Stat6-Independent Tissue Inflammation Occurs Selectively on the Ocular Surface and Perioral Skin of IκBζ−/− Mice

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PURPOSE. IκBζ−/− mice have been reported to be affected by allergic dermatitis. This study was conducted to analyze the pathophysiological role of IκBζ and to address the functional relevance of Th2-mediated immune responses in the development of ocular surface inflammation and dermatitis by IκBζ−/− mice.

METHODS. BALB/c background IκBζ−/− mice were established without individual differences; IκBζ/Stat6 double-knockout (WKO) mice unable to produce Th2 cytokine were created; and microscopic-, histologic-, and immunochemical studies were performed. In IκBζ−/− mice the serum IgE levels were examined by ELISA, and quantitative PCR was used to study the gene expression of IFN-γ, IL-4, IL-10, TNFα, IL-6, IL-17α, and CCL11 in eyelid tissue.

RESULTS. IκBζ−/− mice exhibited a severe inflammatory phenotype on the ocular surface and perioral skin. The inflammatory infiltrates in the perioral skin consisted primarily of CD4+ and CD8+ cells; CD4+ and CD45RB+B220+ cells were mainly detected in the conjunctiva. In eyelid and perioral skin tissue, the expression of IL-17α and of Th1 and Th2 cytokines, but not of CCL11, was augmented. IκBζ−/− and IκBζ−/− mice did not differ significantly in their serum total IgE levels before, 0 to 4 weeks, and 5 to 9 weeks after disease onset. IκBζ/Stat6 WKO mice showed the same or slightly more severe inflammation than did IκBζ−/− mice.

CONCLUSIONS. IgE and Stat6 are not responsible for the immune pathologic response leading to the development of ocular surface and perioral skin inflammation in IκBζ−/− mice. IκBζ−/− mice may be a suitable model for Stevens-Johnson syndrome, but not for atopic dermatitis. (Invest Ophthalmol Vis Sci. 2008;49:3387–3394) DOI:10.1167/iovs.08-1691

IκBζ (also known as MAI1 and INAP) is an ankyrin-repeat containing nuclear protein that is highly homologous to the IκB family member Bcl3.¹⁻³ IκBζ was originally reported to be a regulator of transcription factor NF-κB, which is strongly induced by interleukin (IL-1) and lipopolysaccharide (LPS).¹⁻⁴ IκBζ, induced by diverse PAMPs (pathogen-associated microbial products), such as peptidoglycan (PGN), bacterial lipoprotein, flagellin, MALP-2, R-848, and CpG DNA,³ regulates NF-κB activity, possibly to prevent the excessive inflammation caused by bacterial components.³⁻⁶

We have reported that IκBζ−/− mice with a 129/Ola×C57BL/6 background expressly exhibit severe, spontaneous ocular surface inflammation accompanied by the eventual loss of almost all goblet cells and suggested that IκBζ participates in the negative regulation of ocular surface inflammation.⁶ We also proposed IκBζ−/− mice as a suitable model for Stevens-Johnson syndrome (SJS), an ocular surface inflammatory disease, because they manifest the loss of goblet cells that occurs in human SJS.⁶

Another group reported that MAI (molecular-possessing ankyrin repeats induced by LPS, equal to IκBζ−/−) mice, also from a 129/Ola×C57BL/6 background, represent a valuable new animal model for research on atopic dermatitis, because these animals were affected by allergic dermatitis.⁷

The inflammatory phenotypes of previously reported 129/Ola×C57BL/6 background IκBζ−/− mice were not uniform, and there were individual variations. For example, although all IκBζ−/− mice manifested ocular surface and perioral skin inflammation, only some developed dermatitis in the perioral area, neck, or ventral trunk.⁵⁻⁷ To analyze the pathophysiolog-ical role of IκBζ, we established BALB/c background IκBζ−/− mice.

