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Skin immune sentinels in health and disease

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Abstract

Human skin and its immune cells provide essential protection of the human body from injury and infection. Recent studies reinforce the importance of keratinocytes as sensors of danger through alert systems such as the inflammasome. In addition, newly identified $CD103^+$ dendritic cells are strategically positioned for cross-presentation of skin-tropic pathogens and accumulating data highlight a key role of tissue-resident rather than circulating T cells in skin homeostasis and pathology. This Review focuses on recent progress in dissecting the functional role of skin immune cells in skin disease.

The skin, as the primary interface between the body and the environment, provides a first line of defence against microbial pathogens and physical and chemical insults. Immunosurveillance of such a large and exposed organ presents unique challenges for immune sentinels and effector cells. If an immune response is inadequate then overwhelming infections or tumours may ensue, but if an immune response is excessive then chronic inflammation and autoimmunity may develop. Controlling the extent of an immune response is thus a major challenge for maintaining skin integrity, which is of paramount importance for host survival. Therefore, both active defence mechanisms and tolerogenic pathways are used by the host to achieve immune homeostasis, ensuring that immune responses in the skin are properly adjusted to various challenges.

Owing to its accessibility, the skin is an ideal organ system in which to study both tissue and whole-organism responses to local and systemic insults. A growing body of data supports the notion that the skin has essential immunological functions, both during tissue homeostasis and in various pathological conditions.

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DATABASES

UniProtKB: http://www.uniprot.org

ASC | caspase 1 | caspase 8 | CCL20 | CCR2 | CCR10 | CD1a | CD1c | CD1d | CD14 | CD16 | CD83 | CD103 | CD115 | CD163 | CD206 | CTGF | CX_3CR1 | CXCL1 | CXCL8 | CXCL9 | CXCL10 | CXCL11 | CYP27B1 | DC-SIGN | EPCAM | factor XIIIa | FGF9 | IFNγ | IGF1 | IL-1α | IL-1β | IL-1F6 | IL-4 | IL-6 | IL-10 | IL-17A | IL-18 | IL-22 | iNOS | JUN | JUNB | KGF | langerin | LL37 | LRP1 | LY6C | LY6G | MICA | MICB | NKG2D | NLRP3 | RAE1α | TLR1 | TLR2 | TLR3 | TLR4 | TLR5 | TLR6 | TLR7 | TLR9 | TNF

FURTHER INFORMATION

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Although early studies highlighted individual cell types in the skin, it was the visionary concept of the skin-associated lymphoid tissue (SALT), first described by Streilein in 1983 (REF. [1]), and later the 'skin immune system' (REF. [2]) that provided a modern interpretation and overall paradigm for investigators interested in cutaneous immunology. The initial SALT concept introduced the idea of distinct circuiting immune cells that continually traffic in a directed manner between the skin, the draining lymph nodes and the circulation, thereby providing optimal immunosurveillance.

Although considerable attention was directed at the function of epidermal Langerhans cells[3], it became apparent that other types of dendritic cells (DCs) and innate immune cells present in the dermis also have a relevant role, resulting in the emergence of the concept of a 'dermal immune system' (REF. [4]). Human skin has two main compartments: the epidermis and the dermis (FIG. 1). The epidermis is the outer compartment and contains four strata. The stratum basale is the bottom layer of the epidermis and is responsible for constantly renewing the cells of the epidermis. This layer contains just one row of undifferentiated epidermal cells, known as basal keratinocytes, that divide frequently. Basal keratinocytes differentiate and move to the next layer (the stratum spinosum; also known as the prickle cell layer) to begin a maturation process, but also divide to replenish the basal layer. Cells that move into the stratum spinosum change from being columnar to being polygonal in shape and start to synthesize keratins that are distinct from the basal-layer keratins. Keratinocytes in the stratum granulosum are characterized by dark clumps of cytoplasmic material and these cells actively produce keratin proteins and lipids. The stratum corneum, as the ultimate product of maturing keratinocytes, is the outermost of the four strata of the epidermis and is largely responsible for the barrier function of the skin. Cells in this layer, known as corneocytes, are dead keratinocyte-derived cells that are devoid of organelles. They provide the barrier that excludes many toxic agents and prevents dehydration[5]. Specialized cells of the epidermis include melanocytes, which produce the pigment melanin, and Langerhans cells, which are the main skin-resident immune cell. In addition, T cells, mainly $CD8^+$ T cells, can be found in the stratum basale and stratum spinosum[6].

Langerhans cell

A type of dendritic cell that is resident in the epidermal layer of the skin.

Keratinocytes

The major cell type of the epidermis, constituting more than 90% of epidermal cells. Keratinocytes form an effective barrier against the entry of foreign matter and infectious agents into the body and minimize moisture loss.

The epidermis has a simple histology, but the underlying dermis is anatomically more complicated, with greater cell diversity. It contains many specialized immune cells, including DCs, $CD4^+$ T helper (T_H) cells, γδ T cells and natural killer T (NKT) cells. Moreover, macrophages, mast cells, fibroblasts and nerve-related cell types are also present (FIG. 1). The dermis is drained by lymphatic and vascular conduits, through which migrating cells can traffic[4].

