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EDITORIAL

CD44 ligands enhance allergen-specific sublingual immunotherapy in a murine model of chronic asthma

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Asthma is a common respiratory disease characterized by reversible airway obstruction, airway hyperresponsiveness (AHR), and chronic airway inflammation with eosinophils. We developed the *Dermatophagoides farinae* (Df)-allergen induced mouse model of acute and chronic asthma, in which mice exhibit AHR and airway inflammation, as well as airway remodeling [1-3]. On the basis of studies using anti-CD44 mAbs, its ligands, and CD44-deficient mice, we found the role of cell surface adhesion receptor CD44 differs between acute and chronic eosinophilic airway inflammation.

CD44 is a highly glycosylated protein that regulates cell adhesion to inflamed endothelial cells, activation of lymphocytes, tumor metastasis, and several other cellular processes [4]. Hyaluronan (HA) is the principal ligand of CD44, but only a few cell type use CD44 to recognize HA. Glycosylation of CD44, especially sialic acid residues, negatively regulates its recognition of HA [5]. We found that Galectin-9 (Gal-9), which is a β-galactoside-binding protein having roles in cell adhesion, chemoattraction, activation, and apoptosis [6], is a CD44 ligand that blocks the CD44-HA binding [2].

Role of CD44 in a murine model of acute asthma

Gal-9 and anti-CD44 mAbs block lymphocytes and eosinophils from accumulating in the lung, and suppress both the allergen-induced increase in Th2 cytokines in the bronchoalveolar lavage fluid (BALF) and AHR [2]. CD44 deficiency is associated with decreased mite allergen-induced Th2 cell-mediated eosinophilic airway inflammation and AHR in sensitized mice. Asthmatic responses to allergen-sensitized splenic CD4+ T cells transferred from CD44-deficient mice are weaker in wild-type mice after intranasal allergen challenge. Administration of anti-CD44 mAbs preferentially suppresses the airway accumulation of allergen-specific Th2 cells induced by allergen challenge, without affecting Th1 and Th17 cells [7,8]. Further, increased HA-binding of CD44 and expression of Neu1 sialidase are observed on allergen-specific Th2 cells compared with allergen-specific Th1 and Th17 cells [7-9]. Finally, in a mouse model of acute asthma, neuraminidase 1-deficient SM/J mice exhibit a lower Th2 cytokine concentration and a lower absolute Th2 cell number in the BALF, as well as an attenuated AHR [9]. Our findings indicate that CD44 expressed on CD4 T cells critically contributes to the allergen challenge-induced airway accumulation of allergen-specific Th2 cells, without affecting Th1 and Th17 cells. CD44 is critically involved in Th2 cell-mediated eosinophilic airway inflammation and AHR in a murine model of acute asthma [10].

Role of CD44 ligands in allergen-specific sublingual immunotherapy in a murine model of chronic asthma

Gal-9 suppresses the generation of Th17 and promotes the induction of regulatory T (Treg) cells in a murine model of autoimmune arthritis [11]. It also negatively regulates Th2-mediated chronic eosinophilic inflammation of the lung, partly due to its ability to modulate Foxp3+ Treg cells in the BALF. Gal-9 is a potential negative regulator of Th2-related inflammation, such as chronic asthma [12]. Wu et al. reported that the Gal-9 and CD44 interaction enhances the stability and function of Treg cells through smad3-dependent mechanisms [13]. Because Treg cells are thought to contribute to the efficacy of allergen-specific sublingual immunotherapy (SLIT) [14], CD44 ligands may enhance the effect of allergen-specific SLIT in allergic asthma. We demonstrated that Gal-9 enhances the effect of SLIT in a mouse model of Df-induced chronic asthma in a Treg cell-dependent manner [3]. Recently, in a new SLIT model of Df-induced chronic asthma using HA as an adjuvant to the Df allergen, we found that low molecular-weight HA enhanced the effect of SLIT in a CD44-dependent manner [15]. Treatment with this novel SLIT and HA might provide a cure for allergic asthma, because Df allergen treatment in the presence of HA normalized both the early asthmatic response and AHR. In addition, the BALF interlukin-13 and serum Df-specific IgE levels were significantly decreased by HA when used as an adjuvant to the Df allergen. The addition of HA also inhibited Df-induced eosinophilic airway inflammation related to low interlukin-5 levels. The enhancing effects of HA on the Df allergen-specific SLIT, however, were diminished in CD44-deficient mice. CD44 contributes to the induction of Treg cells in the presence of the Df antigen in vivo and in vitro. In a model of chronic eosinophilic airway inflammation induced by Df sensitization in CD44 deficient mice, we observed increased Th2-mediated eosinophilic airway inflammation and serum Df antigen-specific IgE levels, and decreased numbers of CD4+CD25+Foxp3+ Treg cells in the BALF, compared with wild-type mice. Treg cells might negatively regulate Th2-mediated chronic eosinophilic airway inflammation. Further, the enhanced effect of HA on Df allergen-induced Treg cells was diminished in CD44 deficient mice in vitro. Treg cells are induced by HA in the presence of allergen in a CD44-dependent manner in vitro. The CD44-HA interaction enhances the induction of Treg cells, which might contribute to cure the murine model of chronic asthma induced by the Df antigen. In conclusion, administration of HA as an adjuvant in this Df-allergen specific SLIT model inhibited Th2-associated eosinophilic airway inflammation as well as the allergen-induced early asthmatic response and production of antigen-specific IgE, and might thus be an effective cure for allergic asthma in humans.

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Contribution to the Field: This editorial demonstrates the different role of CD44 between acute and chronic mouse asthma model and CD44 ligands enhance allergen-specific sublingual immunotherapy in a murine model of chronic asthma.

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