

Natural killer cells in atopic and autoimmune diseases of the skin

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Natural killer (NK) cells are best known for their ability to recognize and kill tumor cells and virally infected cells and for their ability to produce large amounts of some cytokines, such as IFN- γ . Recent research has substantially expanded our view on the function of NK cells in the immune system in health and disease. In addition to the better-studied functions in cancer and autoimmunity, contributions from NK cells to allergies and various skin diseases have emerged. We briefly recount the traditional NK cell functions before focusing on their roles in atopic dermatitis, psoriasis, alopecia areata, and pemphigus vulgaris. Although this field is still developing, strong data are available that indicate NK cell involvement. In patients with allergic diseases, the production of T_H2 cytokines by NK cells contributes to the known immune deviation. In patients with psoriasis, their pathophysiologic role seems to be especially the production of IFN- γ . NK cell overactivation can be found in patients with alopecia areata and pemphigus vulgaris. Many details are still unclear; however, we believe that there is solid evidence that NK cells actively participate in a number of diseases that have not been traditionally linked to this type of lymphocyte. (*J Allergy Clin Immunol* 2010;125:60-8.)

Key words: Natural killer cells, skin, allergy, autoimmunity

NATURAL KILLER CELLS

Definition and functions of natural killer cells

Natural killer (NK) cells are a third type of lymphocyte in addition to T and B cells. In human subjects they are phenotypically defined as CD3⁺CD56⁺ lymphocytes. The major functional properties of NK cells are cytotoxicity and cytokine production. Cytotoxicity can be further subdivided into (1) natural cytotoxic activity predominantly directed toward tumor cells and virally infected cells in the absence of prior stimulation or

Abbreviations used

AA:	Alopecia areata
AD:	Atopic dermatitis
AR:	Activating receptor
CHS:	Contact hypersensitivity
CMV:	Cytomegalovirus
DC:	Dendritic cell
IDEC:	Inflammatory dendritic epidermal cell
ILT2:	Immunoglobulin-like transcript 2
IP:	Immune privilege
IR:	Inhibitory receptor
KIR:	Killer immunoglobulin receptor
LC:	Langerhans cell
LTi:	Lymphoid tissue inducer
MICA:	MHC class I chain-related protein
MIF:	Macrophage migration inhibitory factor
NK:	Natural killer
NKT:	Natural killer T
PNM:	Proximal nail matrix
PV:	Pemphigus vulgaris
Tip-DC:	Dendritic cell (CD11c ⁺ CD1c ⁺) that secretes TNF- α and produces inducible nitric oxide synthase

immunization and (2) antibody-dependent cellular cytotoxicity directed against antibody-coated target cells.¹⁻⁶ In this situation the constant part of the antibody triggers the Fc γ receptor CD16. Although present in resting NK cells, cytotoxicity strongly increases when NK cells are stimulated by cytokines like IL-2, IL-15, IL-18, and many others. NK cell-mediated lysis of target cells is mainly mediated by the release of the cytotoxic molecules perforin and granzymes A and B. Cytokine production occurs on triggering of activating receptors (ARs), stimulation by cytokines present in the microenvironment, or both.

Cytotoxicity and cytokine production by NK cells contribute to innate immune responses and thus to the first line of defense of the organism before adaptive immunity develops. In addition, NK cells directly participate in the induction and regulation of adaptive immune responses: they stimulate maturation of dendritic cells (DCs),^{7,8} eliminate immature DCs,^{7,8} produce cytokines that influence CD4⁺ helper and CD8⁺ effector T cells,^{9,10} and regulate T-cell activation and proliferation through direct cellular contacts.^{11,12}

NK cell inhibition and activation

NK cell functions are governed by a balance between activating messages transmitted by their ARs and inhibitory signals transmitted by their inhibitory receptors (IRs).^{1,13,14} Inhibitory NK cell receptors specific for HLA class I molecules recognize either (1) restricted numbers of classical HLA class I alleles (mainly HLA-B and HLA-C alleles) in the case of killer immunoglobulin receptors (KIRs); (2) a broad panel of classical HLA class I molecules, as well as HLA-G, in the case of immunoglobulin-like

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transcript 2 (ILT2); and (3) the nonclassical MHC class I molecule HLA-E. This molecule presents peptides derived from the signal sequences of classical HLA class I molecules and is recognized by the C-type lectin heterodimer CD94/NKG2A.^{13,14} The most potent ARs of NK cells are the antibody-dependent, cellular cytotoxicity–mediating molecule CD16¹; NKG2D^{1,15}; and the natural cytotoxicity receptors NKp30, NKp44, and NKp46.¹⁶ The ligands of NKG2D are MHC class I chain–related proteins A and B (MICA and MICB) and retinoic acid early transcript 1, also called UL-16–binding proteins. These molecules are mostly absent from healthy cells but are induced on cellular stress, as in case of infection or malignant transformation.¹⁵ Viral proteins, such as hemagglutinins^{17,18} and pp65 from human cytomegalovirus (CMV),¹⁹ have been suggested as ligands for natural cytotoxicity receptors. A ligand of NKp30 also seems to be expressed on human DCs because NK cell–mediated killing of immature DCs depends on NKp30 engagement.²⁰ In addition, B7-H6, a member of the B7 family specifically expressed by human tumor cells but absent from normal cells, has been shown to be a ligand of NKp30.²¹

Healthy cells express normal amounts of HLA class I molecules and no or few ligands for major ARs. On encounter with an NK cell, an excess of inhibitory messages is transmitted to the NK cell through its IR, rendering an MHC class I–expressing target cell resistant to NK cell–mediated killing. This is in contrast to what is known about the effect of MHC on T cells: MHC (plus peptide) normally activates T-cell recognition and function. If the target cell becomes infected or malignant, it might lose expression of HLA class I molecules partially (weak NK cell inhibition) or totally (no NK cell inhibition), whereas stress-induced ligands for NK cell ARs are upregulated at the same time (strong activation). The balance in this case is in favor of activation, and the target will be killed by the NK cell.^{13,14}

It has recently become clear that only NK cells that express at least 1 IR (KIR or NKG2A) for a self-HLA class I molecule are functionally mature and are able to perform cytotoxicity and cytokine production, whereas those NK cells without such a receptor remain hyporesponsive. The first population is called “educated,” “licensed,” or “armed,” whereas the latter (up to 20% of all NK cells in peripheral blood) is called “unlicensed” or “disarmed.”^{22–25}

NK cell markers and subpopulations

The relative expression of the NK cell markers CD16 and CD56 (a homotypic adhesion molecule) allows definition of several different NK cell subsets.⁶ In peripheral blood the numerically predominant population is CD56^{dim}CD16^{bright} (90% of all NK cells in healthy subjects). A maximum of 10% of NK cells belong to the CD56^{bright} subset, which can be further subdivided into CD16[–] (30% to 50% of CD56^{bright} cells) and CD16^{dim} (50% to 70% of CD56^{bright} cells) fractions.⁶

The 2 main peripheral blood NK cell subsets are quite different in terms of phenotype and function. CD56^{bright} NK cells are less cytotoxic than CD56^{dim} NK cells but produce many more cytokines and proliferate in response to picomolar concentrations of IL-2, which is due to their constitutive expression of the high-affinity IL-2 receptor. CD56^{bright} NK cells express CD94/NKG2A at high levels but are mostly devoid of KIRs and ILT2. In contrast, KIRs and ILT2 are frequently found on subpopulations of CD56^{dim} NK cells together with CD94/NKG2A. The repertoire of chemokine receptors and adhesion molecules is also very different between the 2 subsets, with CD56^{bright} NK cells being equipped for migration to secondary lymphoid organs and sites

