photomicrographs in the article are striking and clearly visualize the effects of this innate immune mechanism. Interestingly, other studies have shown that this same molecule is also expressed in the airways and has antibacterial functions in the respiratory tract. Understanding the regulation and function of RegIIIγ may lead to new insights into the pathogenesis and treatment of inflammatory and infectious diseases in both anatomic locations.

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James E. Gern, MD
Madison, WI

Galectin-9 Induced by Dietary Synbiotics Is Involved in Suppression of Allergic Symptoms in Mice and Humans

PURPOSE OF THE STUDY. To investigate whether galectin-9 has a role in the mechanism of suppression of allergic skin reactions and mast cell degranulation induced by dietary synbiotics.

STUDY POPULATION. Three-week-old specific pathogen-free C3H/HeOuJ mice were studied in a cow’s milk allergy model with or without a probiotic or prebiotic. Ninety human infants with atopic dermatitis were studied in a double-blind, placebo-controlled multicenter trial in which they received a hydrolyzed formula with or without synbiotics.

METHODS. Mice were sensitized orally to whey while being fed a diet containing a specific prebiotic (9:1 mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides), a specific probiotic (Bifidobacterium breve M-16V), a combination of both, or a control diet (4 groups). Galectin-9 expression was determined by immunohistochemistry in the intestine and measured in the serum by enzyme-linked immunosorbent assay. T-cell differentiation was determined in the mesenteric lymph nodes as well as in galectin-9–exposed peripheral blood mononuclear cell cultures via expression of transcription factors T-bet, GATA-3, RORγT, and Foxp3 along with cytokine production assays. Sera from mice were studied for the capacity to suppress mast cell degranulation. Sera from the 90 human infants were evaluated for galectin-9 levels.

RESULTS. Galectin-9 expression by intestinal epithelial cells as well as serum galectin-9 levels were increased in mice and humans after dietary intervention with the symbiotic combination (pre- and probiotic together). In mice, the levels correlated with reduced acute allergic skin reaction and reduced mast cell degranulation. In addition, the dietary synbiotics resulted in enhanced Th1- and Treg-cell differentiation in lymph nodes and in peripheral blood mononuclear cell cultures exposed to galectin-9.

CONCLUSIONS. Dietary supplementation with a symbiotic (prebiotic short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides + probiotic Bifidobacterium breve M-16V) enhances serum galectin-9 levels which is associated with the prevention of expression of components of allergic responses.

REVIEWER COMMENTS. The results of this study show galectin-9, an epithelial product expressed in mucosal surfaces during inflammatory responses, is a significant component of the protective antiallergy effect of symbiotic treatment. This effect is supported by data showing modulation of Th1- and Treg-cell polarization as well as immunoglobulin E sequestration (another study has shown strong binding of galectin-9 to immunoglobulin E) resulting in the reduced mast cell degranulation observed. Galectin-9 may be an important marker for the suppression of food allergy and further studies are warranted.


Stuart L. Abramson, MD, PhD
San Angelo, TX

TSLP Promotes Interleukin-3-independent Basophil Haematopoiesis and Type 2 Inflammation

PURPOSE OF THE STUDY. Allergic diseases involve epithelial surfaces, and the epithelial cytokine thymic stromal lymphopoietin (TSLP) has been described as the “master switch” for allergic inflammation. The purpose of this study was to determine how TSLP contributes to allergic disease pathogenesis.

STUDY POPULATION. Most studies were performed in mice. Human studies were performed with the use of basophils from patients with eosinophilic esophagitis or from healthy controls.

METHODS. TSLP-treated mice were evaluated for changes in circulating immune cells and cytokine secretion. The effect of tissue-specific TSLP production was determined by using transgenic mice overexpressing TSLP in the lung, or an atopic dermatitis model. Bone marrow cells were cultured with either TSLP or interleukin (IL)-3, and basophil differentiation was assessed. Characterization of TSLP-induced basophils from mice or humans was performed by the use of gene expression analysis and immune phenotyping.

