In summary, although a complete understanding of the mechanisms leading to palmoplantar keratoderma and nail dystrophy in PC has yet to be achieved, Krt16-null mice provide additional insights into this process and highlight the importance of KRT16 in the normal structure and function of palmoplantar epithelia.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES

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IL-33: A Novel Danger Signal System in Atopic Dermatitis

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IL-33 is a newly recognized cytokine of the IL-1 cytokine family that has recently been attributed to the epithelial “alarmin” defense system. IL-33 is released by the epithelial cells in various tissues and organs, including keratinocytes, endothelial cells, and immune cells. Recent reports have suggested that IL-33 might be a critical part of the innate immunity, although its precise role is as yet poorly understood. In several organs, IL-33 appears to drive T helper type 2 (Th2) responses, suggesting roles in allergic and atopic diseases, as well as in fibrosis. IL-33 exerts its effects by activating the ST2 (suppression of tumorigenicity 2)/IL-1 aR receptor on different types of cells, including mast cells and Th2 cells. The ST2 receptor is either expressed on the cell surface or shed from these cells (soluble ST2, sST2), thereby functioning as a “decoy” receptor. After binding to its receptor, IL-33 activates NF-κB, suggesting that it regulates the outcome of diseases such as atopic dermatitis. On the other hand, several studies have reported on the inhibitory effects of sST2 in inflammatory and fibrotic diseases, suggesting that IL-33/ST2 is a unique cytokine with potential pro- and anti-inflammatory effects.


Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by an early T helper type 2 (Th2) “immune signature”: patients suffer from relapsing eczematous and occasionally generalized (erythroderma) lesions associated with severe pruritus (Bonness and Biever, 2007; Boguniewicz and Leung, 2011). Scratching reactions to pruritus typically exacerbate the inflammatory skin reactions (Hong et al., 2011). The key events in AD may be subdivided as an interplay among (1) infiltrating immune cells (Th2 cells and—later—Th1 cells, macrophages, dendritic cells, mast cells, and eosinophils); (2) skin-resident keratinocytes and endothelial cells; and (3) activated (“hypersensitive”) peripheral sensory nerves. The multicellular action is believed to orchestrate disease onset and progression (Steinhoff et al., 2006; Cevikbas et al., 2007). Unfortunately, current AD treatments, which suppress inflammation broadly (e.g., steroids, cyclosporin A), are hampered by effects on other cells and pathways that are unrelated to the disease.

The adaptive and innate immune systems have important and bidirectional roles in the pathophysiology of AD (Bieber, 2008; Elias and Steinhoff, 2008). Cytokines such as IL-4 and IL-13 regulate proinflammatory responses of the adaptive immune response in early phases of AD by regulating Th2 activation; thus, they are considered optimal targets for therapies. Keratinocytes, however, as part of the innate immune defense, also contribute to the inflammatory reactions and immune responses in AD by regulating the release of cytokines, chemokines, proteases, and bioactive lipids. Upon stimulation by allergens, toxins, or infectious agents, keratinocytes are capable of initiating a cross-talk between the innate immune system and Th2 cells in patients with AD through the release of key molecules (Horney et al., 2006). Thus, cytokines such as IL-25 and chemokines such as TSLP (thymic stromal lymphopoietin) or CCL27 have important roles in this interactive network (Carmi-Levy et al., 2011).

Recent evidence points to a role for the IL-33/ST2 (suppression of tumorigenicity 2) pathway in epithelial integrity, allergic immune responses, inflammation, autoimmunity, and fibrosis, which are just several examples (Mousson et al., 2008; Ivanov et al., 2010; Rankin et al., 2010). In skin, the functional role of this newly recognized IL-33/ST2 pathway has gained attention. The
findings thus far indicate that the release
of IL-33 by keratinocytes, endo-
thelial cells, or immune cells activates
the IL-33 receptor ST2 on keratinocytes,
fibroblasts, mast cells, or other immune
cells, leading to the expression of factors
implicated in several inflammatory path-
ways (Pushparaj et al., 2009; Liew et al.,
2010). This IL-33/ST2-induced immune
regulation may have a crucial role in
adaptive as well as innate immune
responses in skin.

IL-33 has important roles in the
pathogenesis of several Th2-biased
inflammatory conditions and allergic
reactions (Verri et al., 2008; Figure 1).
An alternative transcript from the ST2
locus encodes a soluble form of the ST2
receptor (sST2), which acts as a natural
IL-33 antagonist (decoy receptor). IL-33–
dependent activation of ST2 signaling
leads to activation of the signaling path-
ways signal transducer and activator
of transcription 5, mitogen-activated
protein kinase, Akt, and NF-κB (Guo
et al., 2009; Ivanov et al., 2010; Ali
et al., 2011; Funakoshi-Tago et al.,
2011), most of which ultimately have
roles in the pathogenesis of AD. The
mature form of IL-33 is released into the
cytoplasm and subsequently stimulates
T cells, mast cells, or keratinocytes.
Similar to IL-1, full-length IL-33 can act
as a transcription factor by trafficking
into the nucleus, where it modulates
several inflammatory responses (Carriere
et al., 2007).

