Exposure: *Staphylococcus aureus* skin colonization predisposes to food allergy in the Learning Early about Allergy to Peanut (LEAP) and LEAP-On studies

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Key words: *Food allergy,* Staphylococcus aureus, *eczema, peanut, egg, milk, IgE, skin, nasal, environment*

Food allergies often begin early in life. Although there is no cure for food allergies, recent efforts to desensitize by using immunotherapy have shown promise in decreasing risk during accidental exposures. In a retrospective study early introduction of milk and peanut associates with reduced incidence of allergy to milk[1] and peanut,[2] respectively. In the prospective Learning Early about Allergy to Peanut (LEAP) and LEAP-On studies,[3] introduction of peanut to 4- to 11-month-old children reduced risk of peanut allergy by age 5 years. However, 9% of children were excluded at the selection phase because they were already sensitized to peanut (defined by wheal size on skin prick tests). Also, 7 of the 319 subjects were excluded because they had an oral response to peanut on initial challenge, and 9 of the 319 subjects of the peanut consumer group had an oral response to peanut. Because peanut reactions can be life-threatening and reactions can occur during initial food challenge and oral immunotherapy protocols, it is critical to identify risk factors for peanut-induced allergic reactions.

A number of host extrinsic and intrinsic factors have been implicated in food allergy sensitization. Host intrinsic factors associated with development of food allergy include skin barrier function gene mutations and atopic eczema. Extrinsic factors predisposing to food allergy include exposure to food and proinflammatory microbes and microbial components. Skin colonization by *Staphylococcus aureus* associates with eczema severity, and the presence and severity of atopic eczema are both risk factors for food allergy. In children with atopic dermatitis, skin colonization with *S aureus* and increased levels of specific IgE to peanut, egg, and milk correlate with a greater than 95% positive predictive value of oral food challenge reactions.[4] Atopic dermatitis and allergies are also associated with fungal and house dust mite (HDM) exposure.[5] House dust is a ubiquitous important environmental source of these extrinsic factors, including *S aureus*, food allergens, HDM, and *Alternaria alternata* (Fig 1, *A*).

Preclinical studies suggest that these environmental skin exposures can induce food allergy and might prevent induction of oral tolerance to food allergens. In neonatal mice with skin barrier gene mutations, food allergy develops after only four 40-minute skin coexposures to peanut or egg, *A alternata*, or HDM extract and detergent to increase allergen adsorption.[6] This allergen sensitization occurs in the absence of any clinical evidence of atopic eczema–like skin inflammation, which typically develops months later and in a manner independent of allergen exposure. Similar to human LEAP studies, development of food allergy in mice can be blocked by pre-exposure to oral peanut before skin sensitization.[6]

However, not all neonatal mice are protected from food allergy. For example, exposure of skin to *A alternata* during the oral peanut extract (PNE) pre-exposure blocked oral peanut-induced tolerance.[6] This emphasizes how environmental factors can limit induction of tolerance during consumption of food allergens. In addition, reports indicate mouse skin exposure to staphylococcal enterotoxin B with food allergen (ovalbumin or peanut) induces a T_H2 phenotype and food allergy.[7] Another relevant environmental exposure for the skin is detergent that decreases epithelial barrier function.[8] Thus impaired skin barrier function (induced by detergents and intrinsic genetic defects) in combination with exposure of the skin to food allergens with meals and dust containing HDM, *A alternata*, *S aureus*, and food allergens likely synergize to promote development of food allergy (Fig 1, *A*). Various preclinical data support the idea that *S aureus* colonization and other environmental factors can predispose to food allergy and interfere with attempts to induce oral tolerance to selected allergens.

In the current issue of the *Journal*, Tsilochristou et al[9] examined associations between *S aureus* skin/nasal colonization, food allergy, and atopic eczema in LEAP and LEAP-On study participants (Fig 1, *B*). As expected, no difference in *S aureus* colonization (skin or nasal) was seen between the LEAP peanut consumer and avoider subgroups. Although there have been studies in human subjects and murine models that have shown that antibiotic courses were associated with development of food allergy, in the current study there were no associations of prior oral or topical antibiotic use with *S aureus* colonization. This suggests that prior antibiotic use is

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Disclosure of potential conflict of interest: M. H. Kaplan is a consultant for Janssen Vaccines. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 5, 2019; revised June 20, 2019; accepted for publication June 21, 2019.

