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Targeting IκBNS in allergic asthma: where it resides, matters

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Since its discovery in 1986 (1), the role and contextual regulation of NF-κB in various forms of inflammation has been a matter of active research. Given its central importance in the inflammatory process, the myriad regulatory pathways involved in activating and inhibiting NF-κB have been a main area of focus in clinical and basic science. NF-κB is an evolutionarily conserved protein that includes five different forms – c-Rel, RelB, p50, p52, and p65. Under resting conditions, NF-κB exists in an inactive dimeric form in the cytoplasm. Activation of NF-κB is controlled by its interaction with inhibitory proteins known as IκB proteins (2). The typical IκB proteins, including IκBα and IκBβ, are cytoplasmic and prevent the nuclear translocation of NF-κB and its DNA binding-induced gene transcription. Under inflammatory conditions, the IκB-mediated inhibition of NF-κB is relieved and the NF-κB dimer translocates into the nucleus to initiate the inflammatory changes via transcriptional control of several downstream genes (3). NF-κB-activated pro-inflammatory genes involved in cell death, immune stimulation, redox metabolism, and production of mediators. Recently, additional regulation, provided by a group of atypical proteins, such as IκBNS, IκBζ, and Bcl-3 has been described. These are nuclear proteins that modulate gene transcription by blocking NF-κB binding sites on the DNA (4).

IκBNS was first described in the context of T-cell development (5). Since then, IκBNS has been identified to play different roles in the development and function of various hematopoietic cells. It is known to suppress Toll-like receptor-mediated induction of IL-6 and IL-12p40, thereby protecting against lipopolysaccharide-induced endotoxic shock and intestinal inflammation (Fig. 1A) (6, 7). IκBNS plays a crucial role in the selection and survival of immature thymocytes (8), and regulates Foxp3 during Treg cell development under conditions of chronic inflammation (Fig. 1B) (9). Its role has also been described in B-cell development (10). While NF-κB activity, directly or via IκB proteins (11), is known to modulate airway inflammation and hyperresponsiveness (12–18), the specific role of IκBNS has not been studied before.

Author contributions

Shaon Sengupta has provided the first draft of the manuscript and the illustration. Angela Haczku edited and finalized the manuscript and the figure.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Yokota et al. (19) in this issue of Allergy elucidate the role of IκBNS in a model of house dust mite-induced allergic asthma. They show that a global deficiency of IκBNS (in *NF-κB id*$^{-/-}$ mice) uncouples allergic inflammation from airway hyperresponsiveness. *NF-κB id*$^{-/-}$ (KO) mice sensitized to house dust mite had higher total cell count, eosinophils, and CD4+ cells as well as greater IL-4 and IL-13 levels in the bron-choalveolar lavage (BAL) when compared with wild-type mice. To dissect the tissue-specific role of IκBNS, bone marrow chimeric mice – those that lacked IκBNS in hematopoietic cells (knockout donors to wild-type recipients; KO→WT) and those that lacked IκBNS in nonhematopoietic cells (wild-type donors to knockout recipients; WT→KO), were studied. Sensitization and challenge with house dust mite in mice with a deficiency of IκBNS in hematopoietic cells resulted in enhanced airway hyperresponsiveness without concurrent increase in BAL eosinophil counts but with enhanced mucus production in the airways and increased expression of *Muc5AC*. When they repeated the same experiment with mice deficient in IκBNS in nonhematopoietic cells (wild-type donors to knockout recipients; WT→KO), they noted increased eosinophils in the BAL but attenuated airway hyperresponsiveness. This was seen both in house dust mite and ovalbumin sensitized models of allergic airway hyperresponsiveness. Thus, the presence of IκBNS in nonhematopoietic cells contributes to airway hyperresponsiveness (Fig. 1C). While the results indicated the involvement of IKBNS in Muc5AC production, the underlying mechanisms of how IκBNS contributes to airway hyperresponsiveness were not elucidated in this study. Several intriguing directions may arise out of the experiments with chimeric mice. For example, additional inflammatory targets that could be inhibited or stimulated by IκBNS in airway structural cells such as epithelial cells, fibroblasts or in particular, airway smooth muscle cells could he identified. Moreover, the interplay between IκBNS effects in the structural and hematopoietic/immune cells that could be crucial in regulating allergic asthma awaits clarification.

Yokota et al. (19) further investigated the target for the epithelial IκBNS, based on the observation that *Muc5AC* expression was reduced in the WT→KO mice. They found that IκBNS binds to the promoter region of the Muc5AC gene and stimulates its expression using a reporter assay. Muc5AC is one of the dominant mucins found in the airway. Under normal conditions, mucin helps protect the airways against toxins and harmful organisms. However, overproduction of mucin can lead to lung pathology. It is also notable that *Muc5AC* expression has been associated with asthma and chronic obstructive pulmonary disease (COPD) phenotypes (20–22). In current context, *Muc5AC* was induced without affecting the *Spdef* pathway that is responsible for goblet cell hyperplasia. In lacking goblet cell hyperplasia and detectable IgE levels, it does seem feasible that IκBNS is involved in a very distinct asthma endotype. This is the first report that attempts to investigate the role of IκBNS in the airway epithelium. Future studies using airway-specific knockouts will be crucial in developing this field and understanding of the role of in asthma pathophysiology.