STAT6 is a critical transcriptional factor that regulates IL-4-mediated Th2 immune responses.⁸⁻⁹ It is phosphorylated and activated through an IL-4R-mediated signal. It translocates as a phosphorylated homodimer and subsequently regulates IL-4-mediated transcriptional events, including Th2 differentiation and Ig class switching to IgE. IL-4-mediated STAT6 activation is an efficient cascade for the generation of Th2 cells during primary T-cell activation. The disruption of the STAT6 gene in mice has revealed its requirement for the development of Th2 cells and Th2-specific immune responses, such as IgE hyperproduction and atopic bronchial asthma.¹⁰⁻¹¹

To address the functional relevance of Th2-mediated immune responses in the development of ocular surface inflammation and dermatitis in IκBζ−/− mice, we created mice lacking both IκBζ and Stat6 (IκBζ/Stat6 WKO) that are not able to produce Th2 cytokines, such as IL-4.⁹

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MATERIALS AND METHODS

BALB/c Background IκBζ KO Mice and IκBζ/Stat6 WKO Mice

BALB/c background IκBζ knockout (KO) mice were produced by back-crossing 129/Ola×C57BL/6 IκBζ KO mice with BALB/c mice for six generations. For genotyping we used genomic DNA isolated from the tail of 2- to 3-week-old heterozygous parents (DNasey kit; Qiagen, Valencia, CA). PCR amplification was as previously reported. Briefly, PCR amplification on a thermal cycler (GeneAmp; Applied Biosystems, WKO Mice and IκBζ KO mice were produced by mat- ing BALB/c background IκBζ KO Stat6 KO mice obtained from BALB/c background IκBζ KO mice and BALB/c background Stat6 KO mice. To genotype the Stat6 gene, we performed PCR amplification with the Stat6 gene primer pair for wild Stat6, as previously reported. The use of primer A, specific for the targeted Stat6 gene (TCACAGGGGGGACCGATCCGGGATCTCT), and primer B, specific for the Stat6 gene downstream of the targeting construct (GGCCTAGCTGGGGCCTACA- CACACATTA), resulted in an ~1200-bp fragment from the heterozygotes (IκBζ/Stat6). Both fragments were obtained from the heterozygotes (IκBζ/Stat6).

Quantitative RT-PCR

The upper and lower eyelids were collected and homogenized in liquid nitrogen. Total RNA was extracted (RNaseasy mini kit; Qiagen, Tokyo, Japan) and treated with DNase I (DNase1 kit; Qiagen) to remove any residual genomic DNA. Reverse transcription (SuperScript Preamplification kit; Invitrogen) and real-time quantitative PCR (Prism 7700; Applied Biosystems [ABI], Foster City, CA), according to published procedures. The primers and probes for mouse IκBζ (CCL11, TNF-α, IFN-γ, IL-4, IL-10, IL-6, IL-17a, and mouse GAPDH were from ABI. The quantification data were normalized to the expression of the housekeeping gene GAPDH.

RESULTS

Macroscopic Observations on IκBζ′′′′ Mice

To analyze the pathophysiological role of IκBζ, we established BALB/c background IκBζ′′′′ mice. The phenotype of these mice is uniform, and there are no individual differences, although the phenotype of 129/Ola×C57BL/6 background IκBζ′′′′ mice varies, and there are individual differences. The ratio of wild-type (+/+) to heterozygous (+/−) to homozygous (−/−) mutant mice born from heterozygous intercrosses was 107:220:33 (1:2:0:3), indicating that 70% of IκBζ′′′′ embryos died in utero. The birth ratio of IκBζ′′′′ mice is higher than that of 129/Ola×C57BL/6 background mice (1:1.7:0:1). None of the IκBζ′′′′ or IκBζ′′′′ mice exhibited symptoms of ocular surface- or skin inflammation until the age of 32 weeks (data not shown).