TABLE I. NK cell subsets according to their cytokine production profile

NK subset	Localization	Inducing cytokines	Cytokines produced	References
NK1	PB, LN	IL-12/IL-18	IFN- γ /TNF- α	28-30
NK2	PB, LN	IL-4	IL-5/IL-13	28-30
NK3 or NKreg	PB, LN	IL-2;?	IL-10/TGF- β	31-39
NK-22	Skin, tonsils, gut mucosa	IL-23	IL-22	40

LN, Lymph nodes; NKreg, NK regulatory cell; PB, peripheral blood.

of chronic inflammation, whereas CD56^{dim} NK cells preferentially migrate to acute inflammatory sites. Accordingly, NK cells in lymph nodes are predominantly of the CD56^{bright} type.⁶

For murine NK cells, most of the discussed aspects are the same. One exception is the fact that murine NK cell IRs are all of the C-type lectin superfamily (Ly49 and CD94/NKG2A) and not of the immunoglobulin superfamily, as in human subjects (KIR and ILT2). Murine Ly49 receptors are thus structurally different but functionally equivalent to human KIRs.^{26,27}

Cytokine production, antigen presentation, and memory

NK1 and NK2 cells. NK cells are an important source of IFN- γ , but they can also produce type 2 cytokines.^{1–6} The former are called NK1 cells, by analogy with T_H1 T cells, and have to be stimulated by type 1 cytokines, such as IL-12 (Table I).²⁸ The combination of IL-12 and IL-18 is the most efficient stimulator of IFN- γ production by NK cells.²⁹ NK2 cells arise after stimulation with the type 2 cytokine IL-4 and produce the type 2 cytokines IL-5 and IL-13.²⁸ According to Loza et al,³⁰ the cytokine production profile is closely related to the developmental stage of NK cells, with immature NK cells producing type 2 cytokines and mature NK cells producing type 1 cytokines.

NK regulatory cells. TGF- β – and IL-10–producing NK3-like cells have also been described.³¹ This has led to the concept of the NK regulatory cell. Some authors consider all NK cells to be regulatory because they influence innate and adaptive immune responses. By analogy with regulatory T cells, however, it would be better to limit this designation only to those NK cells that indeed suppress other immune cells. Several recent articles nicely describe this phenomenon, which is in most cases due to IL-10 secretion by NK cells but can also rely on the killing of, for example, regulatory T cells.^{32–39}

NK-22 cells. Most recently, mucosa-associated IL-22–producing NK cells have been discovered and are called NK-22 cells.⁴⁰ IL-22 is a cytokine that protects the epithelial cell barrier, notably in the gut and the skin, from pathogens, which can have both proinflammatory and anti-inflammatory capacities (depending on the inflammatory context). This molecule is also secreted by T_H17 T cells, natural killer T (NKT) cells, and $\gamma\delta$ T cells.^{40,41} Interestingly, NK-22 cells do not produce IL-17,⁴⁰ although conventional NK cells are able to release this cytokine.^{42,43} (the best studied IL-17–producing cells are the proinflammatory T_H17 T lymphocytes, the pathogenic role of which in psoriasis and atopic dermatitis [AD] is well known⁴⁴).

Antigen presentation. NK cells have also been described as being equipped with the potential to process and present antigens to T cells. On activation, NK cells express HLA class II molecules and several ligands for T-cell costimulatory receptors (CD80, CD86, CD70, and OX40 ligand). Under these conditions,

NK cells are able to stimulate the proliferation of antigen-specific T cells, although not as efficiently as professional antigen-presenting cells, such as DCs.⁴⁵

NK cells and memory. A very recent finding in the mouse that has yet to be confirmed in human subjects is the existence of memory NK cells. The work on a murine model of hapten-induced contact hypersensitivity (CHS) by O'Leary et al⁴⁶ was historically the first to describe "adaptive," memory-like NK cell responses. Mice devoid of T and B cells were able to mount CHS responses, which persisted for several weeks and were hapten specific. CHS could be transferred by NK cells from sensitized mice to naive recipients.⁴⁶ The molecular mechanism of these recall responses is not known.

After infection of the animals with murine CMV, Ly49H⁺ (an NK cell AR involved in the recognition of a CMV-encoded protein) NK cells selectively proliferate and persist in the host for several months. On reinfection, they respond faster and stronger in terms of cytotoxicity and cytokine production than naive NK cells. Transfer of these adaptive NK cells into naive hosts results in further expansion and protective immunity.⁴⁷ Memory-like NK cells in the mouse have likewise been described by Cooper et al.⁴⁸

NK CELLS AND AD

AD is a pruritic, relapsing, and often chronic skin inflammation, the prevalence of which has doubled or tripled over the last 3 decades. It affects up to 30% of children and up to 10% of adults in industrialized countries.⁴⁹ These subjects often have a family background of other atopic diseases, such as allergic keratoconjunctivitis, allergic rhinitis, and allergic asthma. The disease has a strong hereditary component and arises from complex gene-gene and gene-environment interactions. The key defects in AD are related to a disrupted epithelial barrier function caused by loss-of-function mutations in the filaggrin gene and dysfunctions in both the adaptive and innate immune system.^{50,51}

Acute phase of AD and T_H2 and T_H17 cells

In the past, adaptive immune defects have been intensively investigated, showing the inherited dominance of T_H2 responses in atopic subjects.⁵² It has been shown that during the acute phases of AD, normally innocuous proteins trigger the production of IL-4, IL-5, and IL-13, which leads to IgE secretion from plasma cells and eosinophil activation in sensitized subjects.⁵³ Although such a link is commonly accepted only in patients with psoriasis and is controversially discussed in patients with AD, there might be a potential involvement of T_H17 cells in patients with AD, especially during its onset.^{54,55} It has been shown by means of immunohistochemistry that IL-17⁺ cells are increased in numbers in acute, but not in chronic, AD lesions compared with numbers seen in unaffected skin.⁵⁶

Chronic phase of AD (T_H0 cells, T_H1 cells, inflammatory dendritic epidermal cells, and T_H22 cells)

In the chronic phase of eczema, T_H0 cells (cells that share activities of both T_H1 and T_H2 cells) and T_H1 cells are predominant, and the concentration of the T_H1 cytokine IFN- γ increases locally and systemically.⁵⁷ This is followed by a peak of IL-12 expression that coincides with the appearance of inflammatory dendritic epidermal cells (IDECs) in the skin.⁵⁸ The IDEC subset, which can be distinguished from Langerhans cells (LC) by its expression of

the macrophage mannose receptor CD206, is predominant in chronic AD skin lesions and is even present in the mild residual infiltrate in normal-looking skin between flares.^{59,60} By producing IL-12 and IL-18 and by releasing proinflammatory cytokines, IDECs seem to contribute to the chronification of the eczema. The genetically inherited barrier dysfunction together with the enhanced expression of the high-affinity receptor for IgE, Fc ϵ RI, on LCs and IDECs in the epidermis of lesional atopic skin facilitates allergen uptake, allergen binding, and IgE sensitization.⁶¹⁻⁶³ Recently, a different subset of T cells with skin-homing potential, which produces IL-22 but not IL-17 or IFN- γ (ie, the so-called T_H22 cells) has been identified and seems to accumulate in chronic AD lesions.^{43,54,64,65} In the skin IL-22 mediates keratinocyte proliferation and epidermal acanthosis and might account for the lichenification seen in chronic AD skin lesions.⁶⁶

