Editorial: Leukocyte-targeting toxins as therapeutics in allergic asthma

By Namit Sharma and Andrew W. B. Craig

Department of Biomedical and Molecular Sciences, Queen’s University, Kingston, Ontario, Canada

RECEIVED OCTOBER 1, 2014; REVISED OCTOBER 31, 2014; ACCEPTED NOVEMBER 9, 2014. DOI: 10.1189/jlb.3CE1014-462R

Asthma is a prevalent inflammatory disorder of the airway, characterized by immune cell infiltration, epithelial barrier defects, mucous hypersecretion, and obstruction of airflow [1]. In allergic asthma, patients are sensitized to inhaled allergens in a Th2-driven process of allergen-specific IgE production. Subsequent exposures to inhaled allergens result in inflammatory mediator release from mast cells and basophils that enhance blood vessel permeability, leukocyte recruitment, and chronic inflammation (Fig. 1) [5]. Relevant integrins in asthma and autoimmunity are CD11a/CD18. In asthmatic airways, ligands for these integrins are expressed at high levels, including VCAM-1 and ICAM-1 [6]. This promotes firm adhesion and tissue invasion by immune cells expressing VLA-4 and LFA-1 and has led research into therapeutic blockade of these integrins in asthma and autoimmune disorders. Efilizumab (Raptiva) is an inhibitory LFA-1 antibody that was approved by the U.S. Food and Drug Administration in 2003 for treatment of an autoimmune disease but was withdrawn in 2009 as a result of risk of developing fatal brain infections [7]. One potential drawback with Efilizumab is that it targets all LFA-1-positive cells, whereas targeting only activated LFA-1 would be preferable for therapeutic applications.

LtxA is a toxin secreted by the gram-negative bacterium Aggregatibacter actinomyctetemcomitans that binds activated LFA-1 on leukocytes leading to cell death [8]. The therapeutic potential of LtxA was first demonstrated in a leukemia model, showing that LtxA preferentially targets leukemic cells expressing activated LFA-1 compared with normal leukocytes [8]. Moreover, LtxA treatment was effective in treating leukemias that had relapsed on standard chemotherapy [9]. In addition, LtxA was tested in a xenograft model of human psoriasis and shown to allow resolution of disease by preferential targeting of proinflammatory leukocytes [10]. In this issue of the Journal of Leukocyte Biology, Gupta et al. [4] have now extended studies of LFA-1 expression in allergic asthma patient samples and effects of LFA-1 blockade with LtxA in a mouse model of allergic asthma [4]. They identified a circulating cell population with elevated levels of LFA-1 (CD11a\textsuperscript{hi}) in asthma patients that were not found in healthy controls. This population was composed of CD14\textsuperscript{hi}CD11a\textsuperscript{hi} monocytes and CD3\textsuperscript{hi}CD4\textsuperscript{hi}CD11a\textsuperscript{hi} non-Th cells. The authors went on to show that these CD11a\textsuperscript{hi} cells undergo apoptosis upon LtxA treatment ex vivo, whereas CD11a\textsuperscript{lo} cells within the same samples were unaffected. These findings were tested further in mice chronically exposed to HDM extract. The authors validate high expression of LFA-1 in leukocytes from bronchoalveolar lavage fluid of allergic mice compared with control mice. This provides further evidence for the potential targeting of LFA-1\textsuperscript{hi} cells in allergic asthma. The authors go on to compare treatment of HDM mice directly with LtxA or dexamethasone, the current gold standard corticosteroid used as a general immunosuppressant. Importantly, the authors demonstrate that LtxA outperforms dexamethasone by several metrics. LtxA-treated mice were protected from airway infiltration of all major leukocyte subtypes, including neutrophils, eosinophils, macrophages, and B and T cells. LtxA-treated mice were protected from airway remodeling induced by HDM exposure and had reduced expression of several cytokines implicated in asthma pathogenesis within the lung. LtxA treatment was more effective than dexamethasone in blocking neutrophil

Abbreviations: HDM = house dust mite, LtxA = Leukotoxin A

\[\begin{align*}
\text{Abbreviations: HDM = house dust mite, LtxA = Leukotoxin A} \\
\end{align*}\]
infiltration and expression of Th2 cytokines (IL-4, IL-5), which are key drivers of IgE production, mucous secretion, and allergic inflammation. As LtxA targets only activated leukocytes, it may provide a viable alternative to corticosteroids, whose chronic use can lead to multiple side-effects. However, an important extension of this work will involve testing of LtxA for efficacy against other allergens or pathogens that induce asthma. It would also be worth comparing LtxA with Efalizumab in both allergic asthma models and in mice infected with bona fide pathogens. For LtxA to progress beyond an experimental tool, it will be important to demonstrate that LtxA does not increase risk of infections, as observed in patients treated with Efalizumab [7]. Future studies will also be required to test the efficacy of LtxA across a larger cohort of allergic asthma patients as a result of the genetic heterogeneity of this disease.

Overall, the study by Gupta et al. [4] will undoubtedly spur further testing of LtxA as a new therapeutic in allergic asthma. If LtxA continues to outperform current therapies and lacks side-effects associated with Efalizumab, then it may prove to be a more targeted approach to treat LFA-1-driven diseases.

REFERENCES


KEY WORDS:
allergy · integrins · airway remodelling
Editorial: Leukocyte-targeting toxins as therapeutics in allergic asthma

Namit Sharma and Andrew W. B. Craig

Access the most recent version at doi:10.1189/jlb.3CE1014-462R

Subscriptions Information about subscribing to Journal of Leukocyte Biology is online at http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Permissions Submit copyright permission requests at: http://www.jleukbio.org/site/misc/Librarians_Resource.xhtml

Email Alerts Receive free email alerts when new an article cites this article - sign up at http://www.jleukbio.org/cgi/alerts

© Society for Leukocyte Biology