In this review, we focus on new concepts relating to the main skin cell types that have immunological functions and act as immune sentinels. We discuss previously unappreciated roles of tissue-resident epithelial and immune cells in tissue homeostasis and pathology.

γδ T cells

T cells that express heterodimers consisting of the γ- and δ-chains of the T cell receptor (TCR). They enter tissues such as the gut and skin without priming in lymphoid tissues, express limited or invariant TCRs and display a 'pseudo-memory' T cell phenotype allowing them to respond rapidly to antigen challenge.

Keratinocytes as immune sentinels

Similar to gut epithelial cells, keratinocytes can sense pathogens and mediate immune responses to discriminate between harmless commensal organisms and harmful pathogens. Eukaryotic cells sense microbial products using receptors that recognize various evolutionarily conserved microbial components termed pathogen-associated molecular patterns (pAMps), which include lipopolysaccharide (LpS), peptidoglycan, flagellin and nucleic acids[7]. The Toll-like receptors (TLRs) are the best studied of these receptors and ligation of TLRs by pAMps leads to the activation of host cell signalling pathways and subsequent innate and adaptive immune responses. Epidermal keratinocytes express several TLRs, located either on the cell surface (TLR1, TLR2, TLR4, TLR5 and TLR6) or in endosomes (TLR3 and TLR9)[8] (FIG. 2). In addition, TLR7 expression is induced through triggering of TLR3 by double-stranded RNA, which makes keratinocytes responsive to TLR7 agonists of the imidazoquinoline antiviral immune response modifier family[9]. TLR expression by keratinocytes might be crucial for promoting skin immune responses, as activation of these receptors on human keratinocytes leads to a predominant T_H1-type immune response and to the production of type I interferons (IFNs)[10].

A recently discovered class of proteins that are encoded by the nucleotide-binding domain, leucine-rich repeat-containing (NLR) gene family can also recognize PAMPs and endogenous danger-associated molecular patterns (DAMPs), such as irritants and toxins. Activation of these receptors results in the activation of pro-inflammatory signalling pathways through the inflammasome — a large multiprotein complex formed by an NLR, the adaptor protein ASC (apoptosis- associated speck-like protein containing a caspase recruitment domain) and pro-caspase 1 (REF. [11]). The assembly of the inflammasome leads to the activation of caspase 1, which cleaves pro-interleukin-1β (pro-IL-1β) and pro-IL-18 to generate the active pro-inflammatory cytokines[11]. It has recently been established that ultraviolet (UV) irradiation activates the inflammasome in human keratinocytes[12,13]. In addition, contact sensitizers, such as haptens, applied to the skin induce inflammasome-dependent IL-1β and IL-18 processing and secretion and thus allergic contact dermatitis reactions[14].

Thus, following skin exposure to haptens or high doses of uv irradiation, intracellular sensors contained in the inflammasome complex in keratinocytes are activated, leading to the activation of caspase 1 and to the processing and secretion of key pro-inflammatory cytokines. This in turn results in the activation of tissue-resident immune cells that induce and perpetuate an inflammatory response.

Hapten

A molecule that can bind antibody but is thought not to elicit an immune response itself. Antibodies that are specific for a hapten can be generated when the hapten is chemically linked to a protein carrier that can elicit a T cell response.

Allergic contact dermatitis

A cutaneous inflammatory condition caused by a T cell-mediated hypersensitivity to defined allergens.

β-defensins and cathelicidins

Members of a family of small antimicrobial polypeptides that are abundant in neutrophils and epithelial cells. They contribute to host defence by disrupting the cytoplasmic membrane of microorganisms such as *Escherichia coli* or *Candida albicans*.

Keratinocytes produce innate immune mediators

The production of antimicrobial peptides (AMPs) is an evolutionarily conserved defence mechanism of eukaryotic cells against pathogens. They are produced at damaged epithelium surfaces, where they prevent microbial invasion of the host by direct killing of the pathogen, recruitment of host immune cells and modulation of cytokine production[15,16]. In the skin, keratinocytes are an important source of cationic AMPs, namely β-defensins and cathelicidins. During skin infections, the local production of AMps by keratinocytes can be increased by T cell-derived cytokines. In particular, IL-17A and IL-22, which are produced by T_H17 cells[17], increase AMP production by keratinocytes[18] and are therefore important regulators of skin and mucosal immunity[19], providing a link between keratinocytes and adaptive immune cells. AMPs are also expressed at high levels in the skin of patients with psoriasis, and are thought to be responsible for the lack of skin infection observed in these individuals[20]. Furthermore, it has been suggested that keratinocytes can contribute to the breaking of self tolerance in patients with psoriasis by producing the cathelicidin antimicrobial peptide LL37 (REF. [21]) (see later).