IκBζ′′′′ mice manifested a severe inflammatory phenotype on the ocular surface, especially along the eyelids, and on the perioral skin. Kinetic monitoring of the inflammatory phenotype in the eyes and perioral skin revealed that the phenotype was absent at the time of birth. When these mice were between 4 and 6 weeks of age, the inflammatory phenotype of the eyelids became evident. Its appearance was followed by inflammatory symptoms in the perioral skin and became more severe as the animals grew older (Fig. 1A). Their severe eyelid inflammation was characterized by eyelid swelling, alopecia, and abnormal hair growth. No inflammation appeared on the abdominal and dorsal skin (data not shown). Severe perioral skin inflammation in these mice was characterized by erythema with excoriation and partial hair loss. Their dermatitis gradually progressed during the observation period until 32 weeks and resulted in lichenified chronic dermatitis. No morphologic or behavioral abnormalities were evident.

Histologic Analysis of IκBζ′′′′ KO Mice

Histologic analysis of the perioral skin of IκBζ′′′′ mice at 6 weeks of age, 2 weeks after symptom onset, revealed hyperplasia and spongiosis in the epidermis, including the hair follicles, inter- and intracellular edema in the epidermis, and heavy infiltration of the dermis by inflammatory cells (Fig. 1B). Histologically, the abdominal and dorsal skin of IκBζ′′′′ mice did not manifest this inflammatory phenotype (data not shown). In the perioral skin of IκBζ′′′′ mice of the same age, we detected neither obvious pathologic changes nor infiltrated inflammatory cells (Fig. 1B). Before the manifestation of inflammation, the perioral skin of IκBζ′′′′ mice exhibited no distinct histologic changes (data not shown).

Histologic Analysis of IκBζ′′′′ Mice

Histologic analysis of the eyes of the same IκBζ′′′′ mice, performed 2 weeks after symptom onset, showed heavy infiltration by inflammatory cells into the submucosal area of the conjunctiva. Moreover, there was a severe decrease in the number of goblet cells in conjunctival epithelia (Fig. 1C). Similar to the perioral skin, histologic analysis of the periorcular skin (eyelids) of the same IκBζ′′′′ mice revealed hyperplasia.
and spongiosis in the epidermis, inter- and intracellular edema in the epidermis, and infiltration of the dermis by inflammatory cells (data not shown). Neither obvious pathologic changes nor infiltrated inflammatory cells were detected in the eyes of IκBζ−/− mice of the same age (Fig. 1C). Before the manifestation of inflammation, the periocular skin and conjunctiva of IκBζ−/− mice exhibited no distinct histologic changes (data not shown). However, within 1 week after symptom onset, the infiltration of inflammatory cells into the conjunctival epithelia was evident, and we observed a moderate loss of goblet cells (Fig. 1C), possibly as a consequence of inflammatory cell infiltration. No pathologic changes were evident in other eye compartments such as the lens, retina, uvea, and sclera of the IκBζ−/− mice (data not shown), or in other tissues such as the thymus, spleen, liver, kidney, lung, small intestine, large intestine, and brain (data not shown).

Immunohistologic Analysis of the Ocular Surface and Perioral Skin of IκBζ KO Mice

The inflammatory infiltrates in the perioral skin of 10-week-old IκBζ−/− mice (6 weeks after symptom onset) consisted primarily of CD4+ and CD8+ cells (Fig. 2). A few CD45R/B220+ cells were present (Fig. 2). CD8+ cells infiltrated the outer sheet of
hair follicles, and CD4\(^+\) cells infiltrated between the hair follicles (Fig. 2). Moreover, CD4\(^+\) and CD8\(^+\) cells infiltrated not only the dermis but also the epidermis. These cells were not detected in the perioral skin of \(I_{\kappa}\beta_\zeta^{-/-}\) mice.

On the other hand, the inflammatory infiltrates in the subconjunctival tissue of the eyelids of the same mouse were mainly composed of CD4\(^+\) and CD45R/B220\(^+\) cells. CD8\(^+\) cells were detected in conjunctival epithelium, but not in subconjunctival tissue (Fig. 3). Moreover, like their perioral skin, the dermis of the eyelids of \(I_{\kappa}\beta_\zeta^{-/-}\) mice was infiltrated by many CD4\(^+\), some CD8\(^+\), and a few CD45R/B220\(^+\) cells (Fig. 3). No CD4\(^+\), CD45R/B220\(^+\), or CD8\(^+\) cells were detected in the subconjunctival tissue and eyelids of \(I_{\kappa}\beta_\zeta^{-/-}\) mice.
Serum Total IgE