Available online June 27, 2019.

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J Allergy Clin Immunol 2019;144:404-6.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2019.06.014

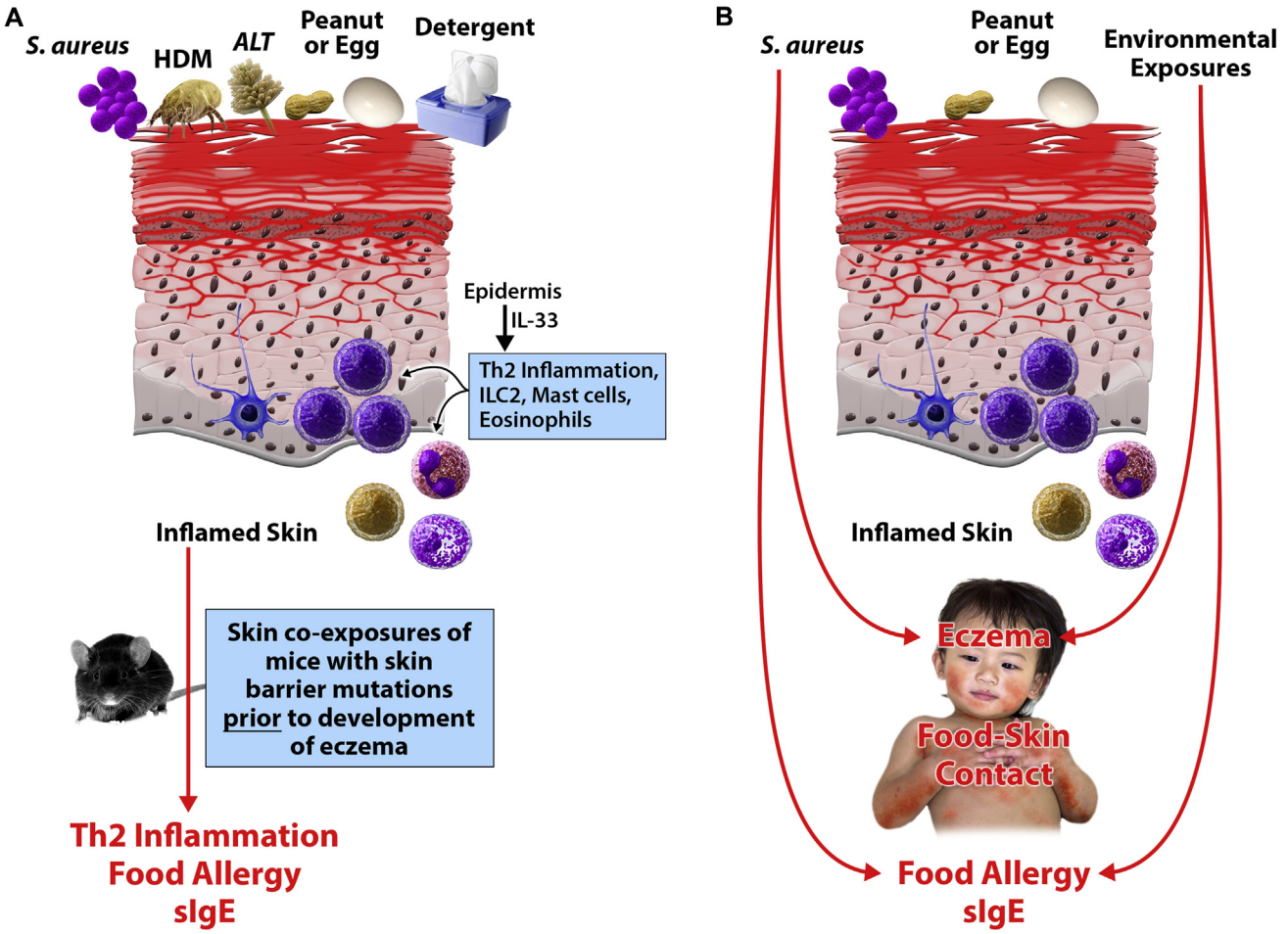

FIG 1. Skin coexposures in development of food allergy. **A,** Preclinical models suggest that a combination of skin exposures induce T_H2 inflammation and food allergy. Skin is exposed to food allergens, environmental allergens, and detergents. Many of these components are in household dust. Household dust contains food allergens, HDM, *A alternata*, and *S aureus*. Also, *S aureus* is present on household surfaces. Skin exposures to food allergens also occur during meals. Adsorption of allergens is promoted by detergents left on the skin from wet wipes and cleansing products. Combinations of these components and genetic skin barrier mutations readily induce food allergy. *ALT, A alternata*; *ILC2,* group 2 innate lymphoid cells. **B,** In the LEAP and LEAP-On studies skin *S aureus* colonization levels associate with eczema severity. Prior skin colonization with *S aureus* associates with food allergy and specific IgE levels, but this is independent of eczema severity. There is an association of *S aureus* skin colonization with food allergy, even after adjustment for eczema and total IgE levels. Thus there is an association of skin *S aureus* with food allergy in children.

not confounding the current associations with *S aureus* colonization, skin barrier, and development of peanut allergy. Similar to other studies, concurrent *S aureus* skin colonization was associated with increasing atopic eczema severity. In addition, prior colonization with skin *S aureus* was associated with persistence or worsening of eczema severity at later time points. Notably, prior skin colonization with *S aureus* at 0 to 60 months of age was associated with increased peanut-, hen's egg white–, and cow's milk–specific IgE levels in a manner independent of total IgE, eczema severity, or severity of infection and across the entire cohort. In the entire cohort participants with prior skin or nasal *S aureus* colonization had a 2.9- or 2.4-fold increased odds, respectively, of peanut allergy at 60 months of age, regardless of eczema severity. For peanut allergy, subgroup analysis of peanut consumers showed that there was a 7-fold increased odds of peanut allergy with prior skin *S aureus* colonization. Persistence of peanut or egg allergy at 60 and 72 months of age was more likely in participants with skin or nose *S aureus* colonization before 0 to 60 months of age, regardless of eczema severity. Nasal *S aureus* association with food allergy was not as strong an association as skin *S aureus.* Persistence of egg allergy was associated with skin colonization of *S aureus*, irrespective of peanut ingestion. A potential clinical implication is that the protective effect of peanut ingestion on peanut allergy was less marked in those with *S aureus* colonization. For those patients in whom induction of tolerance to peanut failed, skin exposures to *S aureus* or other environmental factors associated with *S aureus* might have contributed to development of peanut allergy. Thus these LEAP and LEAP-On analyses demonstrate that early-life cutaneous