In addition, a link between AMP production, TLR expression and vitamin D has been described: keratinocytes surrounding a wound have increased expression of TLR2, LL37 and 25-hydroxyvitamin D_3 1α hydroxylase (also known as CYP27B1), which converts inactive 25-hydroxyvitamin D_3 ($25(OH)VD_3$) to active 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2VD_3$)[22]. $1,25(OH)_2VD_3$ also acts in synergy with T cell-derived IL-17A to enhance LL37 expression by keratinocytes[23]. Thus, the skin epithelium is an effective cathelicidin-regulating environment that might be dysregulated in diseases with increased IL-17A production, such as psoriasis (see later).

In addition to AMPs, keratinocytes constitutively secrete, or are induced to release, numerous cytokines, including IL-1, IL-6, IL-10, IL-18 and tumour necrosis factor (TNF)[24]. Of particular interest with regard to the skin in health and disease is the production of IL-1 by keratinocytes. IL-1 is a pleiotropic cytokine with a broad range of biological effects, including the activation of T_H cells and DCs and the promotion of B cell maturation and clonal expansion[25]. In healthy skin, keratinocytes constitutively synthesize both pro-IL-1α and pro-IL-1β but cannot process them or secrete them in their active forms. Following exposure to stimuli such as UV irradiation, keratinocytes process and release IL-1β through activation of the inflammasome[12]. Regulation of IL-1α secretion in keratinocytes is less clear. A recent study has shown that loss of caspase 8 leads to the secretion of active IL-1α from a large reservoir of pro-IL-1α in mouse epidermal keratinocytes, suggesting a negative regulatory role for caspase 8 (REF. [26]). A role for IL-1α in skin inflammation is suggested in a transgenic mouse model of IL-1α overexpression by keratinocytes, and these mice have an inflammatory skin phenotype[27]. There are also other IL-1 family members, such as IL-1F6, that have a role in skin immunopathology. Transgenic overexpression of IL-1F6 by keratinocytes led to an inflammatory skin phenotype[28]. In addition, the expression of IL-1F6 was shown to be increased in psoriatic epithelium, suggesting a possible role in the immunopathogenesis of psoriasis. Keratinocytes might also condition DCs to promote a dysregulated immune response, for example through the secretion of thymic stromal lymphopoietin in allergic inflammation[29].

Keratinocytes are also an important source of chemokines and express chemokine receptors, and therefore can modulate an immune response by attracting different cell types into the skin.

By expressing CC-chemokine ligand 20 (CCL20), CXC-chemokine ligand 9 (CXCL9), CXCL10 and CXCL11 activated keratinocytes selectively attract effector T cells to the skin during diseases that are characterized by T cell infiltration, such as psoriasis and cutaneous T cell lymphoma[24]. Activated keratinocytes can also recruit neutrophils to the inflamed epidermis of patients with psoriasis by producing CXCL1 and CXCL8 (also known as IL-8) [24]. Furthermore, keratin ocytes regulate the trafficking of Langerhans cell precursors to the epithelium through the expression of CCL20 (REF. [30]).

So, keratinocytes are pro-inflammatory effector cells that are strategically positioned at the outermost layer of the body to react in a timely fashion to harmful insults by the coordinated production of AMPs, pro-inflammatory cytokines and chemokines.

Keratinocytes as non-professional antigen-presenting cells

Keratinocytes were first shown to express MHC class II molecules in studies of graft-versus-host disease[31], and subsequent studies showed that keratinocytes express MHC class II molecules in several skin disorders characterized by significant T cell infiltrates[31], thus suggesting that they might act as non-professional antigen-presenting cells (APCs). We now know that IFNγ can upregulate MHC class II expression on primary human keratinocytes and keratinocyte cell lines *in vitro*[31].

Keratinocytes generally induce T cell anergy or tolerance rather than T cell activation in certain *in vitro* and *in vivo* models[32]. However, keratinocytes can support superantigen-driven proliferation in resting T cells, indicating that they can provide requisite signals for T cell proliferation[33]. A recent study showed that keratinocytes could induce functional responses in epitope-specific $CD4^+$ and $CD8^+$ memory T cells: they could process peptide antigen and present it to $CD4^+$ T cells, resulting in the production of both T_H1- and T_H2-type cytokines, and could process virally encoded or exogenous peptide and present it to $CD8^+$ T cells, resulting in cytokine production and target cell lysis[34]. Therefore, it seems that although keratinocytes cannot prime naive T cells, they can potentially induce a recall immune response in antigen-experienced T cells.

The emerging view is that keratinocytes display features of APCs with the potential for both antigen-specific tolerization and activation.

Tolerance

Denotes lymphocyte non-responsiveness to antigen, but implies an active process, not simply a passive lack of response.

LL37

A member of the cathelicidin family of antimicrobial peptides. LL37 has been proposed to have a specific role in psoriasis pathogenesis, contributing to breaking the tolerance to self DNA.

Graft-versus-host disease (GVHD)

A disease that results from donor allogeneic T cells that are transferred along with an allograft (such as a bone marrow, liver or gut allograft) attacking target recipient organs or tissues (such as the skin or gut). GVHD occurs in graft recipients that cannot eliminate the host-reactive donor T cells owing to immunosuppression, immunological immaturity or tolerance.

