

COMMENTARY

Eosinophils, galectins, and a reason to breathe

Helene F. Rosenberg^{a,1} and Kirk M. Druey^b

Asthma is a common and incurable inflammatory respiratory disease leading to wheezing, shortness of breath, and cough, that affects nearly 300 million people worldwide (1). Although the precise molecular cause of asthma remains unknown, diverse risk factors including environmental allergies, chronic sinusitis, gastrointestinal reflux disease, obesity, and respiratory virus infection have been linked to the onset and/or exacerbation of this disorder. Regardless of etiology, asthma is uniformly characterized by the exaggerated spasm of airways to an array of contraction triggers, a response termed "airway hyperresponsiveness."

Eosinophils have long been linked to the asthma phenotype and airways dysfunction. By virtue of their capacity to release potentially tissue-damaging cationic proteins along with proinflammatory cytokines, chemokines, and growth and remodeling factors, eosinophils certainly have the potential to promote the hallmark features of this disorder (2). However, demonstration of their direct pathogenic role in this disease has until recently remained elusive (3). Among the confounding issues, initial clinical trials performed in patients with uncontrolled asthma symptoms using antibodies against interleukin-5 (IL-5), the T helper 2 (Th2) cytokine crucial for eosinophil development and survival, failed to demonstrate any clinical or symptomatic benefit (4). However, recent studies have led to a complete reconsideration of both asthma as uniform disease and of eosinophils as contributory factors, leading to the identification of distinct asthma phenotypes, or endotypes. It has become clear that not all asthma is eosinophil driven; however, severe eosinophilic asthma, a disease driven primarily by Th2-type responses, is also distinguished by the relative abundance of eosinophils in peripheral blood and in the airways compared with other endotypes. Individuals with severe eosinophilic asthma respond to anti-IL-5 therapy, with reductions in asthma exacerbations reaching nearly 50% (5). These studies establish the effector function of eosinophils in a specific subset of human asthmatics and provide a vivid example of the need

for precision medicine approaches for both diagnosis and therapy.

Mouse models of asthma, or allergic airways dysfunction, have been used extensively to elucidate basic mechanisms of proinflammatory signaling leading to cellular recruitment and remodeling of the respiratory tract (6). These models routinely involve one or two intraperitoneal sensitizations with antigen in complex with adjuvant (typically alum) followed by multiple, sequential challenges directly to the respiratory tract. Antigens eliciting allergic responses include simple proteins such as ovalbumin and, more recently, have featured those associated with more complex, pathogen-associated molecular patterns (for example, extracts of fungi, dust mites, and cockroach). Likewise, models involving short- and long-term repetitive stimulation limited to respiratory tract, without systemic sensitization, have been explored (7). Recruitment of eosinophils to the airways is the hallmark of allergic airways disease in mouse models, accompanied by cytokine, chemokine, and mucus production, tissue remodeling, and airways hyperreactivity. Studies performed using allergen challenge models in eosinophil-deficient mice indicate that these cells play critical roles in promoting one or more features of allergic airways dysfunction (8) (Fig. 1).

In PNAS, Ge et al. (9) expand our understanding of allergic airways dysfunction in their study featuring interactions of eosinophils with galectin-1 (Gal-1). Galectins comprise an extensive family of evolutionarily conserved glycan binding proteins (10). All galectins include at least one carbohydrate recognition domain, via which the minimal unit, the disaccharide *N*-acetyl-lactosamine, is recognized on *N*- and *O*-glycans on numerous cell surface-binding partners on leukocytes, endothelial cells, and epithelial cells, as well as on microorganisms and pathogens. A unique feature of galectins is their ability to form complex lattices, due in large part to their ability to form galectin multimers and to identify multiple binding partners within a target cell monolayer. In addition to their numerous roles in modulating responses in autoimmunity, cancer, and chronic

^aInflammation Immunobiology Section, Laboratory of Allergic Diseases, National Institutes of Health, Bethesda, MD 20892; and ^bMolecular Signal Transduction Section, Laboratory of Allergic Diseases, National Institutes of Health, Bethesda, MD 20892

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¹To whom correspondence should be addressed. Email: hrosenberg@niaid.nih.gov.

