

Shifting paradigms in the immunology of atopic dermatitis

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Atopic dermatitis (AD) is a complex and heterogeneous disease. Although the exact underlying mechanism is not known, it is believed to be attributable to barrier dysfunction and an altered immune response.¹ These factors are closely interrelated and characterized by positive feedback loops, whereby increased inflammation results in increased barrier disruption and *vice versa*.

Much of our current understanding of the immunologic pathways involved in the induction of AD lesions was based on studies from the early 90s using an *in vivo* model for AD called the Atopy Patch Test (APT).² In this test, application of allergens, for example, house-dust mite dissolved in petrolatum, applied on nonlesional skin of patients with AD, is used to induce an acute eczema that macro- and microscopically resembles acute AD lesions. Thepen et al,³ for example, used immunohistochemical staining for cytokines on skin biopsies from APT-induced eczema lesions and counted the number of cytokine-expressing inflammatory cells. They found an initial predominance of IL-4-expressing lymphocytes (T_H2 cells), 24 hours after allergen application, which changed to mostly IFN- γ -expressing lymphocytes (T_H1 cells) after 48 and 72 hours. Studies investigating chronic lesional AD skin also found high levels of IFN- γ expression, suggesting a T_H1 profile. Other studies used T cells that were cloned from skin biopsies, or *in situ* hybridization. The results of these studies lead to the hypothesis that acute AD was predominantly driven by T_H2, with a shift to a T_H1-dominant milieu in the chronic phase. This has been the prevailing hypothesis over the last 3 decades.

By inducing eczema in nonlesional skin the APT allows the investigation of pathways involved in the early induction of eczema lesions in humans, but also the factors that contribute to the switch from acute to chronic AD. Although this experimental model gave us important first insights into the complexity of the immune response of AD, it was also hampered by several issues, such as lack of standardization of extracts and patch material. In addition, the eczematous response induced with the APT is self-limiting, in contrast to “normal” eczema lesions in patients with AD, which suggests that different pathways are involved.

However, in the absence of good mouse models for AD, the APT has taught us a lot about the immunology of AD.

Another approach that is used to study the induction of eczema lesions and switch to chronicity is by taking biopsies from “acute” and “chronic” lesional skin in patients with AD. In studies using this approach, patients with AD are being asked to indicate lesions that recently developed (so-called acute lesions), for example, lesions that developed within the last 72 hours, or chronic lesions that had been present for more than 72 hours. This duration of 72 hours is somewhat arbitrary, and pointing out lesions that developed over the last 72 hours has proven difficult for patients. Therefore, studies using this approach usually introduce an additional histopathological validation step. Lesions that patients pointed out as acute lesions, but showing increased epidermal thickness and parakerosis, which are markers of chronicity, are excluded on the basis of these histopathologic findings.

Although in dermatology we are used to diagnose skin diseases by just using the naked eye, in this era of technological advances we should soon have more advanced tools available to indicate acute lesions. For example, serial, high-resolution, full-body photography or more advanced imaging tools such as infrared photography might allow detection of early changes that are not visible to the naked eye. Ideally this should be done by the patients themselves, at home using their smartphones. This may ultimately lead to a better understanding of the earliest changes responsible for the induction of AD lesions and possible new targets for therapy.

In this issue of the *Journal*, Tsoi et al⁴ investigated the transcriptomic changes that characterize the transition from acute to chronic lesional skin. They used RNA sequencing of nonlesional, acute and chronic lesional skin from patients with AD and normal control skin using the criteria for acute and chronic lesional skin as discussed above. Tsoi et al showed that genes related to most T_H-cell subsets, including T_H1-, T_H2-, T_H17-, and T_H22-related genes, are dysregulated in acute lesions; in other words, there is broad immune activation in acute lesions, and these genes remain or are further dysregulated in chronic lesions. In contrast to the old paradigm suggesting a T_H2 to T_H1 switch, they did not find an immunologic switch associated with the transition from acute to chronic, but rather progressive immune activation of all T_H subsets (summarized in Fig 1). This also explains why drugs specifically targeting T_H2 cytokines, including dupilumab (blocking the IL-4 receptor) and tralokinumab (blocking IL-13), are effective not only in preventing acute eczema but also in treatment of chronic eczema.