skin exposure to *S aureus* and early-life eczema associate with subsequent food allergy development, including peanut-consuming children who had food allergy during early introduction of peanut.

A limitation to the study was that evidence for *S aureus* was based on bacteriological culture techniques rather than DNA-based testing. This approach might explain the lower prevalence of cutaneous and nasal *S aureus* colonization compared with prior studies.[10] In addition, this detection method does not genotype the isolated strains and cannot detect nonviable components of *S aureus*, such as staphylococcal enterotoxin B and *S aureus* antigens that act as immune stimulants. A second limitation to consider is the small number (n = 9) of study participants in the peanut consumption groups of the LEAP and LEAP-On studies who had peanut allergy. As noted by the authors, prospective collection of larger numbers of subjects will be needed to further investigate the relationship between *S aureus* colonization and development of peanut allergy. Also, as discussed by the authors, even though eczema was adjusted for and there were associations of *S aureus* with food allergy to peanut or egg, it does not exclude that other environmental factors that associate with *S aureus* can function in the development of food allergy.

In summary, the current longitudinal prospective study by Tsilochristou et al[9] provides convincing evidence for an association between prior *S aureus* colonization and food allergy to egg or peanut, independent of atopic eczema severity (Fig 1, *B*). The study suggest that *S aureus* colonization or factors associated with *S aureus* colonization act as adjuvants that block induction of oral tolerance and promote sensitization to allergens introduced through epicutaneous exposure. Moreover, it suggests that *S aureus* colonization can negatively affect clinical approaches to induce oral tolerance to peanut and potentially other allergens in some patients. It would be important to determine whether attempts to induce oral tolerance to peanut, egg, or other allergens in *S aureus*–colonized subjects are augmented by eradication of *S aureus* colonization. Given that the number of LEAP consumers who had peanut allergy was small, larger studies will be needed to determine whether there is a consistent association of food allergy with prior *S aureus* colonization. The current study has helped define new questions and consideration of novel approaches (eg, *S aureus* skin decolonization) that might ultimately improve efforts to induce oral tolerance.

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