AD and NK cell subsets (NK2, NK-22, and lymphoid tissue inducer-like cells)

Over the last few years, numerous innate immune defects important for defense at the interface between epithelial cells and the environment have been described in patients with AD. These innate immune defects can promote inflammation and therefore aggravate or even trigger the development of AD. Atopic subjects are specifically susceptible to cutaneous staphylococcal, streptococcal, and herpes simplex virus infections. This is due to the inflammatory T_H2-biased microclimate that leads to functional impairment of Toll-like receptor-mediated activation of epithelial cells and that reduces the production of antimicrobial peptides locally.⁶⁷⁻⁶⁹ Reports have shown that T_H17 cells, with their propensity to produce IL-17 and IL-22, are essential for first-line defense against several fungal and bacterial infections.⁷⁰ A severely impaired IL-17-mediated immune response can lead to recurrent and persistent infections of the skin and mucosal membranes, as seen in patients with chronic mucocutaneous candidiasis.⁷¹ The relative deficiency of IL-17 found in chronic AD skin lesions might add to the reduced efficiency of innate defense molecules to skin-tropic pathogens.⁵⁴

Very recently, 2 distinct NK cell populations have been identified in human skin, as well as in the intestine (Peyer patches), mucosal-associated lymphoid tissue, and tonsils, which have the capacity to produce either IL-22 or both IL-22 and IL-17 and are therefore prime candidates for constituting a link to skin pathophysiologies, such as AD and psoriasis. NK-22 cells are a special subset of NKp46⁺ NK cells with a diminished capacity to degranulate and produce IFN- γ .^{72,73} Instead, NK-22 cells express the nuclear hormone receptor retinoic acid receptor-related orphan receptor γ t and produce large amounts of IL-22 in response to IL-23, which serves to induce the production of antimicrobial molecules in epithelial tissues.⁷⁴ The other subset, referred to as human lymphoid tissue inducer (LTi)-like cells, is a committed NK cell precursor population that was shown to initiate lymph node organogenesis during embryogenesis and that probably gives rise to the NK-22 cell. LTi-like cells are able to produce both IL-17 and IL-22 after stimulation *in vitro*.^{23,75} It is a plausible hypothesis that NK-22 cells and LTi-like cells, given this cytokine profile and their location in these distinct anatomic sites, contribute to those specific inflammatory skin disorders that are characterized by the contribution from IL-17 and IL-22.

Histologically, atopic skin lesions are not only characterized by the well-described infiltrate of CD4⁺ and, to a lesser extent,

TABLE II. Findings about NK cells in various skin diseases

Disease	Findings on NK cells	References
Atopic dermatitis, human	Lesional skin: CCL2 and CCL22 (NK cell chemoattractant) levels increased	76, 79, 80
	PB: activated NK cells, more NK2 cells	86
Atopic dermatitis, murine	Eczema vaccinatum: impaired NK cell activity	77
Psoriasis, human	Lesional skin: 5% to 8% NK cells (CD56 ^{bright} CD16 ⁻)	107
	NK cells from lesional skin: high IFN- γ and TNF- α production	107
	NK cells from lesional skin: expression of chemokine receptors CXCR3 and CCR5	107
	Lower number of NK cells in PB: accumulation at sites of inflammation?	108
Alopecia areata, human	Breakdown of immunoprivilege, increased NK cell activity	121
	Lesional IFN- γ levels increased, NKG2D expression increased on lesional NK cells	121
	Lesional MICA expression increased, lesional MIF expression increased	122
	PB: NKG2C and NKG2D expression increased, KIR expression decreased	122, 124
Pemphigus vulgaris, human	PB: increased NK cell numbers	125
	Activated state	125, 126
	Decreased responses to T _H 1 cytokines	125
	Higher expression of IL-5	125
	Antigen presentation?	126

PB, Peripheral blood.

CD8⁺ T lymphocytes, Fc ϵ RI⁺ LCs, and Fc ϵ RI⁺ IDECs, CD56⁺ NK cells are also present in the epidermis and even more in the dermal atopic infiltrate.^{76,77} Recent studies have shown that patients with AD harbor an increased frequency of L-selectin-positive CD16⁺ NK cells in the peripheral blood compared with that seen in healthy control subjects.⁷⁸ In addition, increased levels of the NK cell chemoattractants monocyte chemoattractant protein 1/CCL2 and macrophage-derived chemokine/CCL22, which are derived from keratinocytes and CD1a⁺ DCs, are expressed in lesional skin of patients with AD (Table II).^{76,79,80} In accordance with these findings, in *Malassezia* species atopy patch test-positive skin, where the yeast *Malassezia* species acts as an allergen in the skin of patients with AD, numerous CD3⁻CD56⁺ NK cells have been found in the dermal lesions.⁷⁶ These NK cells were in close contact with CD1a⁺ DCs. *In vitro* *Malassezia* species can be taken up by immature monocyte-derived DCs, leading to their maturation and to the production of cytokines with the potential to skew the immune outcome toward a T_H2-like response. The DCs pretreated with *Malassezia* species showed a reduced susceptibility to NK cell-induced cell death and might therefore have an increased capacity to sustain the atopic inflammation.

Reported results regarding the potential role of NK cells in patients with AD are complex but compatible with a common interpretation at closer inspection.^{81,82} The main focus has been the number of NK cells in peripheral blood and their level of activation. In patients with AD, a numeric decrease of NK cells in the periphery has been most consistently reported.^{81,83} NK cells leaving the circulation and accumulating in tissues could account for the lower number of NK cells reported in these studies. This shift of NK cells to the site of allergic inflammation was also evident in earlier studies in animal models of allergic asthma⁸⁴ or allergic peritonitis.⁸⁵ In human vernal keratoconjunctivitis, a complex type I-mediated hypersensitivity reaction of the conjunctiva also involving IgE-independent pathogenic mechanisms, NK cells constitute a significant proportion of the immune cells infiltrating the conjunctiva.⁸⁶ Here again, concomitant with the accumulation of NK cells at the site of allergic infiltration, a decrease in circulating NK cell numbers in the blood was observed. The transient increase

of NK cell numbers in the blood of patients with AD shortly after stress exposure (up to 1 hour) underlines the potential immunologic relevance of these cells, especially if the IFN- γ production by NK cells is considered.⁸⁷

The alterations in cytokine production by NK cells in patients with AD has been studied, with somewhat contradictory results. One group found that patients with AD harbored highly activated NK cells *in vivo*, as indicated by a high spontaneous release of IL-4, IL-5, IL-13, and IFN- γ from isolated lesional NK cells.⁸⁸ Analogous to the enhanced polarization toward T_H2 cells and their cytokines in early AD lesions, as outlined above, the percentages of IL-5- and IL-13-producing NK cells were significantly higher in patients with AD than in healthy subjects in the same study. On the other hand, several groups have reported a significantly lower production of TNF- α and IFN- γ from NK cells at a single-cell level in patients with AD.^{89,90} An imbalance between T_H1 and T_H2 cells from early infancy on (ie, an inherent reduction in IFN- γ production from T_H1 cells but also from NK cells) has been found consistently in childhood AD.^{81,83} This is thought to shift the subsequent adaptive immune responses toward a type 2 response, thereby promoting allergy and infection.