The serum total IgE levels of IκBζ−/− mice were reportedly significantly higher than those of IκBζ+/− and IκBζ+/+ mice. To confirm this finding, we examined the serum total IgE levels of IκBζ mice at various time points before and after symptom onset. To our surprise, we detected no significant difference between IκBζ−/− and IκBζ−/+ mice before, 0 to 4 weeks, and 5 to 9 weeks after disease onset (Fig. 4A). However, at 10 weeks after onset, the serum total IgE level of IκBζ−/− mice became significantly higher than of IκBζ−/+ mice (data not shown). This result suggests that the high serum total IgE levels in IκBζ−/− mice may be secondary to the observed tissue inflammation.

Quantitative RT-PCR of Eyelid Tissue

To elucidate the cytokine milieu of the observed inflammation, we studied the gene expression profiles. We first confirmed the IκBζ mRNA expression level in eyelid tissues. Although IκBζ−/− mice did not express IκBζ mRNA, in IκBζ−/+ mice, the IκBζ mRNA expression was ~50% of that in IκBζ+/+ mice (Fig. 4B). The CCL11 mRNA level did not significantly among IκBζ−/−, IκBζ−/+ mice, and IκBζ−/−/− mice (Fig. 4C). The expression of IFN-γ, IL4, IL10, TNFα, IL6, and IL17α mRNA was upregulated in the eyelids of IκBζ−/− mice (Fig. 4D). It should be noted that IL6 gene expression was upregulated in the eyelid tissues. Our analysis of perioral skin tissue returned the same results as the eyelid tissue (data not shown). These findings suggest that the eyelid- and perioral skin inflammation of IκBζ−/− mice is the result of the interplay among the helper T-cell subsets Th17, -1, and -2.

Severe Inflammatory Symptoms in IκBζ/Stat6 WKO Mice

To address the functional relevance of IgE and Th2-mediated immune responses in the development of ocular surface and perioral skin inflammation in IκBζ−/− mice, we created IκBζ/Stat6 WKO mice that were unable to mount the Th2-polarized IL4-mediated immune response required for IgE class switching. IL4-specific gene expression was actually ablated in IκBζ/Stat6 WKO mice, directly indicating the absence of Th2-mediated immune responses (data not shown). To our surprise, in the IκBζ/Stat6 WKO mice, severe inflammatory symptoms were elicited (Fig. 5A). Moreover, these mice not only presented with severe dermatitis of the facial skin but also of the abdominal skin (Fig. 5A). No obvious dermatitis was seen in Stat6 single-KO mice (Fig. 5A).

Histologic analysis of the perioral skin of 23-week-old IκBζ/Stat6 WKO mice, 19 weeks after symptom onset, revealed epidermal hyperplasia, hyperkeratosis, inter- and intracellular edema in the epidermis, and heavy infiltration of the dermis by inflammatory cells. In the perioral skin of IκBζ−/−/−Stat6−/−/− and IκBζ−/+Stat6−/−/− mice we observed slight acanthosis and mild dermal infiltration by inflammatory cells (Fig. 5B). On the other hand, the abdominal skin of IκBζ/Stat6 WKO, but not of IκBζ−/−Stat6−/−/− and IκBζ−/+Stat6−/−/− mice, showed moderate infiltration of the dermis by inflammatory cells (data not shown).

Our analysis of the eyes of the same 23-week-old IκBζ/Stat6 WKO mice showed heavy inflammatory cell infiltration into the submucosal area of the conjunctiva. Moreover, as in IκBζ−/− mice, PAS staining revealed a severe decrease in the number of goblet cells in conjunctival epithelia (Fig. 5C). No obvious pathologic change and no inflammatory cell infiltration was detected in the eyes of IκBζ−/−/−Stat6−/−/− and IκBζ−/+Stat6−/−/− mice of the same age (Fig. 5C). The other eye compartments such as the lens, retina, uvea, and sclera of IκBζ/Stat6 WKO mice exhibited no pathologic changes, and there was no distinctive difference from IκBζ−/−Stat6−/−/− and IκBζ−/+Stat6−/−/− mice (data not shown).

