

Predicting the future: Early-life biomarkers of atopic dermatitis



Elena Goleva, PhD Denver, Colo

Key words: Birth cohort, atopic dermatitis, prediction, skin lipids, cytokines

Atopic dermatitis (AD) is a chronic, heterogenous, inflammatory skin disease that typically starts in childhood and often persists into adulthood.¹ AD affects up to 20% of children worldwide. Although AD in infants and young children can resolve, there is a well-recognized increased risk of sequential progression from AD to other atopic diseases, including food allergy (FA), allergic rhinitis, asthma, and rhinoconjunctivitis, a process referred to as the atopic march.² The mechanisms underlying the development of AD and its subsequent progression to other atopic comorbidities, particularly FA, are not well understood and are the subject of intense investigations. Skin barrier dysfunction, including filaggrin (*FLG*) gene mutations, variants of other epidermal differentiation complex genes, IL-4/IL-13 (a type 2 cytokine)-driven immune responses, skin lipid abnormalities, and microbial dysbiosis (including *Staphylococcus aureus* colonization and loss of commensal bacteria), are all thought to contribute to skin epicutaneous allergen sensitization and systemic allergy.^{3,4}

In contrast to skin biopsy specimens, stratum corneum specimens are readily accessible for collection. Stratum corneum-derived biomarkers can provide significant information about the skin barrier, including its physical and antimicrobial properties, and local skin-specific immune responses. Recently, the techniques for stratum corneum collection by adhesive skin tape strips (STSs) have been introduced into skin research.⁵ This procedure is simple, robust, and minimally invasive. Given these features, STSs have become particularly useful for serial sampling in longitudinal studies (in which repetitive skin sampling is required) and pediatric studies (in which biopsy collection is fraught with high risk and often prohibitive). The utilization of STSs has rapidly expanded into a wide variety of research areas, and this has coincided with the advancements in omics and multiplexing techniques, including proteomics, lipidomics, metabolomics, and transcriptomics.

Currently, several ongoing birth cohort studies worldwide are performing longitudinal collection of STS samples from newborns and young infants to establish the patterns of skin maturation during the first year of life and identify potential biomarkers that can help distinguish individuals at risk for the development of AD and atopic march. To name a few, these

studies include the Systems Biology of Early Atopy Study (SUNBEAM), which is being conducted in the United States; Stopping Eczema and Allergy (SEAL), which is being conducted in the United States; Prevention of Eczema By a Barrier Lipid Equilibrium Strategy (PEBBLES), which is being conducted in Australia; a Korean birth cohort study by Samsung Medical Center in Seoul, South Korea; and the Barrier dysfunction in Atopic newBorns (BABY) study, which is being conducted in Denmark.

The studies by Rinnov et al⁶ and Halling et al⁷ (the latter of which is published in the current issue of the *Journal of Allergy and Clinical Immunology*) are the first publications in this area of research from the group in Denmark (the BABY cohort). For the initial report by Rinnov et al,⁶ 44 matched case patients and controls were selected from 300 full-term birth cohort participants. All of the case patients developed clinical AD in their first year of life, whereas the controls did not develop AD. The case patients and controls were matched by sex and season of birth. The study analyzed STS samples collected when the subjects were aged 2 months, before the onset of AD. At 2 months, no differences in skin transepidermal water loss, corneocyte protrusions, or FLG breakdown products (natural moisturizing factor [NMF]) were found. But there were differences in thymus- and activation-regulated chemokine/C-C motif chemokine ligand 17 (TARC/CCL17), phytosphingosine, and selected skin lipid ratios between the group with future onset of AD and the group of healthy controls at 2 months. Specifically, low levels of phytosphingosine were found in the subjects with future onset of AD when those subjects were only 2 months old, several months before they developed clinical features of AD disease. Among the parameters examined, phytosphingosine was identified as the best single predictor for development of AD in the future (76% accuracy). When combined with the 5 lipid ratios, TARC/CCL17, NMF, and corneocyte protrusions data, the prediction accuracy for AD development improved to 89% (Table I).

Given these findings, the new study by Halling et al⁷ has now analyzed samples from the entire birth cohort, which included 300 full-term and 150 preterm birth cohort participants and examined STS samples collected from the dorsal aspects of the hands and the back at 0 to 3 days of life and age 2 months to determine predictors of AD development by 2 years of age. Halling et al⁷ have selectively focused on the analysis of levels of NMF and a panel of cytokines in STS samples. At the time of subjects' birth, none of these biomarkers were able to predict future AD development. When subjects were aged 2 months, elevated TARC/CCL17 levels and reduced NMF (urocanic acid) levels increased the risk of AD development about 2-fold (Table I). At the same time, elevated TARC/CCL17, IL-8, IL-1a, and IL-18 levels when subjects were aged 2 months increased the risk of moderate-to-severe AD up to 5-fold. Of note, the study concluded that elevated levels of TARC/CCL17 are associated with an increased risk of AD in both the preterm and term infant groups.

