Relationships among aeroallergen sensitization, peripheral blood eosinophils, and periostin in pediatric asthma development

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Background: Biomarkers, preferably noninvasive, that predict asthma inception in children are lacking.
Objective: Little is known about biomarkers of type 2 inflammation in early life in relation to asthma inception. We evaluated aeroallergen sensitization, peripheral blood eosinophils, and serum periostin as potential biomarkers of asthma in children.
Methods: Children enrolled in the Childhood Origins of ASThma study were followed prospectively from birth. Blood samples were collected at ages 2, 4, 6, and 11 years, and serum-specific IgE levels, blood eosionophil counts, and periostin levels were measured in 244 children. Relationships among these biomarkers, age, and asthma were assessed.
Results: Serum periostin levels were approximately 2- to 3-fold higher in children than previously observed adult levels. Levels were highest at 2 years (145 ng/mL), and did not change significantly between 4 and 11 years (128 and 130 ng/mL). Age 2 year periostin level of 150 ng/mL or more predicted asthma at age 6 years (odds ratio [OR], 2.3; 95% CI, 1.3-4.4). Eosinophil count of 300 cells/μL or more and aeroallergen sensitization at age 2 years were each associated with increased risk of asthma at age 6 years (OR, 3.1; 95% CI, 1.7-6.0 and OR, 3.3; 95% CI, 1.7-6.3). Children with any 2 of the biomarkers had a significantly increased risk of developing asthma by school age (≥2 biomarkers vs none: OR, 6.6; 95% CI, 2.7-16.0).
Conclusions: Serum periostin levels are significantly higher in children than in adults, likely due to bone turnover, which impairs clinical utility in children. Early life aeroallergen sensitization and elevated blood eosinophils are robust predictors of asthma development. Children with evidence of activation of multiple pathways of type 2 inflammation in early life are at greatest risk for asthma development. (J Allergy Clin Immunol 2017;139:790-6.)

Key words: *Biomarkers, children, asthma development, periostin, aeroallergen sensitization, peripheral blood eosinophils*

Asthma is one of the most common chronic diseases in children. Recurrent wheezing during the preschool years is frequently the presenting sign of asthma; however, many children who wheeze during early life do not go on to develop childhood asthma.[1] Predicting which children will develop asthma remains challenging. Furthermore, once asthma is established, there is significant heterogeneity in response to therapy. The emergence of biomarkers in asthma and allergic airway disease is being used for the paradigm of "personalized" medicine and is an area of active research, although this has been primarily in adult patient populations to date. Biomarkers that predict asthma inception and/or response to therapy in children are currently lacking.

Type 2 inflammation is characterized by the production of a unique profile of cytokines by a host of cells including epithelial cells, mast cells, innate lymphoid cells, and T_H2 cells. These proinflammatory cytokines include, but are not limited to, IL-4, IL-5, IL-13, IL-25, IL-33, and thymic stromal lymphopoetin, and are thought to play a central role in the pathophysiology of allergic asthma.[2] A small number of biomarkers of type 2 inflammation have emerged as potentially useful and relevant for asthma.

Personal atopic history in early life is one of the most important factors determining an individual's risk of persistent asthma.[3] In fact, a National Institutes of Health expert panel on biomarkers in asthma concluded that of all the biomarkers, only multiallergen screening to define atopy is recommended as a core asthma outcome for asthma clinical trials.[4] Many studies have demonstrated a significant relationship between inhalant aeroallergen

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Abbreviations used
COAST: Childhood Origins of ASThma
GM: Geometric mean
OR: Odds ratio

sensitization and asthma development.[5-9] Specific patterns of aeroallergen sensitization have identified differential impact on asthma risk, and sensitization to multiple allergens in early life has been strongly associated with an increased asthma risk.[10]

Peripheral blood eosinophils have been identified as a surrogate marker of type 2 inflammation, and eosinophils are considered a principle effector cell in the pathophysiology of asthma.[11] High levels of peripheral blood eosinophils are recognized as an important biomarker for the eosinophilic asthma phenotype and has been identified as a readily available biomarker that correlates with disease severity and may predict response to asthma therapy, specifically as it relates to immunologic-based interventions.[12,13] However, the role of peripheral blood eosinophilia and risk of asthma development is less clear. The pediatric asthma predictive index[14,15] identifies peripheral blood eosinophil percentage (≥4% of total white blood cells) as a minor risk factor; however, existing predictive models for asthma development in children have inadequate accuracy and are, generally, better at excluding asthma than at predicting it.[16] Small prospective cohorts of infants hospitalized with wheezing illness have demonstrated that elevated eosinophils at convalescence predicted increased asthma risk later in life.[17,18] Notably, there is a clear association between peripheral blood eosinophilia and atopy in children, which potentially complicates the utility of peripheral blood eosinophils as an isolated biomarker in children.[11,19]