The inflammatory infiltrates in the perioral skin of the 23-week-old IκBζ/Stat6 WKO mice were mostly CD4+ cells; a few CD8+ and a few CD45R/B220+ cells were present (Fig. 5D). In the perioral skin of IκBζ/Stat6 WKO mice, CD4+ and CD8+ cells infiltrated not only the dermis but also the epidermis (Fig. 5D). On the other hand, in the perioral skin of IκBζ−/− Stat6−/−/− and IκBζ−/+ Stat6−/−/− mice, only a few CD4+ cells infiltrated the dermis and epidermis (Fig. 5D). In IκBζ/Stat6 WKO mice, as in IκBζ−/− mice, the inflammatory infiltrates in the subconjunctival tissue of the eyelids were CD4+ and CD45R/B220+ cells (data not shown). As in their perioral skin, many CD4+, a few CD8+, and few CD45R/B220+ cells infiltrated the dermis of the eyelids of IκBζ/Stat6 WKO mice (data not shown).
DISCUSSION

Unlike 129/OlaxC57BL/6 background mice that exhibited individually varying disease symptoms, BALB/c background IκBζ−/− mice manifested a uniform disease phenotype. This renders them useful for the pathologic investigation of chronic inflammatory symptoms on the human ocular surface. One of the typical pathologic phenotypes confirmed in this study is a concurrent loss in the conjunctival epithelia of goblet cells and the presence of intensive inflammatory infiltrates the submucosa of the conjunctival epithelia, and the dermis and epidermis of the perioral skin. Our findings suggest that IκBζ−/− mice may be a suitable model for Stevens-Johnson syndrome and that these mice may be useful for mimicking the secondary conjunctival inflammation that often occurs in patients with SJS.

SJS is an acute-onset mucocutaneous disease induced by infectious agents and/or inciting drugs. The pathobiologic mechanisms underlying the onset of SJS/TEN have not been fully established. Patients with SJS manifest vesiculobullous skin lesions and severe conjunctivitis in the acute stage. Ocular surface complications such as dry eye due to loss of goblet cells persist in the chronic stage. Thus, loss of goblet cells is an important ocular surface feature of SJS in the chronic stage. Moreover, in a patient with conjunctival inflammation due to SJS, CD4+ T-cells were identified in the cell population infiltrating the conjunctivalized tissues over the cor-
The complete loss of goblet cells in the conjunctival epithelia of IκBα−/− mice made the ocular surface inflammation in these mice distinct from that previously reported in mice with allergic conjunctivitis, other rodent models of allergic conjunctivitis, and NC/Nga mice with spontaneous atopic dermatitis. Rodent models of allergic conjunctivitis display no change in these cells and NC/Nga mice with spontaneous atopic dermatitis manifest an increase in goblet cell density.

There have been no rodent models showing the spontaneous loss of goblet cells in their conjunctiva as observed in IκBα−/− mice. Of note, the reduction of goblet cells followed the infiltration of inflammatory cells. Thus, we posit that the observed loss of goblet cells may be a consequence of inflammatory cell infiltration into the conjunctival epithelium of IκBα−/− mice. On the ocular surface in SJ8, inflammation distinct from allergic inflammation may be involved in the loss of goblet cells in the conjunctiva. IκBα was expressed, not only on the ocular surface, but also in mucosal tissues such as the trachea and small intestine. The inflammatory disorders were recognized in limited tissues of IκBα−/− mice. In these animals, spontaneous chronic inflammation was selectively elicited on the ocular surface and in perioral skin but not in other tissues. Canker sores, oral mucositis, and ocular surface inflammation may actually be essential to SJ8 with ocular surface complications in the acute stage.

To the best of our knowledge, there are no reports describing the association between the IκBα gene and SJ8. However, in our investigation of the disordered innate immune response in SJ8, the gene expression of IκBα by peripheral CD14 mononuclear cells of SJ8 patients was found to be reduced compared with that in healthy control subjects (unpublished data, 2007). Thus, we speculate that, in part, IκBα gene expression may participate in the onset of SJ8.