T cell anergy

A state of T cell unresponsiveness to stimulation with antigen. It can be induced by stimulation with a large amount of specific antigen in the absence of the engagement of co-stimulatory molecules.

Keratinocytes as instigators of inflammation

A key insight into the immunological role of keratinocytes came from an analysis of human skin reactions following topical application of contact sensitizers, such as poison ivy, which showed that keratinocytes are activated before T cells enter the skin[35]. This finding, together with those of studies of keratinocyte-derived cytokines[36–38], led to the conclusion that epidermal keratinocytes could function as instigators of cutaneous inflammation.

Studies carried out in mice showed that dysregulation of keratinocyte function can trigger systemic autoimmune responses by lymphocytes. Overexpression of CD40 ligand in keratinocytes led to a greater than 90% reduction in epidermal Langerhans cells and increased dermal DC numbers, suggesting enhanced migration of CD40-activated Langerhans cells[39]. This was associated with massive lymphadenopathy and autoantibody formation, suggesting that lymphocyte tolerance to skin antigens was disrupted. Moreover, mice with targeted deletion of JUN and JUNB (both components of the transcription factor AP1) in keratinocytes spontaneously developed chronic inflammation in the skin and joints, with some features resembling psoriasis and psoriatic arthritis[40]. Targeted inhibition of the nuclear factor-κB (NF-κB) pathway by deleting its crucial regulatory kinase, IκB kinase-β (IKKβ), in keratinocytes also resulted in enhanced cutaneous inflammation[41], which supports the role for NF-κB as a double-edged sword in inflammation[42]. Furthermore, mice with constitutive activation of the transcription factor signal transducer and activator of transcription 3 (STAT3), which is downstream of cytokine receptors such as the IL-23 receptor, in keratinocytes developed a psoriasis-like condition[43]. Thus, genetic alteration of key signalling pathways involved in inflammatory immune responses in keratinocytes can alter skin homeostasis and induce immunopathology.

Alterations in the expression of keratinocyte-derived molecules that are known to activate immune cells may also modulate the threshold for the development of skin tumours. For example, constitutive expression of the natural-killer group 2, member D (NKG2D) ligand retinoic acid early transcript 1 (RAE1) by keratinocytes results in downregulation of the expression of the activating receptor NKG2D on NK cells, γδ T cells and $CD8^+$ αβ T cells. This in turn resulted in defects in NK cell-mediated cytotoxicity and enhanced tumour susceptibility[44]. Moreover, an acute rather than sustained upregulation of RAE1 expression by keratinocytes leads to an inflammatory phenotype that involves the redistribution of γδ T cells and Langerhans cells in the epidermal compartment, followed by an influx of unconventional αβ T cells, suggesting that acute changes in NKG2D ligand expression may initiate a rapid, multifaceted immune response[45].

Remarkably, all of these model systems that target molecular events in keratinocytes result in a phenotype involving both local and distant organs and systemic alterations of immune responses, thus supporting a pivotal role for keratinocytes in modulating systemic immune responses.

Plasmacytoid DC

A dendritic cell (DC) that lacks myeloid markers such as CD11c and CD33 but expresses high levels of HLA-DR and CD123. These cells produce high levels of type I interferon after activation (for example, when stimulated through Toll-like receptors).

Cross-presentation

The initiation of a $CD8^+$ T cell response to an antigen that is not present within antigen-presenting cells (APCs). This exogenous antigen must be taken up by APCs and then re-routed to the MHC class I pathway of antigen presentation.

Birbeck granules

Membrane-bound rod- or tennis racket-shaped structures with a central linear density, found in the cytoplasm of Langerhans cells. Their formation is induced by langerin.

Skin-resident DCs as immune sentinels

Skin DCs can be classified according to their localization in distinct anatomical compartments of the skin: Langerhans cells are the main DC subset in the epidermis, where they constitutively reside in the suprabasal layers and are regularly spaced among keratinocytes, whereas dermal DCs reside in the dermis immediately below the dermal–epidermal junction and are dispersed throughout the whole dermal compartment (FIGS 1,3 and TABLE 1). In addition to their different anatomical locations, different DC types in the skin might have specific functional properties, such as secretion of pro-inflammatory mediators (inflammatory DCs), production of type I IFNs (plasmacytoid DCs (pDCs)) or cross-presentation (CD103 (also known as integrin αe)$^+$ skin DCs). Progress in the field of skin DC research gained momentum when a subset of langerin (also known as CLEC4K and CD207)$^+$ DCs were described in mouse dermis that are clearly distinct from langerin$^+$ Langerhans cells that reside in the epidermis[46–49]. A distinguishing feature of Langerhans cells is the expression of epithelial cell adhesion molecule (EPCAM), which is not expressed by langerin$^+$ dermal DCs[49]. A comprehensive review on Langerhans cells has been recently published[50], and therefore we only briefly discuss the role of Langerhans cells as immune sentinels.