In general, changes in NK cell numbers have to be interpreted with some caution because of the rapid redistribution of these cells.^{91,92} In addition, differing experimental outcomes can also result from variations in disease parameters, such as activity, chronicity, and treatment modalities, and do not necessarily indicate NK cells as a key prerequisite for AD pathogenicity.

The most reliable evidence for an impaired activity of NK cells in atopic lesional skin comes from a murine model of eczema vaccinatum, a disseminated vaccinia infection resulting from smallpox vaccination of subjects or animals with AD.⁷⁷ In the murine model it is the production of IL-17A and probably other T_H17-related cytokines in the inflamed atopic skin that reduces the ability of NK cells to kill virus-infected cells. This leads to viral spreading, with an increased susceptibility of mice with AD to experience eczema vaccinatum.

In summary, several NK cell subsets are present and implicated in the different stages of AD and AD-associated cutaneous infections.

NK CELLS AND PSORIASIS

Psoriasis is a genetically determined, autoinflammatory, chronic relapsing skin disorder without involvement of known infectious agents or antigens.^{93,94} Clinically, the disease is characterized by scaly and raised erythematous plaques. An imbalance between steady-state levels of environmental and genetic factors induced by, for example, bacterial products initiates the inflammatory process. So-called inflammatory dermal DCs (CD11c⁺CD11c⁻) that secrete TNF- α and produce inducible nitric oxide synthase (Tip-DCs) are of major pathophysiologic relevance for psoriatic inflammation.⁹⁵ Effective treatment of psoriasis downmodulates Tip-DC products, such as TNF- α -inducible nitric oxide synthase, IL-20, and IL-23.⁹⁵ Because of their production of IL-23, Tip-DCs are also able to stimulate the differentiation and activation of T_H17 cells.⁹⁵ During disease progression, activated myeloid DCs migrate to the draining lymph nodes, present autoantigens to T cells, and lead further to the differentiation of T_H17 cells, type 17 cytotoxic T (T_C17) cells, and T_H1 or type 1 cytotoxic T (T_C1) cells.⁹³ The production of IL-17A and IL-17F by T_H17 and T_C17 cells upregulates the expression of specific chemokines (eg, CXCL1, CXCL9 to CXCL11, and CCL20) that are increased in psoriatic lesions. IL-22 from T_H17 cells downregulates keratinocyte differentiation genes and is involved in keratinocyte hyperplasia.^{66,96} Both IL-17 and IL-22 induce the synthesis of antimicrobial peptides (eg, cathelicidin and β -defensins) from various epithelial cell types in human subjects, including keratinocytes, suggesting their participation in host defense.^{23,97-100} IFN- γ and TNF- α produced by T_H1 and T_C1 cells are largely proinflammatory mediators in patients with psoriasis, leading to the activation and proliferation of antigen-presenting cells and keratinocytes.¹⁰¹ The importance of TNF- α is stressed by the clinical success of an anti-TNF- α therapy in psoriasis treatment.¹⁰²

More recently, intrinsic cutaneous factors have been shown to predispose skin to psoriasis development, requiring the innate immune system.^{103,104} Autologous human lymphocytes with NK cell receptors (NK and NKT cells), when injected into nonlesional skin grafts from psoriatic patients on mice with severe combined immunodeficiency, caused the classic pathology of psoriasis, such as epidermal thickness, proliferation, and expression of epidermal HLA-DR, intercellular adhesion molecule 1, CD1d, and K-16.¹⁰⁵ NKT cells are a subset of lymphocytes that express T-cell receptors and NK cell receptors, such as CD94 and CD161. NKT cells (CD3⁺CD56⁺) are thought to belong to the innate immune system and seem to play an important role in psoriasis by recognizing glycolipids through CD1d-expressing keratinocytes, thereby activating IFN- γ -producing or self-reactive lymphocytes.¹⁰⁶ In lesional psoriatic skin, about 5% to 8% of CD3⁺CD56⁺ true NK cells are located to the mid and papillary dermis.¹⁰⁷ These NK cells mostly belong (up to 80%) to the immunoregulatory CD56^{bright}CD16⁻ NK subtype that is recruited from the about 5% to 10% circulating NK cells that home to secondary lymphoid organs and modulate adaptive immune responses.¹⁰⁷ When isolated, NK cells from lesional psoriatic skin produce high amounts of IFN- γ and (although to a lesser extent) TNF- α . It has been speculated that immigrating papillary DCs activate these NK cells, leading to the release of high amounts of type 1 cytokines, which then polarize T cells toward the T_H1 type. Psoriatic NK cell supernatants are potent in inducing intercellular adhesion molecule 1 and MHC class II expression on cultured psoriatic

keratinocytes and can promote the release of the chemoattractants CXCL10, CCL5, and CCL20 by keratinocytes.¹⁰⁷ CD56^{bright}CD16⁻ NK cells from psoriatic skin express the chemokine receptors CXCR3 and CCR5 and bind to keratinocyte-derived CXCL10 and CCL5, leading to their accumulation in inflamed skin. Such findings are very significant because they are about NK cells isolated directly from diseased skin. The number of NK cells in the peripheral blood of patients with psoriasis has been found to be decreased, but levels of T cells, activated T cells, and NKT cells are normal.¹⁰⁸ This constellation can be also found in other autoinflammatory-related disorders, such as lupus erythematosus.^{109,110} There seems to be evidence that NK cell depletion can lead to a T_H1 cytokine bias and that NK cells regulate autoimmunity.¹¹¹ However, as already outlined, assessment of peripheral blood NK cell counts is of questionable significance and therefore of limited value because of the rapid redistribution of these cells.^{91,92}

In conclusion, these results can be considered strong evidence of an active participation of NK cells in psoriasis development.

NK CELLS AND ALOPECIA AREATA

Alopecia areata (AA) is an inflammatory, often reversible hair loss affecting mainly children and young adults. Clinically, round hairless patches appear on the scalp while hair follicles remain intact. Normally, in the distal part of the human hair follicle immune system, interacting intraepithelial T cells and LCs build up an effective defense strategy. During the growth stage of the hair cycle (anagen phase), hair follicles belong to the few immunoprivileged sites in the mammalian body.¹¹² A collapse of the immune privilege (IP) of the hair follicle results in the loss of hair, as seen in patients with AA.^{113,114} The cause of this collapse is, however, diverse and seems to involve T cell-mediated immunologic changes, neuropeptides, genetic disposition to autoimmunity, and distress.¹¹⁵ Histologically, the disease is characterized by an abundance of catagen follicles in lesional skin and the presence of intrafollicular and perifollicular inflammatory cell infiltrates consisting of many CD4⁺ and even more CD8⁺ T lymphocytes, mast cells, macrophages, and LCs that target hair follicle keratinocytes, melanocytes, and dermal papillary fibroblasts.¹¹⁶

