NEWS & VIEWS

AUTOIMMUNE DISEASE

Skin deep but complex

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The antimicrobial peptide LL37 is essential for normal immune responses to infection or tissue injury. But in the autoimmune skin disorder psoriasis, LL37 propagates disease by forming complexes with host DNA.

The innate (nonspecific) immune system is responsible for detecting pathogens and inducing effector molecules to coordinate subsequent immune responses and combat infection. Genes encoding the receptors of innate immunity are hard-wired in the host genome, and honed to near perfection by the selective pressures of evolution to respond only to non-self targets. When tolerance (non-responsiveness to self) is broken, this can result in autoimmune disease. In a paper published on *Nature*'s website today, Lande *et al.*[1] report a costly glitch in the innate immune response that seems to underlie the development of the common autoimmune skin disease psoriasis.

Psoriasis is marked by chronic inflammation and excessive proliferation and turnover of the keratinocyte skin cells, which result in characteristic silvery white scaly patches overlying the inflamed skin[2]. The specific causes of psoriasis are unknown, but environmental triggers — including bacterial skin infections, mild trauma and stress — and strong genetic factors underlie the development of the disease. At a cellular level, an accumulation of inflammatory cells largely consisting of activated T cells and antigen-presenting cells, particularly plasmacytoid dendritic cells (pDCs), precedes other aspects of the disease's pathology. Therefore, psoriasis is currently thought of as an autoimmune inflammatory disorder, but what initiates and perpetuates it has remained enigmatic.

Typically, psoriatic lesions contain high levels of several peptide immune mediators such as cytokines, chemokines and antimicrobial peptides. It is likely that these molecules cause the activation and influx of inflammatory cells to, and perhaps other abnormalities in, the skin lesions. For example, previous studies[3,4] had identified high levels of antimicrobial peptides, including β-defensin 2 and cathelicidin LL37, in these lesions.

Cathelicidins are a large family of antimicrobial peptides found in mammals and other vertebrates, and are expressed in both neutrophils and epithelial cells of many tissues[5]. Studies in mice have established an essential role for these peptides in innate immune responses to bacterial infection. Besides protecting the host through their antimicrobial activity, cathelicidins coordinate many actions, including migration of white blood cells and wound-healing.

Humans have only one known cathelicidin, LL37, which contributes to efficient antibacterial defence in psoriasis[4]. But Lande *et al.*[1] describe an alternative activity of this antimicrobial peptide in psoriasis. Normally, the immune mediator interferon-κ (IFN-κ) is the predominant member of the large family of type-I interferons in the skin. In psoriasis, however, its levels are reduced[6], and instead, large amounts of IFN-α are produced locally by pDCs[7], which accumulate in the skin lesions. Increased production of IFN-α is not only central to the development of psoriasis[8] — other autoimmune diseases such as systemic lupus erythematosus have also been linked to the abnormal production and function(s) of this potent immunomodulatory cytokine[9].

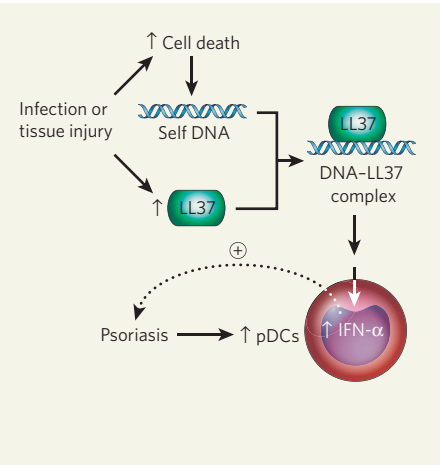

Figure 1 | Role of LL37 in psoriasis. In response to microbial infection or tissue injury, LL37 is produced locally in the skin, where its normal functions include antimicrobial activity and aiding in wound-healing. Lande *et al.*[1] show that LL37 also forms complexes with self DNA that is released from dying cells. In normal skin, these DNA–LL37 complexes probably remain undetected and inconsequential. But in the presence of plasmacytoid dendritic cells (pDCs), which accumulate in the skin lesions of patients with psoriasis, these complexes trigger strong interferon-α (IFN-α) production, which is known to perpetuate the disease[10].

Lande *et al.* analysed psoriatic skin extracts for a factor that could elicit IFN-α production by pDCs. They found that LL37 can bind to self DNA, and that the resulting complexes break tolerance and signal the production of IFN-α (Fig. 1). These findings considerably advance our understanding of psoriasis, and could provide insight into other biological and pathological processes.

But how do the three elements of this response — self DNA, LL37 and pDCs — converge? A high turnover of keratinocytes in the psoriatic lesions, and the associated release of DNA from dying cells, means that high concentrations of human DNA are on hand at the disease site. The high local levels of LL37 can be explained by the pathways that induce its production — infection and tissue injury, which are also known to precede psoriasis onset. Yet the reason for pDC accumulation, a hallmark of psoriasis, is unknown. Could it be that β-defensin 2, the other antimicrobial peptide highly expressed in this disease, attracts pDCs to or retains them in psoriatic lesions? This peptide is known[10] to attract cells that express the chemokine receptor CCR6, and so may recruit CCR6-bearing pDCs[11]. However, as both LL37 and β-defensin 2 are increased in normal skin responses, additional factors specifically associated with psoriasis might lead to an especially robust induction of β-defensin 2 or an exaggerated pDC response.

The deleterious activity of LL37 in psoriatic lesions, as observed by Lande and colleagues, unveils an apparent paradox. It has been shown[12] that microbial stimulation of macrophage cells causes increased expression of the genes encoding the vitamin-D receptor and the enzyme vitamin-D1 hydroxylase. This, in turn, leads to vitamin-D-mediated induction of LL37, which helps macrophages to kill pathogens. If the molecular signalling pathways in skin keratinocytes and macrophages were similar, one might imagine that application of vitamin D to psoriatic lesions would increase LL37 concentrations and perhaps exacerbate the disease. However, the opposite is true. Vitamin-D3 analogues are mainstay drugs for psoriasis[2].

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Possible explanations for this puzzle may include tissue-specific effects of vitamin D, altered responses to vitamin D depending on the cytokine milieu in the lesions, and the already maximal induction of LL37 in skin lesions before therapy. One would certainly expect that several biological effects of vitamin D, beyond increasing LL37 expression, may trump its possible effects on LL37. Investigation of this apparent paradox may lead to even more effective therapies for psoriasis.

Abnormal levels of LL37 in the skin have also been linked to other human diseases, including a skin disorder of unknown cause called rosacea[13], and the allergic skin disorder atopic dermatitis, which is associated with susceptibility to skin infections[4,14]. These findings, together with those of Lande *et al.*[1], highlight the importance of tightly controlled LL37 expression for healthy skin. Moreover, that LL37 can bind to self DNA and subsequently activate pDCs may mark a seminal discovery in the field of autoimmunity in general. Earlier work[15] had shown that recognition of complexes of self DNA and antibodies underlies autoimmunity. Thus, complexes of self DNA with components of the immune system, both innate (LL37) and adaptive (antibody), are involved in the perpetuation of autoimmune diseases. Once in complex, self-DNA molecules become strongly immunostimulatory by engaging crucial molecular signalling pathways mediated by Toll-like receptors. The physiological role, if any, of such immunomodulatory complexes remains to be discovered. ■

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