DCs in the epidermis

Langerhans cells are characterized by a special type of intracytoplasmic organelle known as the Birbeck granule. Traditionally Langerhans cells have been distinguished from other cells by the expression of langerin in mice and CD1a in humans[51]. Although they have long been recognized as the prototypic APC in the skin, surprisingly little is known about their function *in vivo*.

Langerhans cells are among the first DCs to come into contact with microbial antigens. *In vitro* studies have shown that Langerhans cells take up and process lipid antigens and microbial fragments for presentation to effector T cells[52]. In addition, human Langerhans cells have been shown to preferentially induce the differentiation of T_H2 cells and can prime and cross-prime naive $CD8^+$ T cells[53]. Although initial evidence pointed to a role for Langerhans cells in cross-presentation *in vivo*[54], recent data suggest that important cross-presenting APCs in the skin are langerin$^+$CD103$^+$ DCs, most likely of dermal origin[55,56].

Given the role of Langerhans cells as the outermost sentinel of the skin immune system, immunoderma tologists have long focused on a potential role for Langerhans cells in the induction of contact hypersensitivity reactions[57]. However, the observation that the removal of Langerhans cells by topical application of steroids resulted in an enhancement rather than a reduction of contact hypersensitivity raised the possibility that Langerhans cells were potential inhibitors of contact hyper sensitivity[58]. More recent data using Langerhans cell-deficient mice indicate that Langerhans cells are indeed dispensable for the induction of certain types of cell-mediated immune responses and may actually dampen inflammation and generate tolerogenic responses[59]. These observations depend on the Langerhans cell ablation model that was used (a detailed discussion can be found elsewhere[50,59]). In the context of infection, *in vivo* studies showed that for cytolytic viruses, such as herpes viruses, langerin$^+$CD103$^+$ DCs

that are not Langerhans cells and that are probably of dermal origin[56] may be the key APC population involved in mounting an immune response[60,61].

An additional epidermal DC subset known as inflammatory dendritic epidermal cells (IDECs), which can be distinguished from Langerhans cells by the expression of the macrophage mannose receptor CD206, is found in the inflamed epidermis of patients with atopic dermatitis[62]. IDECs overexpress high-affinity Fc receptor for Ige (FcεRI), which facilitates their reactivity to IgE-bound allergens, resulting in a pro-inflammatory allergen-specific response[63]. Although IDECs are found in the epidermis, it has been suggested that they are a population of inflammatory DCs that can populate both the epidermis and the dermis[64].

Taken together, these recent insights into the role of epidermal DCs have revealed an unexpected role for Langerhans cells in the induction of tolerance. These findings will require confirmation in further studies, especially for human Langerhans cells, and raise the question of the true role of Langerhans cells in tissue homeostasis and disease.

Contact hypersensitivity

The inflammatory reaction that occurs after the first exposure to a ‘sensitizer’ hapten or antigen. This step requires dendritic cell migration to lymph nodes to prime contact-antigen-specific T cells.

Langerhans cell-deficient mice

Two main Langerhans cell-deficient mouse models have been developed using diphtheria toxin ablation. One model, in which diphtheria toxin receptor is constitutively expressed under the control of the human langerin promoter, shows selective depletion of langerin$^+$ epidermal Langerhans cells. The other model, which uses the mouse langerin promoter, displays conditional depletion of all langerin$^+$ DCs, including Langerhans cells in the epidermis, langerin$^+$ DCs in the dermis and langerin$^+$ DCs in lymph nodes.

DCs and macrophages in the dermis

Dermal DCs migrate rapidly to lymph nodes and colonize micro-anatomical areas in the paracortex of lymph nodes[65]. Recent data from a model of allergic contact dermatitis showed that dermal DCs and not Langerhans cells isolated from draining lymph nodes induced T cell proliferation[66]. On the basis of the discovery of dermal langerin$^+$ DCs some data on the role of Langerhans cells during tissue homeostasis and pathology needed to be revisited[50]. It now seems that in mice the main sub-type of migratory DCs that present antigens from lytic viruses, such as herpes simplex virus (HSV), to CD8$^+$ T cells is dermal langerin$^+$CD103$^+$ DCs[56]. This cell subset has similarities with the mouse CD8$^+$ cross-presenting DCs found in lymphoid organs but is different from langerin$^+$CD103$^-$ Langerhans cells and langerin$^-$ dermal DCs. An additional source of dermal DCs is a population of monocytes that patrol the skin mainly during inflammatory conditions[67,68]. An important role for newly formed monocyte-derived DCs in mouse dermis during infection has been recently described[68].