From the Department of Pediatrics, Division of Pediatric Allergy and Immunology, National Jewish Health, Denver.

Disclosure of potential conflict of interest: E. Goleva reports research grants with Sanofi Genzyme.

Received for publication February 23, 2023; accepted for publication March 2, 2023.

Corresponding author: Elena Goleva, PhD, Department of Pediatrics, Division of Pediatric Allergy and Immunology, National Jewish Health, 1400 Jackson St, K1016a, Denver, CO 80206. E-mail: golevae@njhealth.org.

J Allergy Clin Immunol 2023;151:1479-80.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2023.03.032>

TABLE I. Biomarkers identified in the STS samples of the 2-month-old infants prior to the onset of clinical AD

Study	STS biomarkers	Direction of change (as compared to healthy infants)	Study cohort
Kim et al ⁸	TSLP	Increased	South Korea
Rinnov et al ⁶	Phytosphingosine	Increased	Denmark
	CCL17	Increased	
Berdyshev et al ⁹	TSLP	Increased	South Korea
	IL-13	Increased	
	Protein bound	Decreased	
	EOS ceramides		
	Unsaturated sphingomyelins	Increased	
	Short chain	Increased	
	NS ceramides		
Halling et al ⁷	Short chain	Increased	Denmark
	AS ceramides		
	UCA	Decreased	
	CCL17	Increased	

AS ceramides, Alpha-hydroxy fatty acid sphingosine ceramides; EOS ceramides, esterified omega-hydroxy fatty acid sphingosine ceramides; NS ceramides, non-hydroxy fatty acid sphingosine ceramides; UCA, urocanic acid.

TARC/CCL17, a mediator of type 2 inflammation, is central to the pathogenesis of AD, is known to be produced by keratinocytes and dendritic cells in the skin, acts as a chemoattractant for the T_H2 cells, and is a known marker of patients with AD with established disease that is correlated with disease severity. The presence of TARC/CCL17 suggests that the onset of type 2 inflammation in the skin of patients with future onset of AD is already evident when those subjects are 2 months of age; however, the mechanisms behind this phenomenon have not been explored. Importantly, in an earlier prospective birth cohort study of 87 infants, increased levels of thymic stromal lymphopoietin (TSLP), an alarmin that is guiding the onset of type 2 inflammation, were reported at the age of 2 months in infants who developed AD by age 2 years (Table I),⁸ and these findings were recently replicated in another birth cohort from South Korea (Table I),⁹ again providing evidence for the features of type 2 inflammation that are already being developed at 2 months in the skin of infants at risk for development of AD.

Despite these exciting findings, several study limitations should be pointed out. By design, the study did not have a replication cohort. Therefore, it would be essential to replicate the findings of this study in other independent birth cohort studies. Besides, potential differences may exist among different racial groups (eg, elevated TARC/CCL17 levels in the cohort from Denmark, increased TSLP levels in the South Korean birth cohort); therefore, the validity of these biomarkers should be evaluated in several prospective birth cohorts with different racial makeups. The selection of analyzed cytokines and chemokines in the study by Halling et al⁷ was based on previous findings using a Meso Scale Discovery–based platform and included mainly

proinflammatory cytokines, as cytokines from the adaptive immune system have proved difficult to measure, in part owing to the very superficial layers of the epidermis that were examined. And in the future birth cohort studies, consideration should be given to the specific skin layers and the amount of material designated for the cytokine analysis. In addition, the lipid analysis that was put forward by Rinnov et al⁶ does not allow examination of individual lipid species in various ceramide classes or changes in their fatty acid chain length as 1 of the key features that has been established to be influenced by type 2 inflammation in the skin.¹⁰

These novel findings in the skin of 2-month-old infants, before they exhibit any evidence of clinical AD, are now opening up a new era that will focus on the development of effective strategies to prevent AD and FA, including therapeutic interventions to inhibit the atopic march in early infancy, and they are now introducing yet another avenue for STS research. The new biomarkers in the skin of infants at risk for AD development that were identified in the study by Halling et al⁷ and other prospective birth cohort studies that are still ongoing can be used as tools to assess the effects of potential intervention approaches. Strategies to avoid percutaneous sensitization in the neonatal period by reinforcing the skin barrier function (eg, skin creams) and inhibiting the inflammatory response (eg, use of topical steroids for proactive treatment of eczematous lesions) have emerged as promising new approaches to preventing AD. These studies will also provide insights into the timing of interventions to improve the skin barrier during early life and thereby prevent infant AD, and they will also evaluate the potential for existing and novel biologics in the control of early onset of the type 2 immune responses.

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