Periostin is a matricellular protein whose expression can be induced by type 2 inflammatory cytokines IL-4 and IL-13, as well as by other stimuli such as TGF-β. Specifically, IL-13 induces the secretion of periostin from bronchial epithelial cells.[20] Periostin is secreted basally from airway epithelial cells where it has pleotropic effects on epithelial cell function and on the development of airway fibroblasts, which is thought to promote airway remodeling in patients with asthma, even from a young age.[21] Airway epithelial cells from children with allergic asthma produce greater amounts of periostin than do airway epithelial cells from healthy children.[21] In addition to bronchial epithelial cells, there are other tissue sources of periostin including skin, tendon, and bone.[22] Periostin levels in peripheral blood have been identified as an easily obtained systemic biomarker of type 2 airway inflammation in adults and may also predict responsiveness to therapy.[20,23] Although the literature is quickly evolving, there is a paucity of published studies of periostin in childhood, with conflicting results. One study suggests that elevated serum periostin level correlates with airway hyperresponsiveness, whereas another found that high periostin level was not a predictor of asthma morbidity.[24,25] There are no published studies of early life serum periostin levels in children, specifically as it relates to asthma inception.

Biomarkers, preferably noninvasive, that predict asthma inception and/or response to therapy in children are desirable, but currently lacking. In this study, we used samples from the Childhood Origins of ASThma (COAST) study to assess these biomarkers and their relationship to asthma inception.

METHODS

Study population

Two hundred eighty-nine newborns at high risk for the development of asthma and allergic disease were recruited from November 1998 through May 2000 into the COAST study. Details of the study population and design have been described previously.[26] Briefly, to qualify for the study, at least 1 parent was required to have *respiratory allergies* (defined as ≥1 positive aeroallergen skin test results) and/or a history of physician-diagnosed asthma. Of these children, 244 had serum samples available from age 2 years and were included in this study. Informed consent was obtained from the parents, and the Human Subjects Committee at the University of Wisconsin-Madison approved the study (institutional review board approval no. H-2007-0044).[10]

Measurements

Peripheral blood samples were obtained at annual visits, at ages 2, 4, 6, and 11 years. Serum was stored at −80°C before measurement of periostin level. The serum samples were analyzed using the clinical trial version of the Elecsys Periostin assay (Roche Diagnostics, Penzberg, Germany) intended for use on the Cobas e601. The Elecsys Periostin assay is an automated electrochemiluminescence immunoassay, based on the sandwich principal.[27]

Peripheral blood eosinophil numbers were measured by standard methods. Total and allergen-specific IgE levels were measured by fluoroenzyme immunoassay (UniCAP 100, Pharmacia Diagnostics AB, Uppsala, Sweden) as previously described.[10]

Serum concentrations of specific IgE antibodies for 5 common inhalant allergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, and *Alternaria alternata*) were determined at ages 2, 6, and 11 years. In addition, allergen-specific IgE levels to ragweed, silver birch, timothy grass, and cockroach were measured at ages 6 and 11 years. The detection limit of the assay with regard to specific IgE level was 0.35 kU_A/L, and *aeroallergen sensitization* was defined as at least 1 value of 0.35 kU_A/L or more.

Clinical definitions

Asthma was diagnosed clinically at ages 6 and 11 years as previously described.[28] Briefly, current asthma was defined on the basis of the documented presence of 1 or more of the following during the previous year: (1) physician diagnosis of asthma, (2) use of albuterol for coughing or wheezing episodes (prescribed by physician), (3) use of a daily controller medication, (4) use of a step-up plan including the use of albuterol or short-term use of inhaled corticosteroids during illness, and (5) use of systemic corticosteroids for asthma exacerbation.

Statistical analysis

Periostin measurements over the years were assessed using a longitudinal mixed effect model with fixed effect for sex and years. Periostin levels (ages 2, 4, 6, and 11 years) and eosinophil counts (ages 2, 6, and 11 years) were compared with asthma diagnosis at age 6 and 11 years using longitudinal mixed effect models with fixed effects for years, sex, and asthma status and a random effect for the subject to account for repeated measure. Both outcomes were log-transformed to attain normality. Least square means on the log scale were back-transformed to geometric means (GMs) and associated 95% CIs.

The dichotomous outcome of aeroallergen sensitization at years 2, 6, and 11 years was compared with asthma status at ages 6 and 11 years using generalized linear mixed models adjusted for sex. These relationships were summarized using odds ratios (ORs) with 95% CI.

For the purpose of this article, we determined cutoff points to identify a positive biomarker: peripheral blood eosinophil count, 300 or more (literature-based)[12,13]; any aeroallergen sensitization (at least 1 value ≥0.35 kU_A/L), and serum periostin level of 150 ng/mL or more (approximate median of periostin levels at age 2 years in our population). Logistic regressions were used to predict asthma diagnosis at age 6 and 11 years with both individual and combinations of these 3 markers. A 2-sided P value of less than .05 was

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