In humans, several research groups have recently attempted to identify cell surface molecules that can be used to distinguish various DC subsets that reside in the dermis under normal conditions[69–71]. CD1c (also known as BDCA1) is a useful cell surface marker for dermis-based myeloid DCs[69,72,73]. Future studies will show whether the strongly stimulatory CD1a$^+$ subset of dermal CD1c$^+$ DCs in humans corresponds to the CD103$^+$ cross-presenting DC subset that has been described in mouse skin[56,72,74]. Dermal DCs can exist in an immature state with cytoplasmic ruffles and express pathogen recognition receptors such as TLR2, TLR4, CD206 and DC-SIGN (also known as CD209)[75]. More mature dermal DCs have cytoplasmic

veils and express higher levels of co-stimulatory molecules, such as CD83, and lower levels of pattern recognition receptors. Dermal DCs also express low-density lipoprotein-related protein 1 (LRP1; also known as CD91), which functions as a possible heat shock protein recognition receptor[76].

Activated dermal DCs participate in the inflammatory response[64] by secreting cytokines and chemokines to generate a cytokine network. In some instances the cytokine network is beneficial and contributes to the eradication of infectious agents but in other settings it underlies a pathological tissue response with persistent inflammation. Dermal DCs that produce both TNF and inducible nitric oxide synthase (iNOS) are known as IDCs or TIP (TNF- and iNOS-producing) DCs[77,78]. This type of DC has been proposed to have a major role in psoriasis[78].

pDCs are rare in healthy skin but have been implicated in the pathogenesis of systemic lupus erythematosus and psoriasis[79,80]. It has been suggested that in psoriasis early activation of pDCs triggers an innate immune response, followed by the activation of myeloid DCs and adaptive immune responses[81]. Indeed, the cathelicidin LL37 bound to self-DNA fragments released by stressed or dying cells in the skin was shown to trigger TLR9 activation in pDCs, resulting in IFNα production and activation of an adaptive immune response[21]. This study raises the possibility that high levels of cathelicidins in psoriatic skin can break tolerance to self DNA, leading to a sustained activation of pDCs and type I IFN production.

Skin macrophages are predominantly sessile dermal cells but they can migrate to lymph nodes under inflammatory conditions[82]. A recent study of the phenotypic profile of dermal DCs and macrophages in normal human skin identified a population of macrophage-like cells that expressed CD163, a scavenger receptor that is expressed by most tissue macrophages, and factor XIIIa[69], a component of the coagulation cascade with a potential function in wound healing. Insights into potential precursors of tissue-resident macrophages and DCs have been provided by mouse studies that traced the development of these cell types from circulating monocytes during infection. A subset of mouse $CD115^{+}LY6C^{+}LY6G^{+}CCR2^{+}$ inflammatory monocytes differentiates into inflammatory DCs, whereas patrolling $LY6C^{-}LY6G^{-}CX_{3}CR1^{+}$ monocytes differentiate into alternatively activated macrophages[67]. It has been proposed that the human counterparts of these inflammatory monocytes are $CD14^{+}CD16^{-}$ circulating monocytes[67].

There is a diverse range of DCs and macrophages in the dermis that enable highly differential immunological responses. The most recently discovered are dermal $langerin^{+}CD103^{+}$ cross-presenting DCs in mouse skin, which raises important questions about their wider functional role and their human counterpart.

The functional role of skin T cells

Normal healthy skin contains more than 2×10^{10} skin-resident T cells, which is more than twice the total number of T cells in the blood[83]. Although the presence of lymphocytes in normal healthy epidermis has been suspected since 1949 (REF. [84]), these cells received little attention for almost 40 years. In the late 1980s it was shown that normal epidermis harbours a phenotypically heterogeneous population of T cells, most of which are memory $CD8^{+}$ αβ T cells[85,86]. Epidermal T cells are mainly distributed in the basal and suprabasal keratinocyte layer, often in close proximity with Langerhans cells[86]. In the dermis, T cells are preferentially clustered around postcapillary venules and are often situated just beneath the dermal–epidermal junction or adjacent to cutaneous appendages. $CD4^{+}$ and $CD8^{+}$ T cells are present in equal numbers and most are memory T cells that express cutaneous lymphocyte-associated antigen (CLA)[87]. Skin-specific memory T cells gain skin-homing properties after a process known as imprinting, which involves contact with tissue-derived DCs and possibly mesenchymal

cells[88,89]. Vitamin D has been suggested to have a key role in the guidance of memory T cells to the skin through the upregulation of CCR10 expression[90].