The members of the NF-κB family are evolutionarily conserved pleiotropic transcription factors that play a crucial role in many biological processes. A variety of stimuli lead to the phosphorylation of IκBs. Unlike typical IκB proteins, IκBα rather stably accumulates in the nucleus. In line with its function as a negative regulator of NF-κB, a proapoptotic effect of IκBα has been reported; it antagonizes the antiapoptotic function of NF-κB. The Toll-like receptor-mediated production of IL-6 was inhibited in IκBα-deficient macrophages. We found that compared with IκBα−/− and IκBα+/− mice, in the eyelids of IκBα−/− mice, the mRNA expression of IL-6 mRNA was dramatically increased, as was the expression of TNF-α, IL-10, IL-4, IFN-γ, and IL-17α. This finding suggests that IκBα exerts regulatory effects selectively not only on cytokines through NF-κB, but also in a tissue- or cell-type-specific manner (spatially orchestrated regulation). The regulation of NF-κB varies among distinct mucous tissues. Th1 T-cells can mediate proinflammatory or cell-mediated immune responses, whereas Th2 T-cells promote immediate-type hypersensitivity reactions. Th1 and Th2 responses are often considered to be mutually exclusive. However, there is a growing body of evidence suggesting that interactions between Th1 and Th2 immune elements are not solely antagonistic, but may in fact modulate the immune response in a much more exquisite way. These new findings and considerations should be integrated to explain the observed elevation of Th1/Th2 cytokine genes in the eyelid tissues of IκBα−/− mice and to gain a better understanding of the inflammatory disease observed in these animals.

Our finding that in IκBα/Stat6 KO mice, severe inflammation comparable to that observed in IκBα−/− mice was elicited, indicates that Stat6 and Th2 immunity is not causally related to the development of ocular surface- and perioral skin inflammation in IκBα−/− mice. Allergic reactions acting through IL-4 receptors involve a group of signal transducers and activators of transcription (Stat) proteins. Stat6 appears to have the most prominent role during IL-4-mediated responses, including Th2 differentiation and immunoglobulin-class switching to IgE. With respect to the severe inflammation observed in IκBα/Stat6 WKO mice, it is notable that Stat6, despite its marginal additive effect, may also operate as a negative regulator of proinflammatory mediator production.

In the eyelids and perioral skin of IκBα−/− mice, we observed the augmented gene expression of IL-17α, but not of CCL11. The immune pathologic response on the ocular surface and perioral skin of IκBα−/− mice may not be solely dependent on the Th2 response. There may be a possibility that the Th-17 response, which is elicited by IL-17α, is involved in the immune pathologic response on the ocular surface and perioral skin of IκBα−/− mice. We have begun detailed studies on spatial and temporal regulations, to identify the mechanism(s) that underlies the inflammation on ocular surface- and perioral skin tissues.

Intestinal epithelial cell–specific inhibition of NF-κB spontaneously causes severe chronic intestinal inflammation in mice. Thus, the transcription factor NFκB, a master regulator of proinflammatory responses, functions in gut epithelial cells to control epithelial integrity and the interaction between the mucosal immune system and gut microflora. Of interest, IκBα transcript is predominantly distributed in the epithelia of the ocular surface. Considering the growing body of evidence suggesting the interactions among the Th1, Th2, and -17 immune elements, the sole participation of Th1, Th2, or Th17 may not be plausible, but the interaction among them may be probable in collaboration with TNFα and the newly emerging cytokine IL-17α. Deregulated NF-κB activity in IκBα gene-targeted mice may lead to deregulated homeostasis of conjunctival epithelial cells. The defect may trigger a chronic inflammatory response, initially by innate immune cells but also later by acquired immune responses. Studies are under way in our laboratory to identify the precise molecular mechanisms of IκBα-mediated transcriptional regulation in efforts to gain a better understanding of the immune/inflammatory axis in IκBα gene-disrupted mice.

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References