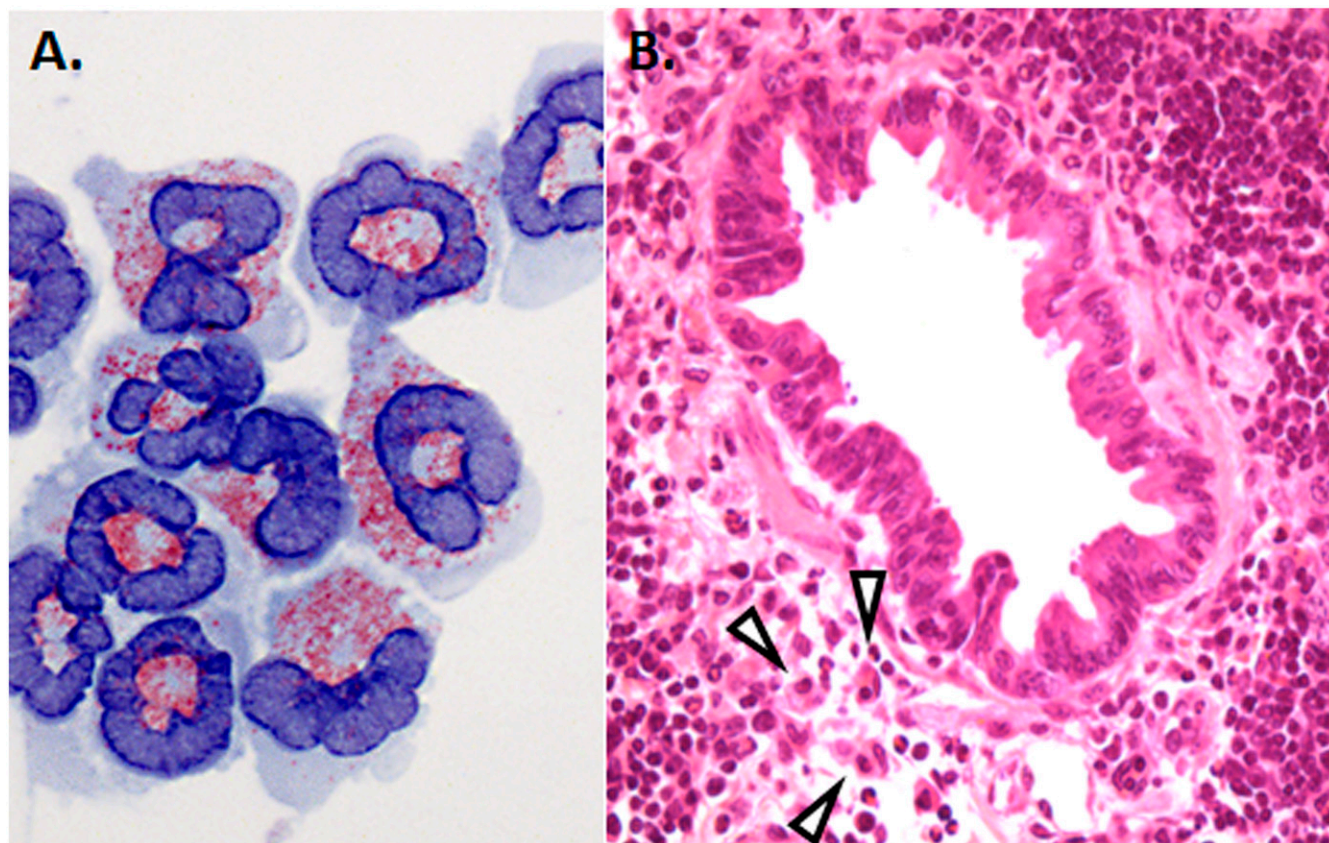


Fig. 1. Eosinophils in allergic airways dysfunction. (A) Mouse eosinophils isolated from peripheral blood of interleukin-5 transgenic mice are recognizable under light microscopy as similar to their human counterparts, with multilobed nuclei and cytoplasmic granules which store cationic secretory mediators and cytokines (original magnification 65 $\times$). (B) Lung tissue from mice sensitized and subsequently challenged with the fungal antigen, *Aspergillus fumigatus*; note the eosinophils at the arrow heads (original magnification 20 $\times$).

inflammation, which have been reviewed extensively (11, 12), the roles of individual galectins in modulating allergic inflammatory responses have been characterized. Among them, galectin-3 (Gal-3), which is a unique “chimera-type” galectin, has the capacity to bind IgE (13). Ovalbumin sensitization and challenge of Gal-3 gene-deleted mice demonstrate diminished eosinophil recruitment and reduced airways hyperreactivity (14), suggesting that endogenous Gal-3 promotes allergic responses in vivo. Further studies indicate that Gal-3 supports eosinophil rolling on the endothelial monolayer, a crucial first step in transit to the lungs (15). Galectin-9, in contrast, inhibits eosinophil recruitment and airways hyperreactivity when administered i.v. during antigen challenge, using the house dust mite model (16). Galectin-10 is expressed prominently in human (but not mouse) eosinophils (17), and was recently identified in CD25⁺ Tregs, where it serves to promote endogenous suppressor function (18).

Gal-1, the subject of this work (9), is expressed ubiquitously and has numerous binding partners on leukocytes and epithelial, neural, and muscle cells (19). Roles for Gal-1 have been identified in such varied processes as embryogenesis, neurogenesis, hematopoiesis, T-cell homeostasis, and, notably, related to this study, in modulating acute inflammation (20). Gal-1 inhibits migration of neutrophils and mast cell degranulation in response to bee venom phospholipase A2 in vivo (21). Furthermore, the results of a study of eosinophils in nasal polyps suggested that the antiinflammatory actions of glucocorticoids might work in part through induction of

Gal-1 (22). However, in some instances, Gal-1 has been shown to have proinflammatory effects, for example, activating the neutrophil oxidative burst (23); the impact of Gal-1 has been described as context dependent (24).

Here, several mechanisms via which Gal-1 suppresses airway inflammation are revealed (9). In studies carried out in vitro, recombinant Gal-1 promoted eosinophil adhesion to the vascular wall and likewise suppressed eosinophil migration to eotaxin-1. At higher concentrations, Gal-1 promoted disruption of cytoskeleton and eosinophil apoptosis together with decreased expression of the adhesion molecule CD49d. To examine the interactions of eosinophils with Gal-1 in vivo, mice were subjected to ovalbumin sensitization and challenge as described above, resulting in expression and detection of Gal-1 in the airways. Interestingly, sensitization and challenge of galectin-1 gene-deleted mice resulted in a significant increase in eosinophils in the airways, in association with elevated levels of the proinflammatory cytokine, TNF- α . As such, a prominent role of Gal-1 in the airways may be as a means to promote resolution of inflammation by limiting eosinophil recruitment via suppressing cell migration and promoting apoptosis.

Given these findings, is there a role for Gal-1 as therapy for eosinophilic asthma? There are certainly many challenges to consider when thinking about Gal-1 as a biotherapeutic. It is already clear that Gal-1 has proinflammatory and antiinflammatory features that are not fully understood and as such may not be fully predictable (24). Nonetheless, Gal-1 in polypeptide form—as a fusion protein, in nanoparticles, and as protein