Conventional T cells in the skin

The three main types of $CD4^+$ T_H cells — that is, T_H1, T_H2 and T_H17 cells — have been found in the skin during various inflammatory diseases. For example, during infection of the skin with intracellular organisms T_H1 cells producing IFNγ and lymphotoxin are present and activate macrophages to kill intracellular organisms. Traditionally, T_H1 cell responses were associated with autoimmunity and immune-mediated pathologies, such as psoriasis, whereas T_H2 cell responses were linked to allergic diseases, such as asthma and atopic dermatitis. More recently, however, T_H17 cells have been shown to have a potential role in both psoriasis[91] and atopic dermatitis[92], and recent reports have shown that T_H17 cells are essential for the first-line defence against various fungal and bacterial infections[17]. In fact, a severely impaired IL-17-mediated immune response due to genetic defects underlies autosomal-dominant hyper-IgE syndrome and autosomal-recessive susceptibility to mycobacterial disease[93,94] and could also be responsible for chronic mucocutaneous candidiasis[95]. Interestingly, these diseases are characterized by recurrent and persistent infections of the skin and mucosal membranes. As already mentioned, a putative mechanism for host defence against microorganisms involving IL-17 and IL-22 in the skin is the upregulation of AMP production by keratinocytes[18]. Therefore, T_H17 cell-derived cytokines may be seen as a link between immune and epithelial cells that optimizes the host immune response to skin-tropic pathogens. A subset of circulating T cells with skin-homing potential that produce IL-22 but not IL-17 or IFNγ (termed T_H22 cells) has been recently identified[96,97]. pDCs were efficient in generating T_H22 cells in a TNF- and IL-6-dependent manner[96]. T_H22 cells were also identified in skin cell cultures from patients with atopic dermatitis[98]. It will be interesting to further explore the functional role of these cells in conditions of skin pathology and homeostasis.

Alternatively activated macrophage

A macrophage stimulated by interleukin-4 (IL-4) or IL-13 that expresses arginase 1, mannose receptor CD206 and IL-4 receptor-**α**. There may be pathogen-associated molecular patterns expressed by helminths that can also drive alternative activation of macrophages.

Skin-resident T cells as immune sentinels

Initial views of skin immunosurveillance emphasized the importance of immune cells that circulate between skin-draining lymph nodes and peripheral tissue and that can react quickly to antigen challenges[1,99,100]. Recently, however, it has been proposed that skin-resident T cells rather than recruited T cells have a major role in skin immune homeostasis and pathology[81] (FIG. 3). Skin-resident memory T cells are strategically positioned as the first-line defence against secondary antigen challenge and are therefore thought to be important effector cells of tissue pathology.

To assign a role to skin-resident versus circulating T cells in skin pathology, one should consider not only that normal skin contains more than twice as many T cells as the blood but also that 98% of CLA^+ skin-homing lymphocytes in the body reside in the skin under physiological conditions[83]. Studies of skin inflammation have provided evidence supporting a key role for skin-resident memory T cells[101,102]. For example, typical psoriasis lesions developed spontaneously in healthy samples of skin from patients with psoriasis that were grafted onto immunodeficient mice known as AGR mice, which are deficient for type I and type II IFN receptors and recombination activating gene 2 (*Rag2*)[101]. The development of

psoriasis lesions in these immuno-deficient host mice suggests that the skin-resident memory T cells that are present in the graft are sufficient for disease development. In a subsequent study, investigation of the kinetics of T cell expansion showed that an increase in the number of dermal T cells preceded the development of typical psoriatic changes in the epidermis[102]. Progression towards psoriasiform changes took place only when T cells entered the epidermal compartment, implying that T cell activation and expansion preceded epithelium pathology and that crosstalk between intraepithelial T cells and keratinocytes was required for the development of typical skin pathology. Entrance of T cells into the epidermis required the interaction between very late antigen 1 (VLA1; also known as α1β1 integrin) expressed by T cells and collagen IV on the basement membrane, thus providing a key checkpoint for *in situ* migration of tissue-resident T cells.

In addition to the above mentioned human xenotrans-plantation model, convincing evidence supporting and extending the importance of skin-resident memory T cells in mouse skin comes from recent studies focusing on models of HSV infection. Resident memory T cells together with $CD4^+$ T cells were shown to be activated by skin DCs, resulting in the local proliferation of antigen-specific memory $CD8^+$ T cells[103]. In a further study tissue-resident memory T cells were shown to express CD103 and VLA1, to undergo homeostatic proliferation and to provide protection from pathogen challenge[104].

Comparable observations in lung infection models led to the proposal that pathogen-specific recall immune responses involve three phases: a first phase dominated by tissue-resident memory T cells, a second phase that involves nonspecific recruitment of circulating memory T cells and a third phase that follows the migration of antigen-specific DCs to draining lymph nodes 24–72 hours after infection and involves the homing to the skin of pathogen-specific effector T cells previously expanded in draining lymph nodes[105].

Taken together these studies raise important questions about the functional role for tissue-resident memory T cells in controlling localized infection and the role of these cells in inflammatory tissue pathology. A focus on tissue-resident rather than circulating T cells would have major implications for the development of new therapeutics targeted at epithelial inflammatory disorders.

Unconventional T cells in the skin

γδ T cells[106] and NKT cells[107] constitute the majority of unconventional or innate-like T cells (FIG. 4). In the skin, human γδ T cells make up a small proportion of the total T cells in the dermis (2–9%) and the epidermis (1–10%); however, in mice, the $V\gamma5^+$ dendritic epidermal T cells (DETCs) constitute more than 90% of epidermal T cells[108]. DETCs are thought to recognize a specific antigen that is restricted to the epidermis (and thymus) and to downregulate αβ T cell-mediated inflammation, thus contributing to local immune surveillance and immunoregulation[109,110]. In particular, skin-resident γδ T cells that express NKG2D have been linked to the regulation of skin cancer. Engagement of NKG2D by one of its several identified ligands, including MHC class I polypeptide-related sequence A (MICA) and MICB in humans and RAE1α in mice, provides a co-stimulatory function and results in target cell destruction[111]. These ligands are upregulated during cell stress and are expressed by various tumour cells, including melanoma cells[112]. Accordingly, mouse γδ T cells have been shown to negatively regulate inflammation as well as carcinogenesis[112,113], whereas αβ T cells promoted skin tumour responses[114].

