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Commentary Open Access

Just another Lack in the Wall

Lennart M. Rosner*

Department of Dermatology and Allergy, Division of Immunodermatology and Allergy Research, Hannover Medical School (MHH), Hannover, Germany

***Corresponding author:** Lennart M. Rösner, Department of Dermatology and Allergy, Division of Immunodermatology and Allergy Research, Hannover Medical School (MHH), Hannover, Germany, Tel: 4905115325054; Fax: 4905115328111; E-mail: Roesner.Lennart@mh-hannover.de

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Commentary

Talking about the skin, our bodies' outermost barrier to the environment, it is often compared to a tight wall keeping the outside out and the inside in. A more precise metaphor may be the picture of a castle´s moat and a portcullis [1], describing the stratum corneum as an un-crossable ditch and the epidermal keratinocytes with their tight junctions as a strong grid, behind which dendritic cells wait for antigens to be picked up. Only a break-down of the stratum corneum and a loosening of the skin-barrier lead in turn to antigen-presentation to T cells and an immune response.

In atopic dermatitis (AD), an abnormal immune reaction in the skin against per se harmless antigens is observed. AD affects up to 20% of the population in developed countries and is accompanied by comorbidities, social embarrassment, sleep disorder and considerable economical costs [2]. Matching the picture of a disturbed castle´s wall, mutations located in genes of the skin barrier have been discovered by genome-wide association studies that are associated with AD. Mutations in the barrier protein filaggrin (FLG) do show the highest association, even though most patients with AD do not have a FLG mutation, and up to 60% of carriers do not develop AD [3]. As a structural protein of the outer epidermal barrier, FLG is considered to be a key player in establishing the structure and function of the stratum corneum. It aggregates intermediate filaments, promotes cell differentiation, contributes to natural moisturing factors and thereby skin hydration [4]. FLG has been found to be significantly reduced in its expression in acute AD skin even if no mutation was detected [5] and the reduction is correlated with the disease severity [6]. This led supporters of the so-called inside-to-outside theory to promote the idea that the ongoing inflammation and not a loss of function protein perforates the skin. During the last 10 years, several mechanisms have been discovered that show a negative influence of the inflammation process on the skin integrity in AD.

Since in atopic diseases Th2 cytokines represent a hallmark and these are also found in AD skin lesions, the disruptive effect of IL-4 and IL-13 on the skin barrier were discovered first. Keratinocytes being exposed to these cytokines showed significantly reduced FLG gene expression. Aside from FLG, it was described that the expression of the tight junction protein Claudin-1 is inversely correlated with Th2 biomarkers [7]. Further on it was shown that IL-4 and IL-13 cause downregulation of Keratins and Desmogleins in a human skin T cell line [8]. IL-4 is produced by several cell types present in the lesional AD skin, first of all mast cells, basophils, and Th2 T cells. Since the Th2 T cell subset consistently disappears after successful allergen-specific immunotherapy [9,10], the central role of Th2 cells in AD is underlined. Furthermore, a subgroup of $CD8^+$ T cells termed Tc2 has been described to express IL-4. Recently, we described T cells specific to an AD-specific antigen to be of this Tc2 phenotype [11]. Interestingly, this antigen is a human antigen and has therefore been termed Homo sapiens autoallergen 2, Hom s2 [12].

Another cytokine that is produced by Th2 cells is IL-31 and increased IL-31 mRNA levels were detected in AD skin. Although also other cell types present in inflamed skin, including monocytes, dendritic cells, and mast cells may secrete IL-31, a substantial part is T cell derived [13]. It was shown that IL-31 leads to a differentiation defect in human skin equivalents, accompanied by a remarkable down regulation of terminal differentiation markers, especially FLG. By gene expression analysis it could be demonstrated that expression of IL-20 and IL-24 was deregulated after IL-31 exposure and that these cytokines were responsible for part of the effect on FLG expression [14]. Finally, these data were expanded and demonstrated that IL-4, IL-13, IL-31, as well as TNF-alpha enhance TSLP secretion by keratinocytes and diminish the expression of the terminal differentiation markers keratin10, FLG, and loricrin in skin equivalents [15].

But T lymphocytes of other polarization phenotypes can also lead to disruption of the skin barrier. A significant decrease in profilaggrin mRNA levels was observed in keratinocytes cultured in presence of IL-17A [16]. Th17 T cells, one of the main producer cell types of IL-17, gain more and more attention in allergy, since in allergic rhinitis, asthma, and AD a Th2/Th17 double-positive subfraction of human T helper cells was detected [17-20]. While LPS, endotoxins, and other natural adjuvants accompanying mite allergens may be the rationale for this effect, it could also be shown that house dust mite allergens can be detected by Dectin-2, a C-type lectin receptor on antigen-presenting cells, leading to the generation on Th17 cells in mice [21,22]. The list of cytokines expands with IL-25, a dendritic cell-derived cytokine, since stimulation decreases FLG transcript levels in keratinocytes *in vitro* [23,24].

The most recently identified inflammatory threat of an intact skin barrier is IL-33 [25]. Secreted by keratinocytes upon induction with interferon-gamma, IL-33 was shown to be capable of enhancing Interferon-gamma secretion by T cell receptor or IL-12-stimulated T helper cells [26]. Nevertheless, IL-33 is an important cytokine involved in type 2 immunity, since dendritic cells that get activated by IL-33 prime naive T cells into Th2 cells able to secrete IL-5 and IL-13, but not IL-4 [27]. Therefore, the IL-33 may promote Th2 as well as Th1 responses, fulfilling the definition of an innate alarmin.

We could recently show that IL-33 although produced by keratinocytes themselves has skin barrier modulating effects [25]. We applied keratinocytes from patients with atopic dermatitis and observed significant decreases of FLG mRNA upon stimulation with IL-33. This effect was consistent in keratinocytes kept in cell culture in a semi-confluent manner with or without Ca^{2+} differentiation. To investigate the effect in a less artificial system, we subjected human full thickness healthy skin explants to IL-33, resulting in significantly less

FLG expression after 24h as detected by immunostaining. Furthermore, we could show that human skin equivalents raised in the presence of IL-33 were permeable for a labelled allergen, while untreated skin equivalents did prevent its entrance. This effect by IL-33 is especially interesting, since being a direct effect on the down regulation of FLG expression independent of cytokines from mast cells or Th2 cells. IL-33 therefore contributes to the inflammation process in AD on several levels: first, by inducing pro-inflammatory responses in other cells as an alarmin, and second by disrupting the skin barrier.

Taken together, the impact of the numerous inflammatory mediators on the lesional skin is as manifold as the secreting cell types. IL-33 extends the list of pro-inflammatory cytokines capable of weakening the skin barrier, leading to a lack of integrity in the wall.

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