Like other sites of IP, such as the proximal nail matrix (PNM) or the fetomaternal placental unit, the hair follicle area is characterized by low HLA class I expression; reduced capacity of antigen presentation; expression of local immunosuppressants, such as TGF- β and IL-10 from regulatory T cells; and inhibition of NK cell activities.¹¹⁷⁻¹¹⁹ It might be expected that the absence or low expression of HLA class I in these immunoprivileged sites would allow for NK cell activation because NK cells attack cells with low or absent HLA class I expression, but this is clearly not the case. For example, compared with other regions of the nail epithelium, the PNM contains keratinocytes and melanocytes with significantly downregulated MHC class I expression, whereas HLA-G expression is upregulated. This upregulation, together with the NK-suppressing macrophage migration inhibitory factor (MIF) expressed in PNM, likely serves to inhibit NK cell attack on MHC class I-negative PNM.¹¹⁸ In addition, in the placenta human uterine NK cells remain tolerant at the maternal-fetal interface, probably because of the production of vascular endothelial growth factor. This proangiogenic factor is produced by the uterine NK cells themselves and decreases their cytotoxic activity.¹¹⁹

Multiple samples from normal human scalp show that there is no NK cell attack on normal, HLA-low anagen hair follicles.¹²⁰ In AA lesions CD4⁺ and CD8⁺ T cells are clustered at a high density around the anagen hair bulb. In addition, many perifollicular CD56⁺ NK cells with high expression of the NK cell AR NKG2D are present in atrophic AA lesions but not in normal scalp or scalp from patients with AD.¹²¹ At the same time, the ligand for NKG2D, MICA, was found to be expressed at very high levels in the proximal outer root sheath, the dermal papilla, and the connective tissue sheath of AA hair follicles.¹²² This suggests that the upregulation of MICA in lesional AA enhances the susceptibility of these hair follicles for an attack by NKG2D⁺ NK cells, which can then promote anagen termination and AA progression. IFN- γ is now appreciated as a key cytokine in the pathogenesis of AA, presumably by mediating the collapse of the IP of anagen hair follicles.¹²³ IFN- γ is able to upregulate NKG2D on normal NK cells,¹²² which suggests that this is the reason for the increased expression of the AR NKG2D on NK cells from patients with AA. In peripheral blood NK cells of patients with AA express increased levels of the NK cell ARs NKG2D and NKG2C and reduced expression of the NK IR KIR-2DL2/2DL3 compared with that seen in healthy control subjects or patients with other inflammatory diseases.^{122,124} This suggests that NK cells in patients with AA are considerably more responsive to activating stimuli than those in healthy control subjects. In addition to NK cell receptors and their ligands, MIF, which is normally present in IP areas and can potentially suppress NK cell activity, is also aberrantly expressed in lesional AA.¹²² Whereas normal anagen hair follicles show widespread MIF expression throughout most of the epithelium of normal anagen scalp hair follicles, epithelium of lesional skin AA hair follicles displays reduced or absent MIF expression. Hair follicles in patients with AA might therefore have a decreased capacity to suppress undesired NK cell activity.

In conclusion, as in other IP sites of the human body, the level of NK cell activity in the hair follicle seems to be an important parameter to establish an immunosuppressive environment, a condition that seems to be altered in patients with AA.

NK CELLS AND PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is an autoimmune blistering disease affecting the skin and mucous membranes.¹²⁵ It is mediated by anti-desmoglein 3 autoantibodies capable of directly causing acantholysis in the epidermis.^{125,126}

One study found average NK cell values from patients with PV to be similar to those of healthy donors.¹²⁷ In contrast, Takahashi et al¹²⁵ described a significantly higher percentage and absolute number of NK cells (among total peripheral blood lymphocytes) in patients with PV compared with those seen in healthy control subjects. Moreover, a large fraction of these cells are activated, as demonstrated by the expression of CD69. Although not different in terms of cytotoxic activity, NK cells from patients with PV show reduced levels of mRNA for the IL-12 receptor β 2, perforin, and granzyme B, as well as impaired IL-12 signaling.¹²⁵ In the same study IL-10 production was reduced, but IL-5 mRNA was present in NK cells from patients with active disease.¹²⁵ A possible caveat of these studies is that they explored peripheral blood NK cells, which might not necessarily reflect the situation in the diseased skin.

Stern et al¹²⁶ confirm the activation state of at least a fraction of NK cells from patients with PV expressing *ex vivo* HLA-DR and the costimulatory molecule B7-H3. On coculture of NK cells with

autologous CD4⁺ T cells in the presence of desmoglein 3 peptides, T cells proliferated, suggesting that NK cells from patients with PV can function as antigen-presenting cells. However, no data supporting antigen uptake and processing by NK cells are provided in this article. Thus the exogenous peptides might have bound “externally” to the HLA-DR molecules expressed by NK cells without any processing by the latter. The supernatant of cocultures from patients with active PV contained high levels of IL-6, IL-8, and IFN- γ , which might indicate that the NK cells stimulated the T cells to produce these cytokines, although patients’ NK cells are able to produce the same cytokines.¹²⁶

Overall, peripheral blood NK cells seem to be activated in patients with PV and might contribute to the pathogenesis of the disease by promoting T_H2 responses,¹²⁶ inflammatory cytokine production,¹²⁵ or both. Evidence for an antigen-presenting role of NK cells in patients with PV seems weak and thus requires more investigation.

CONCLUSION

Initially seen merely as primitive killers, NK cells have in recent years been increasingly recognized as a group of immune cells that actively participate in the regulation of both innate and adaptive immunity. Given this physiologic role, it is hardly surprising that NK cells also contribute to pathophysiologic situations of immune deviation.

In skin diseases the role of NK cells is just beginning to be understood. There is, however, good evidence that NK cells contribute in particular to those diseases that are, at least in part, determined by IL-22 and IL-17. Future work will no doubt delineate the contribution of NK cells and their subpopulations to the pathogenesis of AD and psoriasis. Increased NK cell activities constitute key features in the breakdown of areas of relative IP, such as the anagen hair bulb epithelium or the PNM. The restoration of the IP collapse by downregulating the IFN- γ -driven inflammation might be an effective future strategy for the treatment of AA. The involvement of NK cells in patients with PV needs to be confirmed, especially with respect to the question of whether NK cell dysfunctions in the periphery are the cause or consequence of the disease.

REFERENCES

1. Smyth MJ, Hayakawa Y, Takeda K, Yagita H. New aspects of natural-killer-cell surveillance and therapy of cancer. *Nat Rev Immunol* 2002;2:850-61.
2. Carayannopoulos LN, Yokoyama WM. Recognition of infected cells by natural killer cells. *Curr Opin Immunol* 2004;16:26-33.
3. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. *Nat Immunol* 2008;9:503-10.
4. Caligiuri MA. Human natural killer cells. *Blood* 2008;112:461-9.
5. Cooper MA, Colonna M, Yokoyama WM. Hidden talents of natural killers: NK cells in innate and adaptive immunity. *EMBO Rep* 2009;10:1103-10.
6. Poli A, Michel T, Thérésine M, Andr  s E, Hentges F, Zimmer J. CD56bright natural killer (NK) cells: an important NK cell subset. *Immunology* 2009;126:458-65.
7. Moretta A. Natural killer cells and dendritic cells: rendezvous in abused tissues. *Nat Rev Immunol* 2002;2:957-64.
8. Degli-Esposti MA, Smyth MJ. Close encounters of different kinds: dendritic cells and NK cells take center stage. *Nat Rev Immunol* 2005;5:112-24.
9. Yokoyama WM, Kim S, French AR. The dynamic life of natural killer cells. *Ann Rev Immunol* 2004;22:405-29.
10. Martin-Fontecha A, Thomsen LL, Brett S, Gerard C, Lipp M, Lanzavecchia A, et al. Induced recruitment of NK cells to lymph nodes provides IFN- γ for TH1 priming. *Nat Immunol* 2004;5:1260-5.
11. Assarsson E, Kambayashi T, Schatzle JD, Cramer SO, von Bonin A, Jensen P, et al. NK cells stimulate proliferation of T and NK cells through 2B4/CD48 interactions. *J Immunol* 2004;173:174-80.

