

Barrier dysfunction in the atopic march—how does atopic dermatitis lead to asthma in children?



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The concept of “atopic march” is based on clinical observations of progression and/or multimorbidity of allergic manifestations, mostly leading from atopic dermatitis (AD) to food allergy (FA), asthma, and/or allergic rhinitis. Only a small proportion of children with AD develop the 3 other allergic manifestations, but it is clear that AD is a robust risk for subsequent development of FA and asthma. The mechanisms of how skin barrier dysfunction and lung epithelial barrier damage—the topics of the present “Paradigms and perspectives”—cause AD and asthma, respectively, are discussed in other articles in this issue, and the mechanisms of how AD leads to FA were discussed elsewhere.¹ However, the mechanisms of how AD can lead to asthma in children are still not fully understood.

It is not easy to diagnose asthma, especially in young children. Approximately 40% of young children worldwide reportedly experience at least 1 episode of asthma, such as wheeze. Among these infant wheezers, 70% have no wheeze at the age of 6 years (transient early wheezers), whereas the remaining 30% have persistent wheeze at the age of 6 years (persistent wheezers) and are diagnosed as having asthma. The factors distinguishing transient early wheezers and persistent wheezers have been extensively analyzed, resulting in a modified asthma predictive index that includes 4 or more wheezing episodes, a parental history of asthma (genetic predisposition), IgE sensitization to aeroallergens, AD, and so forth.² A prospective cohort study demonstrated that regardless of the type of virus, each viral lower respiratory infection (LRI) with wheeze increases the risk of asthma by about 1.5-fold.³

Therefore, this review is focused on the mechanisms of how AD can lead to asthma in young children with wheeze during viral LRI. Approximately 80% of children diagnosed with asthma had

first developed wheeze during a respiratory syncytial virus (RSV) or rhinovirus (RV) infection before age 1 year. Importantly, however, RSV and RV are well-known causes of the common cold (upper respiratory infection [URI]) in most children, and recurrent URI during infancy reportedly protects children from asthma (this phenomenon is the so-called hygiene hypothesis).

Then, how is it that these viruses that cause URI and reportedly protect children from asthma on the one hand may—on the other hand—cause LRI with wheeze? We hypothesized that the primary cause of such seemingly contradictory phenomena is differences in the amount of antiviral IFNs (IFN- $\alpha/\beta/\lambda$) produced by the children, and impairment of that production is due to the presence of AD and AD-derived cytokines.

Our unbiased literature search found that a number of studies have demonstrated that patients with asthma have impaired antiviral IFN production.⁴ Such IFNs reportedly (1) induce antiviral peptides that inhibit replication of viruses, (2) induce production and release of CXCR3 chemokines that recruit cytotoxic T lymphocytes and natural killer cells, (3) activate cytotoxic T lymphocytes and natural killer cells that kill virus-infected cells, and (4) induce apoptosis of virus-infected cells, all leading to suppression of viral expansion. In children with impaired antiviral IFN production, virus-infected nasal epithelial cells release RV or RSV that spread to the lower respiratory tracts, resulting in necrotic cell death that releases active IL-33, which causes type 2 inflammation. Another important role of antiviral IFNs is direct suppression of T_H2 cell and type 2 innate lymphoid cell proliferation and T2 cytokine production.

One of the most important mechanisms underlying impaired antiviral IFN production is cross-linking of IgE molecules on the surface of plasmacytoid dendritic cells (pDCs), the major source of IFN- α on virus exposure. Treatment of patients with severe asthma with anti-IgE mAb (omalizumab) reportedly removes cell surface IgE molecules from pDCs and restores antiviral IFN production.⁵ Fig 1 shows other mechanisms that impair antiviral IFN production by suppressing Toll-like receptor–signaling pathways. IL-4/IL-13–induced suppressor of cytokine signaling 1 suppresses IFN regulatory factor (IRF) 3 and IL-1 receptor–associated kinase (IRAK) 1, leading to inhibition of IRF3/7-dependent IFN production.⁶ IL-13 also induces IRAK-M, a negative regulator of Toll-like receptor signaling that inhibits IRF7-dependent IFN production.⁷ In addition, IL-33 downregulates IRF7 and rapidly degrades IRAK1, both of which result in reduced IRF7-dependent IFN production.⁸

In summary, T2-related molecules (IgE, IL-4/IL-13, IL-33) are likely involved in the suppression of antiviral IFN production. As would be expected, all these molecules have been reported to be upregulated in patients with AD in a severity-dependent manner;