Intriguingly, IL-33 expression is upreg-
ulated in keratinocytes and endothelial
cells in AD (Oboki et al., 2010). Injection
of recombinant IL-33 into mouse skin
in vivo is sufficient to cause infil-
tration of T cells, macrophages, and
eosinophils, all of which are immune
cells that express the functional ST2/
IL-1R4 receptor complex (Kroeger et al.,
2009; Rankin et al., 2010; Anthony et al.,
2011; Eiwegger and Akdis, 2011; Ohno
et al., 2011; Zaiss et al., 2011). Further-
more, IL-33 stimulation leads to the
release of Th2-associated mediators,
suggesting that IL-33 might fulfill a
crucial role in Th2-associated diseases
such as AD. In summary, considerable
evidence points to a key contribution of
the IL-33/ST2 pathway in inflammatory
skin diseases, including AD. In the future,
it will be important to understand the
precise roles of the different subforms of
IL-33 (secreted, intracellular) and ST2
(transmembrane, decoy) in skin.

Saviniko et al. (this issue, 2012) inves-
tigated the expression profiles of IL-33
and ST2 in different mouse models of
atopic-like dermatitis (AD), emphasizing
a regulatory role for this novel cytokine
pathway. In a translational setting, the
authors also quantified the messenger
RNA levels for IL-33 and ST2 in lesional
and nonlesional human skin. Via immu-
nohistochemistry, the authors restricted
the distribution of IL-33+ cells to supra-
basal keratinocytes. The ST2+ cell popu-
lation was found to be dermal and
epidermal in origin, although a precise
characterization of the ST2+ dermal cells
is still lacking. Different allergens, when
applied topically (ovalbumin, house dust
mites, or staphylococcal enterotoxin B) to
mice, led to the upregulation of IL-33
and ST2 messenger RNA expression. These
results indicate that IL-33 as well as its
receptor may be induced in AD when
exposed to AD trigger factors. Whether
these results reflect the human situation
remains unknown. Intriguingly, topical

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**Figure 1. Potential role of IL-33 and ST2 (suppression of tumorigenicity 2) in skin inflammation and pathophysiology of atopic dermatitis.** Trigger factors such as allergens, bacteria, mechanical injury, and exogenous proteases induce the release of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) from keratinocytes. IL-33, alone or in combination with other cytokines and chemokines, activates mast cells, dendritic cells, and potentially lymphocytes of innate lineage in inflamed skin. Activation of mast cells regulates the function of dendritic cells, eosinophils, T cells, and nerves (not shown) via release of cytokines, chemokines, growth factors, proteases, and leukotrienes, for example. Via the IL-33–induced release of IL-25 and IL-18, dendritic cells regulate the function of T helper type 2 (Th2) cells and B cells (early) and (probably later) Th1 cells. Via IL-33 induction, innate lymphoid cells (ILCs) regulate Th2-driven immune responses in various organs. The role of these potentially important cells in Th2 regulation has not been verified in skin. ILCs have been described to be important in the early stage of immune signaling and probably enhance the Th2 immune response pathway in the skin. The arrows illustrate the interaction among the various immune cells and their cell-specific secretion products involved in inflammatory skin diseases, including atopic dermatitis. Thus, IL-33 may be involved in orchestrating early inflammatory responses in the onset and perpetuation of atopic dermatitis. His, histamine; Lkt, leukotriene; OX40 (gp34), a member of the TNF superfamil; TNF-α, tumor necrosis factor-α (Modified from Carmi-Levi et al., 2011).
COMMENTARY

Clinical Implications

- The newly recognized cytokine IL-33 influences atopic dermatitis variously, up and down.
- The mechanism of action establishes IL-33/ST2 as a potential target to treat atopic dermatitis.
- Lympocytes of innate immunity may be regulated by IL-33 in human skin disease.

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Toward Personalized Medicine in Scleroderma: Classification of Scleroderma Patients into Stable “Inflammatory” and “Fibrotic” Subgroups

Andrew Leask

There is no universally agreed-upon treatment for the fibrosis of scleroderma. Recently, much information has been generated relating to the fundamental mechanisms underlying this disease. Partly based on these observations, both anti-inflammatory and anti-fibrotic agents have been considered as possible therapies. However, this information has not been successfully translated into clinical practice. In this issue, Pendergrass et al. use genome-wide expression profiling to provide valuable insights into scleroderma. Previously, the authors showed that morphea and “limited” scleroderma patients and a small subset of diffuse scleroderma (dSSc) patients express an “inflammatory” profile, whereas the majority of dSSc patients express a “fibroproliferative” profile. In the current study, the investigators show that the gene expression profile of these patients is fixed over time; i.e., in contrast to a previously held belief, the inflammatory patients do not go on to become fibrotic, and vice versa. These data suggest that expression profiling might be used to design clinical trials for scleroderma. The inflammatory patients might be treated with anti-inflammatory agents, whereas fibroproliferative patients might be treated with antifibrotic agents.

A connective-tissue disorder of unknown etiology, scleroderma (also called systemic sclerosis or SSC), is a multisystem disease characterized by the presence of autoantibodies, vascular damage, and organ fibrosis (Abraham and Varga, 2011). In this issue, Pendergrass et al. (2012) use genome-wide expression profiling to provide novel insights into scleroderma. The investigators show that the gene expression profile of these patients is fixed over time, i.e., in contrast to a previously held belief, the inflammatory patients do not go on to become fibrotic, and vice versa. These data suggest that expression profiling might be used to design clinical trials for scleroderma. The inflammatory patients might be treated with anti-inflammatory agents, whereas fibroproliferative patients might be treated with antifibrotic agents.

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