12. Zingoni A, Sornasse T, Cooks BG, Tanaka Y, Santoni A, Lanier LL. Cross-talk between activated human NK cells and CD4+ T cells via OX40-OX40 ligand interactions. *J Immunol* 2004;173:3716-24.
13. Lanier LL. NK cell recognition. *Annu Rev Immunol* 2005;23:2225-74.
14. O'Connor GM, Hart OM, Gardiner CM. Putting the natural killer cell in its place. *Immunology* 2006;117:1-10.
15. Raulat DH. Roles of the NKG2D immunoreceptor and its ligands. *Nat Rev Immunol* 2003;3:781-90.
16. Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, et al. Activating receptors and coreceptors involved in human natural killer cell-mediated cytotoxicity. *Annu Rev Immunol* 2001;19:197-233.
17. Mandelboim O, Lieberman N, Lev M, Paul T, Arnon TI, Bushkin Y, et al. Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. *Nature* 2001;409:1055-60.
18. Arnon TI, Lev M, Katz G, Chernobrov Y, Porgador A, Mandelboim O. Recognition of viral hemagglutinins by NKp44 but not NKp30. *Eur J Immunol* 2001;31:2680-9.
19. Arnon TI, Achdout H, Levi O, Merkel G, Saleh N, Katz G, et al. Inhibition of the NKp30 activating receptor by pp65 from human cytomegalovirus. *Nat Immunol* 2005;6:515-23.
20. Ferlazzo G, Tsang ML, Moretta L, Melioli G, Steinman RM, Münz C. Human dendritic cells activate resting natural killer (NK) cells and are recognized via the NKp30 receptor by activated NK cells. *J Exp Med* 2002;195:343-51.
21. Brandt CS, Baratin M, Yi EC, Kennedy J, Gao Z, Fox B, et al. The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans. *J Exp Med* 2009;206:1495-503.
22. Fernandez NC, Treiner E, Vance RE, Jamieson AM, Lemieux S, Raulat DH. A subset of natural killer cells achieves self-tolerance without expressing inhibitory receptors for self-MHC molecules. *Blood* 2005;105:4416-23.
23. Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song YJ, Yang L, et al. Licensing of natural killer cells by host major histocompatibility complex class I molecules. *Nature* 2005;436:709-14.
24. Raulat DH, Vance RE. Self-tolerance of natural killer cells. *Nat Rev Immunol* 2006;6:520-31.
25. Anfossi N, André P, Guia S, Falk CS, Roeytynck S, Stewart CA, et al. Human NK cell education by inhibitory receptors for MHC class I. *Immunity* 2006;25:331-42.
26. Anderson SK, Ortaldo JR, McVicar DW. The ever-expanding Ly49 gene family: repertoire and signaling. *Immunol Rev* 2001;181:79-89.
27. Kane KP, Silver ET, Hazes B. Specificity and function of activating Ly-49 receptors. *Immunol Rev* 2001;181:104-14.
28. Perritt D, Robertson S, Gri G, Showe L, Aste-Amezaga M, Trinchieri G. Cutting edge: Differentiation of human NK cells into NK1 and NK2 subsets. *J Immunol* 1998;161:5821-4.
29. Fehniger TA, Shah MH, Turner MJ, Vandeusen JB, Whitman SP, Cooper MA, et al. Differential cytokine and chemokine gene expression by human NK cells following activation with IL-18 or IL-15 in combination with IL-12: implications for the innate immune response. *J Immunol* 1999;162:4511-20.
30. Loza MJ, Zamai L, Azzoni L, Rosati E, Perussia B. Expression of type 1 (interferon gamma) and type 2 (interleukin-13, interleukin-5) cytokines at distinct stages of natural killer cell differentiation from progenitor cells. *Blood* 2002;99:1273-81.
31. Zhou R, Wei H, Tian Z. NK3-like NK cells are involved in protective effect of polyinosinic-polycytidylic acid on type 1 diabetes in nonobese diabetic mice. *J Immunol* 2007;178:2141-7.
32. Zhang C, Zhang J, Tian Z. The regulatory effect of natural killer cells: do "NK-reg cells" exist? *Cell Mol Immunol* 2006;3:241-54.
33. Brillard E, Pallandre JR, Chalmers D, Ryffel B, Radlovic A, Seilles E, et al. Natural killer cells prevent CD28-mediated Foxp3 transcription in CD4+ CD25- T lymphocytes. *Exp Hematol* 2007;35:416-25.
34. Maroof A, Beattie L, Zubairi S, Svensson M, Stager S, Kaye PM. Posttranscriptional regulation of IL10 gene expression allows natural killer cells to express immunoregulatory function. *Immunity* 2008;29:295-305.
35. Deniz G, Erten G, Küçüksezer UC, Kocacik D, Karagiannis C, Aktas E, et al. Regulatory NK cells suppress antigen-specific T cell responses. *J Immunol* 2008;180:850-7.
36. Kheradmand T, Trivedi PP, Wolf NA, Roberts PC, Swanborg RH. Characterization of a subset of bone marrow-derived natural killer cells that regulates T cell activation in rats. *J Leukoc Biol* 2008;83:1128-35.
37. Lo CK, Lam QL, Sun L, Wang S, Ko KH, Xu H, et al. Natural killer cell degeneration exacerbates experimental arthritis in mice via enhanced interleukin-17 production. *Arthritis Rheum* 2008;58:2700-11.
38. Giuliani M, Giron-Michel J, Negrini S, Vacca P, Durali D, Caignard A, et al. Generation of a novel regulatory NK cell subset from peripheral blood CD34+ progenitors promoted by membrane-bound IL-15. *PLoS ONE* 2008;3:e2241.
39. Roy S, Barnes PF, Garg A, Wu S, Cosman D, Vankayalapati R. NK cells lyse regulatory T cells that expand in response to an intracellular pathogen. *J Immunol* 2008;180:1729-36.
40. Colonna M. Interleukin-22-producing natural killer cells and lymphoid tissue inducer-like cells in mucosal immunity. *Immunity* 2009;31:15-23.
41. Zenewicz LA, Flavell RA. IL-22 and inflammation: leukin' through a glass onion. *Eur J Immunol* 2008;38:3265-8.
42. Roark CL, Simonian PL, Fontenot AP, Born WK, O'Brien RL. $\gamma\delta$ T cells: an important source of IL-17. *Curr Opin Immunol* 2008;20:353-7.
43. Benghiet FS, Charbonnier LM, Vokaer B, De Wilde V, Le Moine A. Interleukin 17-producing T helper cells in alloimmunity. *Transplant Rev* 2009;23:11-8.
44. Louten J, Boniface K, de Waal Malefyt R. Development and function of T_H17 cells in health and disease. *J Allergy Clin Immunol* 2009;123:1004-11.
45. Hanna J, Gonen-Gross T, Fitchett J, Rowe T, Daniels M, Arnon TI, et al. Novel APC-like properties of human NK cells directly regulate T cell activation. *J Clin Invest* 2004;114:1612-23.
46. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. *Nat Immunol* 2006;7:507-16.
47. Sun JC, Beilke JN, Lanier LL. Adaptive immune features of natural killer cells. *Nature* 2009;457:557-61.
48. Cooper MA, Elliott JM, Keyel PA, Yang L, Carrero JA, Yokoyama WM. Cytokine-induced memory-like natural killer cells. *Proc Natl Acad Sci U S A* 2009;106:1915-9.
49. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
50. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121:1337-43.
51. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007;39:650-4.
52. Akkoc T, de Koning PJ, Ruckert B, Barlan I, Akdis M, Akdis CA. Increased activation-induced cell death of high IFN- γ -producing T(H)1 cells as a mechanism of T(H)2 predominance in atopic diseases. *J Allergy Clin Immunol* 2008;121:652-8, e1.
53. von Bubnoff D, Geiger E, Bieber T. Antigen-presenting cells in allergy. *J Allergy Clin Immunol* 2001;108:329-39.
54. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for the upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol* 2009;123:1244-52, e2.
55. Koga K, Kabashima K, Shiraishi N, Kobayashi M, Tokura K. Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol* 2008;128:2625-30.
56. Toda M, Leung DY, Molet S, Boguniewicz M, Taha R, Christodoulouopoulos P, et al. Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol* 2003;111:875-81.
57. Oyoshi MK, He R, Kumar L, Yoon S, Geha RS. Cellular and molecular mechanisms in atopic dermatitis. *Adv Immunol* 2009;102:135-226.
58. Wollenberg A, Klein E. Current aspects of innate and adaptive immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 2007;33:35-44.
59. Wollenberg A, Kraft S, Hanau D, Bieber T. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. *J Invest Dermatol* 1996;106:446-53.
60. Wollenberg A, Mommaas M, Oppel T, Schottdorf EM, Günther S, Moderer M. Expression and function of the mannose receptor CD206 on epidermal dendritic cells in inflammatory skin diseases. *J Invest Dermatol* 2002;118:327-34.
61. Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, et al. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. *Nat Genet* 2009;41:602-8.
62. Kerschenlohr K, Decard S, Przybilla B, Wollenberg A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol* 2003;111:869-74.
63. Novak N, Valenta R, Bohle B, Laffer S, Haberstok J, Kraft S, et al. Fc ϵ RI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. *J Allergy Clin Immunol* 2004;113:949-57.
64. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)17, T(H)1 and T(H)2 cells. *Nat Immunol* 2009;10:864-71.
65. Duhon T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. *Nat Immunol* 2009;10:857-63.