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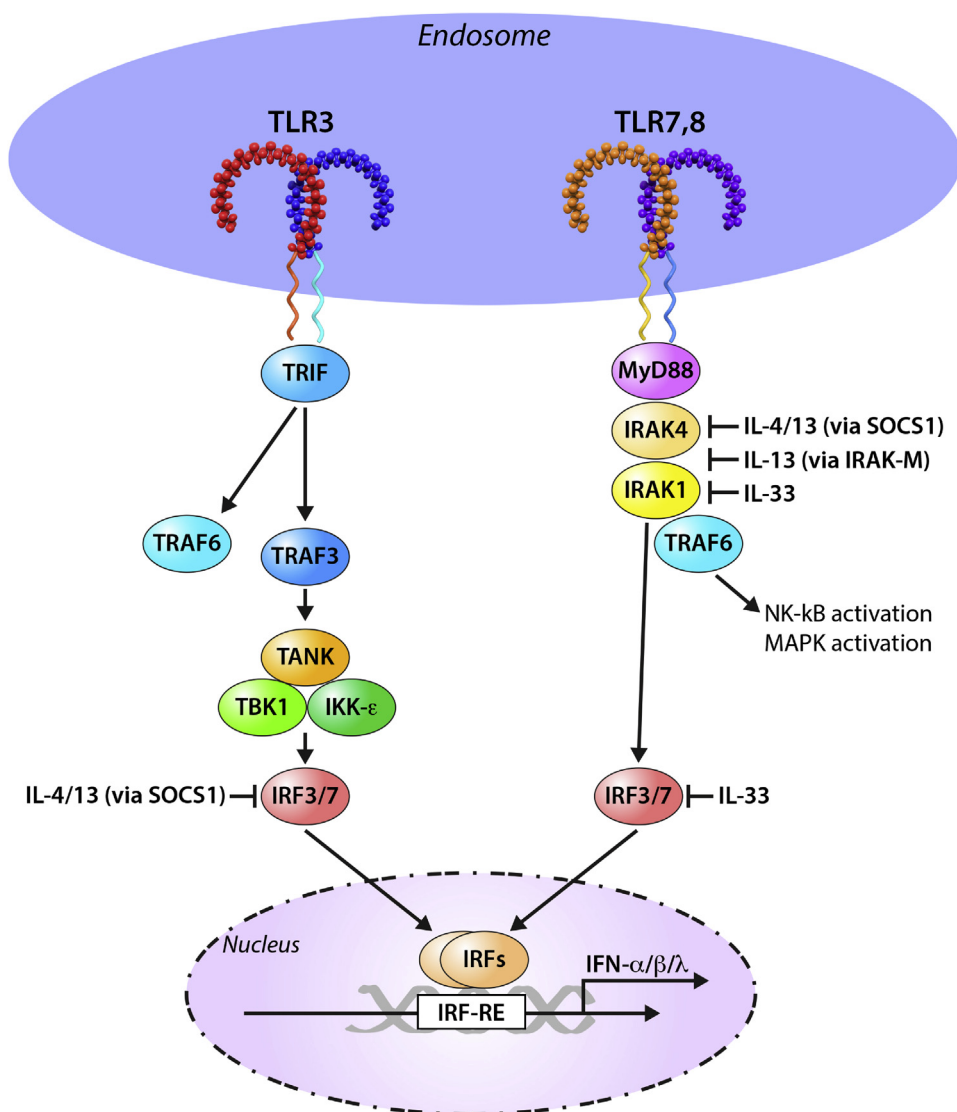


FIG 1. Toll-like receptor (TLR)-mediated TIR domain-containing adapter-inducing IFN- β (TRIF)-dependent and myeloid differentiation primary response 88 (MyD88)-dependent IFN-producing pathways. Signaling molecules, activation pathways, and inhibition points of IL-4/IL-13 or IL-33 are diagrammed. *IKK*, I- κ B kinase; *IRF-RE*, IRF-responsive element; *MAPK*, mitogen-activated protein kinase; *NF- κ B*, nuclear factor kappa B; *SOCS*, suppressor of cytokine signaling; *TANK*, TRAF family member-associated nuclear factor kappa B activator; *TBK1*, TANK-binding kinase 1; *TIR*, Toll/IL-1 receptor; *TRAF*, TNF receptor-associated factor; *TRIF*, TIR domain-containing adapter inducing interferon-beta.

the serum IL-33 level is reportedly higher in patients with AD, and the IL-33 level correlates with the severity of excoriation. IL-4 and IL-13 are released from type 2 innate lymphoid cells on exposure to IL-33, from T_H2 cells on allergen exposure, and from mast cells on exposure to IL-33 and/or allergens via IgE (Fig 2). The epidemiological fact that IgE sensitization precedes wheeze in children⁹ supports our hypothesis that pDCs are likely to be sensitized with AD-derived IgE and production of antiviral IFN may be impaired before young children first develop wheeze. Further support comes from a study showing that adults with AD experience increased extracutaneous and/or systemic viral/bacterial infections.¹⁰

On the basis of our hypothesis, we propose potential strategies for preventing progression from AD to asthma. First, primary

and secondary prevention of AD by systemic moisturizer use and treatment with a “proactive” regimen, respectively, seems promising for the prevention and effective treatment of AD. A study demonstrated that impaired antiviral IFN production was restored after proper control of type 2 inflammation in asthma; that finding supports this strategy. A Prevention of Allergy via Cutaneous Intervention Study (Japan) is underway to prove this concept. Also, use of a biologic such as dupilumab (anti-IL-4R α mAb) or ANB020 (anti-IL-33 mAb) to block T2 cytokine- and IL-33-dependent IFN suppression may be effective. And finally, intervention with an inhaled antiviral IFN formulation for high-risk young wheezers with impaired IFN production is worthy of testing.