From the translational perspective, this study underscores the challenges in using the NF-κB-IκB pathway as drug targets in asthma or COPD. As is evident from the work of Yokota et al., IκBNS has a tissue-specific and context-specific role in modulating inflammation and airway hyperresponsiveness, and therefore, global targeting of this pathway may not be meaningful. This study adds to the existing literature that highlights the complexities of NF-

κB regulation, and by doing so is hopefully taking us closer in defining molecular pathways and drug delivery techniques to harness their unique therapeutic potential.

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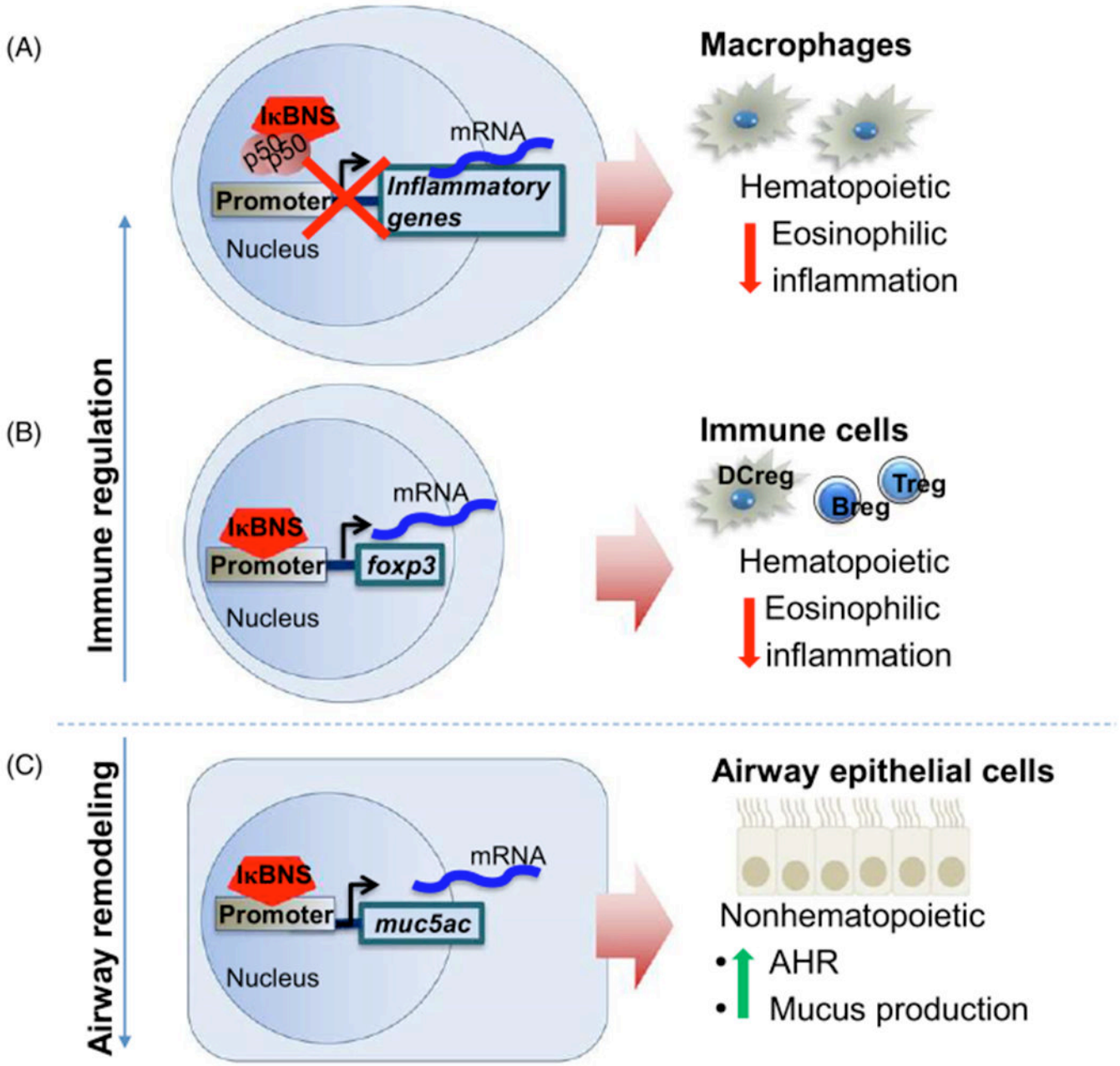

Figure 1.

Role of IkBNS in regulating allergic airway inflammation. (A) During inflammation, the presence of IκBNS stabilizes the p50 homodimers of NFkB (4) thereby inhibiting induction of pro-inflammatory genes in innate immune cells resulting in attenuated eosinophilic airway inflammation. (B) IκBNS induces Foxp3 under conditions of chronic inflammation in dendritic ceils (DCreg), B cells (Breg), and T cells (Treg) that Inhibit allergic airway inflammation. (C) The presence of IκBNS in nonhematopoietic cells contributes to airway remodeling. By direct binding to promoter regions, IκBNS induces mRNA transcription of certain genes in airway structural cells (19).