66. Nogral KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Farínas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008;159:1092-102.
67. Howell MD, Wollenberg A, Gallo RL, Flaig M, Streib JE, Wong C, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 2006;117:836-41.
68. Kisich KO, Carspecken CW, Fieve S, Boguniewicz M, Leung DY. Defective killing of *Staphylococcus aureus* in atopic dermatitis is associated with reduced mobilization of human beta-defensin-3. *J Allergy Clin Immunol* 2008;122:62-8.
69. Rieg S, Steffen H, Seeber S, Humeny A, Kalbacher H, Dietz K, et al. Deficiency of dermicidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo. *J Immunol* 2005;174:8003-10.
70. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007;25:821-52.
71. Eyerich K, Foerster S, Rombold S, Seidl HP, Behrendt H, Hofmann H, et al. Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. *J Invest Dermatol* 2008;128:2640-5.
72. Luci C, Reyniers A, Ivanov I, Cognet C, Chiche L, Chasson L, et al. Influence of the transcription factor RORgammaT on the development of NKp46+ cell populations in gut and skin. *Nat Immunol* 2009;10:75-82.
73. Satoh-Takayama N, Vossheerich CA, Lesjean-Potier S, Sawa S, Lochner M. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. *Immunity* 2008;29:958-70.
74. Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009;457:722-5.
75. Vivier E, Spits H, Cupedo T. Interleukin-22-producing innate immune cells: new players in mucosal immunity and tissue repair? *Nat Rev Immunol* 2009;9:229-34.
76. Buentke E, Heffler LC, Wilson JL, Wallin RP, Lofman C, Chambers BJ, et al. Natural killer and dendritic cell contact in lesional atopic dermatitis skin—*Malassezia*-influenced cell interaction. *J Invest Dermatol* 2002;119:850-7.
77. Kawakami Y, Tomimuri Y, Yumoto K, Hasegawa S, Ando T, Tagaya Y, et al. Inhibition of NK cell activity by IL-17 allows vaccinia virus to induce severe skin lesions in a mouse model of eczema vaccinatum. *J Exp Med* 2009;206:1219-25.
78. Shimada Y, Sato S, Hasegawa M, Tedder TF, Takehara K. Elevated serum L-selectin levels and abnormal regulation of L-selectin expression on leukocytes in atopic dermatitis: soluble L-selectin levels indicate disease severity. *J Allergy Clin Immunol* 1999;104:163-8.
79. Homey B, Meller S, Savinko T, Alenius H, Lauerma A. Modulation of chemokines by staphylococcal superantigen in atopic dermatitis. *Chem Immunol Allergy* 2007;93:181-94.
80. Purwar R, Werfel T, Wittmann M. IL-13-stimulated human keratinocytes preferentially attract CD4+CCR4+T cells: possible role in atopic dermatitis. *J Invest Dermatol* 2006;126:1043-51.
81. Campbell DE, Fryga AS, Bol S, Kemp AS. Intracellular interferon-gamma (IFN-gamma) production in normal children and children with atopic dermatitis. *Clin Exp Immunol* 1999;115:377-82.
82. Schmid-Ott G, Jaeger B, Adamek C, Koch H, Lamprecht F, Kapp A, et al. Levels of circulating CD8(+) T lymphocytes, natural killer cells, and eosinophils increase upon acute psychosocial stress in patients with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:171-7.
83. Katsuta M, Takigawa Y, Kimishima M, Inaoka M, Takahashi R, Shiohara T. NK cells and gamma delta+ T cells are phenotypically and functionally defective due to preferential apoptosis in patients with atopic dermatitis. *J Immunol* 2006;176:7736-44.
84. Schuster M, Tschernig T, Krug N, Pabst R. Lymphocytes migrate from the blood into the bronchoalveolar lavage and lung parenchyma in the asthma model of the brown Norway rat. *Am J Respir Crit Care Med* 2000;161:558-66.
85. Walker C, Checkel J, Cammisuli S, Leibson PJ, Gleich GJ. IL-5 production by NK cells contributes to eosinophil infiltration in a mouse model of allergic inflammation. *J Immunol* 1998;161:1962-9.
86. Lambiasi A, Normando EM, Vitiello L, Micera A, Sacchetti M, Perrella E, et al. Natural killer cells in vernal keratoconjunctivitis. *Mol Vis* 2007;13:1562-7.
87. Schmid-Ott G, Jaeger B, Adamek C, Koch H, Lamprecht F, Kapp A, et al. Levels of circulating CD8(+) T lymphocytes, natural killer cells, and eosinophils increase upon acute psychosocial stress in patients with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:171-7.
88. Aktas E, Akdis M, Bilgic S, Disch R, Falk CS, Blaser K, et al. Different natural killer (NK) receptor expression and immunoglobulin E (IgE) regulation by NK1 and NK2 cells. *Clin Exp Immunol* 2005;140:301-9.
89. Koning H, Baert MR, Oranje AP, Savelkoul HF, Neijens HJ. Development of immune functions related to allergic mechanisms in young children. *Pediatr Res* 1996;40:363-75.
90. Liao SY, Liao TN, Chiang BL, Huang MS, Chen CC, Chou CC, et al. Decreased production of IFN gamma and increased production of IL-6 by cord blood mononuclear cells of newborns with a high risk of allergy. *Clin Exp Allergy* 1996;26:397-405.
91. Grégoire C, Chasson L, Luci C, Tomasello E, Geissmann F, Vivier E. The trafficking of natural killer cells. *Immunol Rev* 2007;220:169-82.
92. Kimura K, Isowa T, Matsunaga M, Murashima S, Ohira H. The temporal redistribution pattern of NK cells under acute stress based on CD62L adhesion molecule expression. *Int J Psychophysiol* 2008;70:63-9.
93. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;361:456-509.
94. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med* 2006;3:e297.
95. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol* 2009;129:79-88.
96. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, Morel F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J Immunol* 2005;174:3695-702.
97. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006;203:2271-9.
98. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 2008;128:1207-11.
99. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a Th17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;445:648-51.
100. Boniface K, Blom B, Liu YJ, de Waal Malefyt R. From interleukin-23 to T-helper 17 cells: human T-helper cell differentiation revisited. *Immunol Rev* 2008;226:132-46.
101. Nickoloff BJ. The cytokine network in psoriasis. *Arch Dermatol* 1991;127:871-84.
102. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367-74.
103. Bos JD, de Rie MA, Teunissen MB, Piskin G. Psoriasis: dysregulation of innate immunity. *Br J Dermatol* 2005;152:1098-107.
104. de Cid R, Riveira-Munoz E, Zeeuwen PL, Robarge J, Liao W, Dannhauser EN, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet* 2009;41:211-5.
105. Gilhar A, Ullmann Y, Kerner H, Assy B, Shalaginov R, Serafimovich S, et al. Psoriasis is mediated by a cutaneous defect triggered by activated immunocytes: induction of psoriasis by cells with natural killer receptors. *J Invest Dermatol* 2002;119:384-91.
106. Cameron AL, Kirby B, Fei W, Griffiths CE. Natural killer and natural killer-T cells in psoriasis. *Arch Dermatol Res* 2002;294:363-9.
107. Ottaviani C, Nasorri F, Bedini C, de Pita O, Girolomoni G, Cavani A. CD56brightCD16(-) NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation. *Eur J Immunol* 2006;36:118-28.
108. Cameron AL, Kirby B, Griffiths CE. Circulating natural killer cells in psoriasis. *Br J Dermatol* 2003;149:160-4.
109. Ricciari V, Spadaro A, Parisi G, Taccari E, Moretti T, Bernardini G, et al. Down-regulation of natural killer cells and of gamma/delta T cells in systemic lupus erythematosus. Does it correlate to autoimmunity and to laboratory indices of disease activity? *Lupus* 2000;9:333-7.
110. La Gruta NL, Van Driel IR, Toh BH, Gleeson PA. The role of natural killer cells in the induction of autoimmune gastritis. *Autoimmunity* 2001;34:147-54.
111. Brodin P, Karre K, Hoglund P. NK cell education: not an on-off switch but a tunable rheostat. *Trends Immunol* 2009;30:143-9.
112. Rückert R, Hofmann U, van der Veen C, Bufo-Paus S, Paus R. MHC class I expression in murine skin: developmentally controlled and strikingly restricted intraepithelial expression during hair follicle morphogenesis and cycling, and response to cytokine treatment in vivo. *J Invest Dermatol* 1998;111:25-30.
113. Paus R, Ito N, Takigawa M, Ito T. The hair follicle and immune privilege. *J Invest Dermatol Symp Proc* 2003;8:188-94.
114. Gilhar A, Kalish RS. Alopecia areata: a tissue specific autoimmune disease of the hair follicle. *Autoimmun Rev* 2006;5:64-9.
115. Cetin ED, Savk E, Uslu M, Eskin M, Karul A. Investigation of the inflammatory mechanisms in alopecia areata. *Am J Dermatopathol* 2009;31:53-60.
116. Christoph T, Muller-Rover S, Audring H, Tobin DJ, Hermes B, Cotsarelis G, et al. The human hair follicle immune system: cellular composition and immune privilege. *Br J Dermatol* 2000;142:862-73.
117. Ito T, Ito N, Bettermann A, Tokura Y, Takigawa M, Paus R. Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. *Am J Pathol* 2004;164:623-34.

