

EDITORIAL

Many ways lead to Rome: a glance at the multiple immunological pathways underlying atopic dermatitis

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In the late 1980s, the discovery of the Th1/Th2 T-cell response in a murine model by Mosmann et al. (1) introduced a new era in our understanding of inflammatory reactions driven by antigen-presenting cells and T cells in human diseases. Although it became rapidly clear that this dichotomic view of the T-cell response is a rather simplified way to understand inflammatory diseases such as atopic dermatitis (AD), it took a while to realize that from an immunological point of view, this disease cannot simply be qualified as a Th2 disease. Indeed, since then, many other T-cell profiles such as Th9, Th17, Th22 and Tregs as well as their more less specific transcription factors have deeply changed our view of what could be a physiological response and what could be a pathological one. Twenty-five years after the discovery of Mosmann, many textbooks and review articles still mention AD primarily as a Th2 disease although there are many immunological arguments which clearly show that there are at least two steps in the inflammatory response underlying AD. In their review on the immunology of atopic dermatitis in this issue of *Allergy*, Eyerich and Novak (2) have compared the immunological mechanisms leading to AD like the many ways leading to Rome: many pathways can lead to one clinical phenotype. This new level of complexity includes many known and unknown elements of the genetic background as well as nongenetic pathways such as environmental factors. Thus, AD represents a paradigmatic genetic complex disease where gene–gene interactions as well as gene–environment interactions form a highly complex mosaic. Indeed, while the epidermal barrier function can be genetically disturbed, it is also clear that the local microenvironment such as Th2 or Th22 cells has a deep impact on the gene expression of filaggrin (FLG) and other structural proteins of the epidermal barrier (3). On the other hand, genetic abnormalities of these structural proteins can induce an unspecific inflammatory response as has been shown for variants of the SPINK5/LEKTI gene. This kind of bidirectional interaction holds also true for the impact of environmental factors on the epidermal barrier function and on the immunological pathways (4). Moreover, it is assumed that epigenetic regulation may also have an impact on the expression of gene variants either at the level of the keratinocytes and/or at the level of immune cells located in the skin and in other organs (5).

Among the various lessons learned over the past years in our understanding of the complex pathophysiology of AD, the increasing awareness of the role of the innate immune response and vitamin D is of paramount importance (6, 7).

The colonization of the skin with *Staphylococcus aureus* (S.a.) in patients suffering from AD is a well-known phenomenon. However, although there are some clear correlations between this colonization and the total serum IgE or the severity in individual patients, we still do not understand fully how S.a.-derived products are modulating the immune response in this particular population. In other IgE-mediated allergic diseases such as asthma, it has been shown that bacteria interaction to Toll-like receptors has a protective effect under some conditions (8, 9) and that it would be of particular interest to better understand the role of the microbiome in inducing tolerance or preventing IgE-mediated sensitization. In AD, the high colonization with S.a. not only seems to amplify the local inflammatory reaction but could also contribute to an increased generation of IgE directed to a large spectrum of different allergens and possibly self-proteins. Does the proper response of immune cells to S.a.-derived products look differently (10) and could a lack of this response (11) be an explanation for the above-mentioned phenomena?

Along the same lines, the lack of appropriate secretion of antimicrobial peptides (AMP) in inflamed skin of AD is another example of the impact of the adaptive immune response (Th2 cells) on the innate immune response. This phenomenon is in sharp contrast to what we see in another chronic inflammatory skin disease such as psoriasis where AMP seem to be overproduced by keratinocytes.

Although several ways lead to Rome, this beautiful city itself recognizes seven historical hills as well as an independent state (the Vatican) in its central part. Similarly, the clinical phenotype of AD is rather heterogeneous and can potentially be divided into several subgroups based on more or less validated biomarkers such as total or specific IgE. This more differentiated view of the complex clinical phenotype (12, 13), besides the complexity of the pathways leading to the phenotype, will allow us to design new strategies for the prevention and treatment of this complex inflammatory skin disease (14). As highlighted in this review paper from Eyerich and Novak, several pathways are probably combined and could result in different clinical phenotypes. Therefore, besides understanding the different genetic and immunological pathways leading to AD, our efforts should also be focused on the discovery and validation of adequate biomarkers that will ultimately help us to stratify the clinical phenotype according to a new molecular taxonomy (15). Progress in genetics and immunology will largely contribute to this important step in translational biomedical research.

Conflict of interest

None.

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References

1. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986;**136**:2348–2357.
2. Eyerich K, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy* 2013;**68**:974–982.
3. Kezic S, O'Regan GM, Yau N, Sandilands A, Chen H, Campbell LE et al. Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. *Allergy* 2011;**66**:934–940.
4. Hinz D, Bauer M, Roder S, Olek S, Huehn J, Sack U et al. Cord blood Tregs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year. *Allergy* 2012;**67**:380–389.
5. Liang Y, Wang P, Zhao M, Liang G, Yin H, Zhang G et al. Demethylation of the FCER1G promoter leads to FcεpsilonRI overexpression on monocytes of patients with atopic dermatitis. *Allergy* 2012;**67**:424–430.
6. Benson AA, Toh JA, Vernon N, Jariwala SP. The role of vitamin D in the immunopathogenesis of allergic skin diseases. *Allergy* 2012;**67**:296–301.
7. Kanda N, Hau CS, Tada Y, Sato S, Watanabe S. Decreased serum LL-37 and vitamin D3 levels in atopic dermatitis: relationship between IL-31 and oncostatin M. *Allergy* 2012;**67**:804–812.
8. Nawijn MC, Motta AC, Gras R, Shirinbak S, Maazi H, van Oosterhout AJ. TLR-2 activation induces regulatory T cells and long-term suppression of asthma manifestations in mice. *PLoS ONE* 2013;**8**:e55307.
9. Conrad ML, Ferstl R, Teich R, Brand S, Blumer N, Yildirim AO et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe *Acinetobacter lwoffii* F78. *J Exp Med* 2009;**206**:2869–2877.
10. Herrmann N, Koch S, Leib N, Bedorf J, Wilms H, Schnautz S et al. TLR2 down-regulates FcεpsilonRI and its transcription factor PU.1 in human Langerhans cells. *Allergy* 2013;**68**:621–628.
11. Kasraie S, Niebuhr M, Kopfnagel V, Dittich-Breiholz O, Kracht M, Werfel T. Macrophages from patients with atopic dermatitis show a reduced CXCL10 expression in response to staphylococcal alpha-toxin. *Allergy* 2012;**67**:41–49.
12. Garmhausen D, Hagemann T, Bieber T, Dimitriou I, Fimmers R, Diepgen T et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy* 2013;**68**:498–506.
13. Dondi A, Ricci L, Neri I, Ricci G, Patrizi A. The switch from non-IgE-associated to IgE-associated atopic dermatitis occurs early in life. *Allergy* 2013;**68**:259–260.
14. Bieber T, Cork M, Reitamo S. Atopic dermatitis: a candidate for disease-modifying strategy. *Allergy* 2012;**67**:969–975.
15. Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy* 2012;**67**:1475–1482.