RESULTS. Mice injected with TSLP had increased numbers of IL-4–secreting basophils in the spleen, as well as increased plasma levels of the proallergic T-helper type 2 (TH2) cytokines IL-4, IL-5, and IL-13. Endogenous
overexpression of TSLP in the lungs or skin also promoted peripheral basophilia. This systemic basophilia resulted from TSLP-triggered expansion of bone marrow precursor cells through a mechanism independent of IL-3 signaling. Basophils were present in TSLP-deficient mice, indicating that TSLP was not essential for normal basophil development. In comparison with classical basophils induced by IL-3, TSLP-elicited basophils expressed higher levels of TH2-skewing cytokines and proinflammatory mediators. Furthermore, basophils obtained from patients with eosinophilic esophagitis, a disease associated with mediators. Furthermore, basophils obtained from patients with eosinophilic esophagitis, a disease associated with aberrant TSLP production, were phenotypically distinct from those found in healthy controls.

CONCLUSIONS. Abnormal TSLP production at 1 barrier surface may promote development of allergic inflammation at other sites by increasing the number and altering the function of circulating basophils.

REVIEWER COMMENTS. It is well known that patients with 1 allergic disorder are likely to develop others, but the mechanisms for this “atopic march” remain obscure. Here, the authors show an important role for the cytokine TSLP, which has been shown to be highly expressed in animal and human tissues with active allergen-driven inflammation. The ability of TSLP to expand and alter the phenotype of peripheral basophils may promote the development of allergic disease at other barrier surfaces and could explain why patients with atopic dermatitis frequently go on to develop asthma or food allergy. In addition to contributing to our understanding of the biology of allergic diseases, these studies also identify TSLP as a potentially important target for pharmacological blockade in vulnerable patients.


Timothy P. Moran, MD, PhD
Brian P. Vickery, MD
Durham, NC

The Wisconsin Approach to Newborn Screening for Severe Combined Immunodeficiency

PURPOSE OF THE STUDY. Severe combined immunodeficiency (SCID) is a life-threatening disease of infants that is curable with hematopoietic cell transplantation if detected early, whereas the outcome is less favorable if treatment is delayed. The study evaluated outcomes of a screening program in Wisconsin.

STUDY POPULATION. Newborns in Wisconsin over a 3-year period.

METHODS. Population-based screening for SCID by using the T-cell receptor excision circle (TREC) assay applied to samples obtained from routine newborn screening (Guthrie) cards has been underway in the state of Wisconsin since 2008.

RESULTS. Five infants with SCID or other forms of severe T-cell lymphopenia (TCL) have been detected out of a total Classification of Diseases, Ninth Revision, codes indicative of immunodeficiency or recurrent infection.

METHODS. This was a retrospective chart review. Patients were classified with PID if they met published diagnostic criteria and were diagnosed with immunodeficiency. Those with PID were evaluated for the presence of warning signs and categorized as those who met 1 or more of the warning signs (WS+) and those who did not (WS−).

RESULTS. Twenty-three percent of patients were diagnosed with PID. Of those with PID, <70% met 1 or more criteria set forth in the warning signs. The most common warning signs met were recurrent otitis media, recurrent sinusitis, and need for intravenous antibiotics. Sensitivity of the warning signs was 63% and specificity was 23%.

CONCLUSIONS. “10 Warning Signs of Primary Immunodeficiency” were found to have low specificity and relatively low sensitivity. Study numbers were too small to draw conclusions regarding the utility of specific warning signs.

REVIEWER COMMENTS. The primary pediatrician’s question of when to refer a patient for workup of PID is a challenging one. The study suggests that this widely used screening tool has relatively low sensitivity and, therefore, the potential to miss PID cases. When clinical suspicion is high, immune evaluation should be considered even if a patient does not meet ≥1 of these 10 warning signs. Further studies are needed to develop a more optimal screening tool and to evaluate which specific signs are most relevant.

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Caroline Hobbs, MD
Wesley Burks, MD
Chapel Hill, NC
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Timothy P. Moran and Brian P. Vickery
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Timothy P. Moran and Brian P. Vickery
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