118. Ito T, Ito N, Saathoff M, Stampachiacchiere B, Bettermann A, Bufone-Paus S, et al. Immunology of the human nail apparatus: the nail matrix is a site of relative immune privilege. *J Invest Dermatol* 2005;125:1139-48.
119. Kalkunte SS, Mselle TF, Norris WE, Wira CR, Sentman CL, Sharma B. Vascular endothelial growth factor C facilitates immune tolerance and endovascular activity of human uterine NK cells at the maternal-fetal interface. *J Immunol* 2009;182:4085-92.
120. Ranki A, Kianto U, Kanerva L, Tolvanen E, Johansson E. Immunohistochemical and electron microscopic characterization of the cellular infiltrate in alopecia (areata, totalis, and universalis). *J Invest Dermatol* 1984;83:7-11.
121. Chiarini C, Torchia D, Bianchi B, Volpi W, Caproni M, Fabbri P. Immunopathogenesis of folliculitis decalvans: clues in early lesions. *Am J Clin Pathol* 2008;130:526-34.
122. Ito T, Ito N, Saathoff M, Hashizume H, Fukamizu H, Nickoloff BJ, et al. Maintenance of hair follicle immune privilege is linked to prevention of NK cell attack. *J Invest Dermatol* 2008;128:1196-206.
123. Freyschmidt-Paul P, McElwee KJ, Hoffmann R, Sundberg JP, Vitacolonna M, Kissling S, et al. Interferon-gamma-deficient mice are resistant to the development of alopecia areata. *Br J Dermatol* 2006;155:515-21.
124. Baadsgaard O, Lindskov R. Circulating lymphocyte subsets in patients with alopecia areata. *Acta Derm Venereol* 1986;66:266-8.
125. Takahashi H, Amagai M, Tanikawa A, Suzuki S, Ikeda Y, Nishikawa N, et al. T helper type 2-biased natural killer cell phenotype in patients with pemphigus vulgaris. *J Invest Dermatol* 2007;127:324-30.
126. Stern JNH, Keskin DB, Barteneva N, Zuniga J, Yunis EJ, Ahmed AR. Possible role of natural killer cells in pemphigus vulgaris—preliminary observations. *Clin Exp Immunol* 2008;152:472-81.
127. Alecu M, Ursaciuc C, Surcel M, Coman G, Ciotaru D, Dobre M. CD28 T-cell costimulatory molecule expression in pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2009;23:288-91.

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