In conclusion, young children with AD tend to have viral LRI with wheeze, and AD-derived cytokines and IgE antibodies are

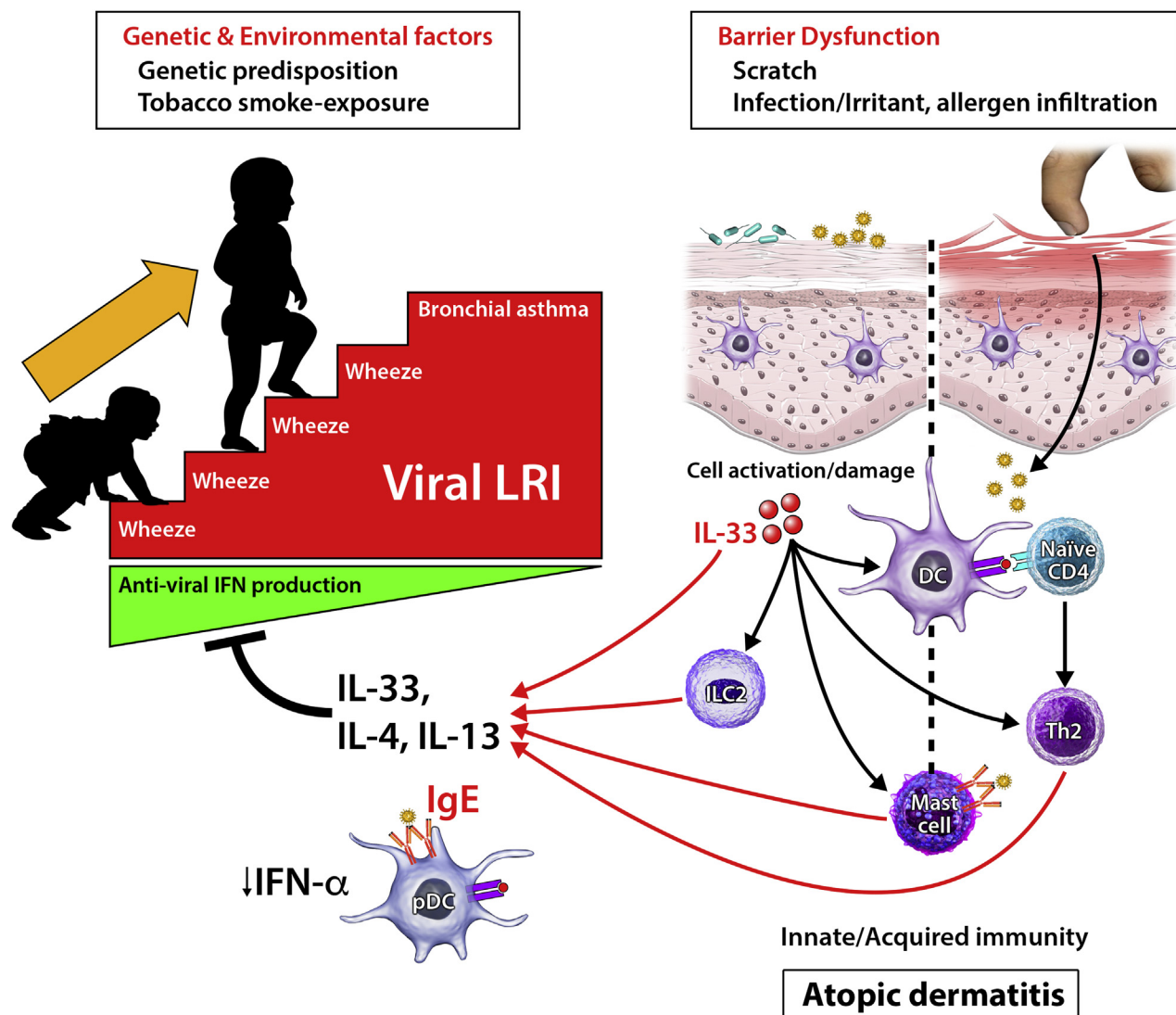


FIG 2. Schematic diagram of how AD leads to asthma in children. Skin barrier dysfunction leads to scratching of the skin, *Staphylococcus aureus* infection, irritant and allergen infiltration, and exacerbation of inflammation of the skin. AD-dependent IL-33 and IL-4/IL-13 and cross-linking of IgE on pDCs suppress anti-viral IFN production, which in turn makes young children with viral LRI with wheeze more likely to develop asthma in a step-by-step fashion.

able to inhibit antiviral IFN production, which can lead to asthma. However, the future seems bright for continued development of effective prevention and treatment modalities.

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