This paradigm shift largely confirms previous data published by Gittler et al.⁵ Gittler et al⁵ used a slightly different (microarray) approach, but largely showed similar patterns of immune activation in acute and chronic lesional skin. Both studies were performed in relatively small sample sizes (11 and 10 patients, respectively), which is probably related to the difficulty in

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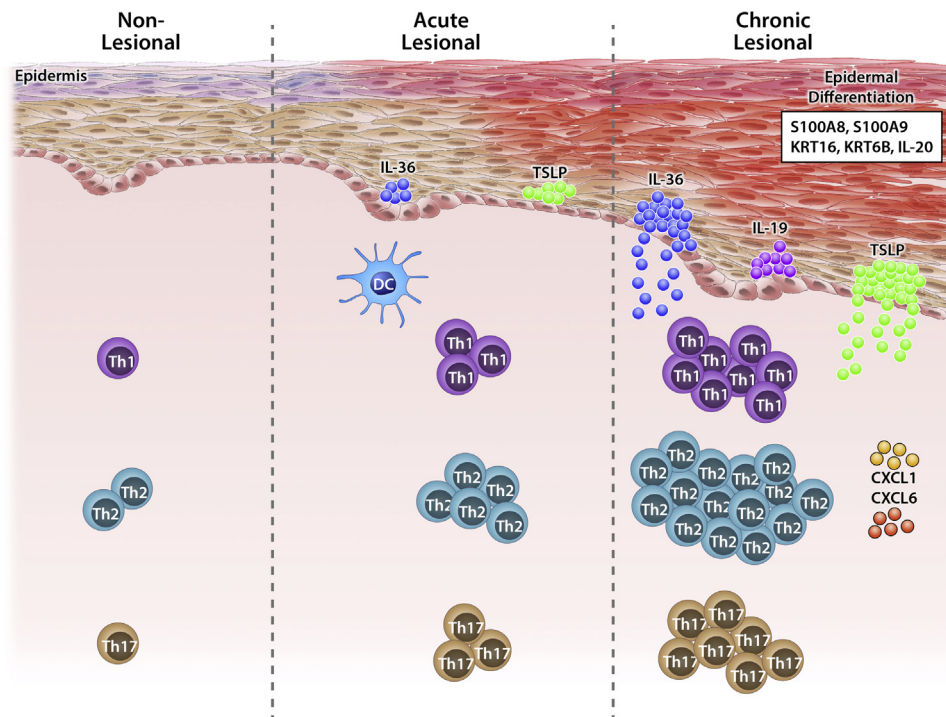


FIG 1. Schematic representation of the immunologic pathways activated in nonlesional, acute and chronic lesional AD skin. AD immunology is characterized by progressive immunologic activation of T_H1 , T_H2 , and T_H17 pathways from nonlesional to acute and chronic lesional AD skin. DC, Dendritic cell; TSLP, thymic stromal lymphopoietin.

collecting paired acute and chronic lesional skin samples. Tsoi et al obtained matched acute and chronic lesional skin biopsy samples from 16 patients with AD. Acute lesional skin samples from 5 patients needed to be excluded from analysis because they showed histopathologic signs of chronic lesional skin. This high exclusion rate (5 of 16) reflects the difficulty of studying “true” acute eczema. Similarly, in the study by Gittler et al,⁵ 7 of 17 patients were excluded because acute lesional skin biopsies did not meet the histopathologic criteria. This emphasizes the need for better ways to study induction of AD lesions. The small sample sizes in these studies are an important limitation, particularly because AD is known to be highly heterogeneous. We have recently shown that there are at least 4 different subsets of patients, also called endophenotypes, that may be driven by different immunologic pathways.⁶ In studies with relatively small sample sizes, signals specifically expressed in one of these endotypes will not show statistically significant differences. The large variation in the inflammatory signatures reported by Tsoi et al may be a reflection of the clinical and molecular heterogeneity that is characteristic for AD.

Tsoi et al found a relatively small number of genes differentially regulated in chronic versus acute AD: only 29 genes showed increased, and 13 decreased, expression levels, suggesting relatively small differences between acute and chronic lesions. Moreover, most genes encoding inflammatory cytokines and chemokines related to all T_H subsets were already found

increased in nonlesional AD skin, confirming previous observations that nonlesional skin in patients with AD is already different from normal skin and there is a continuum with increasing inflammation from nonlesional to acute and chronic lesional skin.⁷

In conclusion, there now is substantial evidence that we should replace the old paradigm of AD showing a biphasic response from T_H2 to T_H1 . After AD immunology has been getting more and more complex over the last years, with several new T_H -cell subsets entering the scene, Tsoi et al have now reduced the immunologic complexity of the pathogenesis of AD by showing that changes underlying the transition from acute to chronic AD are a continuum rather than a shift.

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