $I\kappa B\zeta$  also emerged as an important preventive component by stimulating IgG secretion and Th1 differentiation.<sup>96</sup> Ishiguro-Oonuma et al. also observed that *Nfkbiz*-deficient mice develop atopic dermatitis-like lesions, and keratinocytes in these mice were less proliferative.<sup>97</sup> Considering the significant contribution of  $I\kappa B\zeta$  in the abovementioned inflammation-mediated immune response,  $I\kappa B\zeta$  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.<sup>98,99</sup> Moreover, Johansen et al. demonstrated that  $I\kappa B\zeta$  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.<sup>18</sup> Also, Mandal et al. successfully inhibited NFKBIZ by delivering small interfering RNA in skin with the help of ionic liquids and observed subsequent suppression of psoriasis-related genes and signal.<sup>100</sup> Hence, one can assume that  $I\kappa B\zeta$  is a potential therapeutic target in IL-17-related inflammatory pathologies, including psoriasis. However, clinical inhibition of  $I\kappa B\zeta$  is complicated as  $I\kappa B\zeta$  lacks enzymatic activity making difficult the development of direct  $I\kappa B\zeta$  inhibitors.<sup>101</sup> Small molecule inhibitors or siRNA blocking the stimulation of  $I\kappa B\zeta$  or hindering its downstream

activity could be an alternative seducing pharmacological approach for psoriasis.

## 2 | CONCLUDING REMARKS

The critical involvement of I $\kappa$ B $\zeta$  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 I $\kappa$ B $\zeta$ /NF- $\kappa$ B pathway could be of interest in the management of these disorders.

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