Less is known about the role of γδ T cells in human skin. They have been shown to be increased in numbers in the skin of patients affected by melanoma, Langerhans cell histiocytosis, skin leishmaniasis, leprosy, psoriasis and chronic cutaneous lupus erythematosus, suggesting their involvement in a wide range of human skin pathologies. It has been proposed that highly

restricted intraepithelial Vδ1 T cells act as immune sentinels by responding to stressed epithelial cells, thus controlling epithelial cell integrity[115]. Moreover, human γδ T cells have been shown to produce growth factors that are important in wound healing, such as connective tissue growth factor (CTGF), fibroblast growth factor 9 (FGF9; also known as GAF), keratinocyte growth factor (KGF) and insulin-like growth factor 1 (IGF1)[116]. Finally, they could contribute to antimicrobial defence by producing certain AMPs, such as cathelicidins[117]. Further studies are required to better elucidate the function of γδ T cells in human skin and their involvement in the immunopathogenesis of skin diseases.

A protective role for invariant NKT cells (iNKT cells) in the skin has been suggested, owing to their ability to recognize bacterial glycolipids and hence serve as antimicrobial immune sentinels[107,118]. iNKT cells, which were identified in psoriatic plaques, might also have a role in tissue pathology as a result of dysregulated immune responses[119]. Although keratinocytes in normal human skin express low levels of CD1d, there is significant induction of expression in psoriatic plaques in which $CD1d^+$ keratinocytes are juxtaposed to the glycolipid-rich stratum corneum[120]. This suggests that self-derived glycolipids presented by CD1d-restricted NKT cells might contribute to keratinocyte activation. Similarly, CD1d expression by iNKT cells is higher in the elicitation sites of allergic contact dermatitis than in normal skin, and iNKT cells have been shown to be, at least in part, the source of the IFNγ and IL-4 that are present in allergic contact dermatitis[121], indicating their contribution to disease onset. Finally, it has been shown that α-galactosylceramide-activated iNKT cells can modulate DC trafficking from the skin to draining lymph nodes by inducing high systemic levels of TNF in a contact hypersensitivity mouse model[122].

Progress in our understanding of unconventional T cells such as γδ T cells and iNKT cells has revealed a key role for such cells in the regulation of both skin inflammation and skin carcinogenesis, raising the question of whether skin-specific ligands and stimuli regulate these cell populations.

Invariant NKT cell

A cell type thought to be particularly important in bridging innate and adaptive immunity. iNKT cells are typified by a capacity for self-recognition and rapid release of cytokines such as interferon-γ.

Dysregulated skin immune responses

Numerous skin disorders, such as psoriasis, atopic dermatitis and contact dermatitis are associated with dysregulation of immune responses in the skin. Key insights into the roles of immune sentinels during a skin immune response have been provided by contact dermatitis models. These include the sentinel role of DCs, the effector role of antigen-specific T cells, the pro-inflammatory role of keratinocytes and the important role of the innate immune system[123–126].

Here we focus on the immunopathogenesis of psoriasis as a model for inflammatory pathology of the skin. Some of the most convincing human skin immunology data are based on psoriasis studies[127]. These studies are of relevance not only to other inflammatory skin disorders but also to many common immune-mediated inflammatory disorders, such as rheumatoid arthritis or Crohn's disease owing to shared genetic variants, immunological pathways and therapeutic targets with psoriasis.

Psoriasis is a lifelong inflammatory skin disease characterized by sharply demarcated, scaly, erythematous plaques. Effector cells of the innate immune system, such as keratinocytes, pDCs

and iNKT cells, and innate inflammatory mediators, such as LL37 and type I IFNs, have been shown to have a role in the pathogenesis of psoriasis[21,80]. In addition, a large body of clinical[128] and experimental[101,129] evidence supports the idea that T cells have an essential role in psoriasis. Consistent with other autoimmune-type diseases, psoriasis has been traditionally considered a T_H1-type disease[130]. Some reports have also suggested the presence of activated autoreactive T cells in psoriasis[131].

The current view of psoriasis pathogenesis proposes that a combination of environmental and genetic factors confers susceptibility to the disease and that a dysregulated immune response leads to a series of linked cellular changes in the skin[127,132]. An important genetic component of psoriasis susceptibility is the *PSORS1* locus, which is located in the MHC region on chromosome 6p21 (REF. [133]). In addition, genome-wide association studies have implicated a further ten psoriasis-associated gene variants[127]. These psoriasis-associated genes function in various biological pathways, including epidermal cell differentiation[134], NF-κB signalling[135] and T_H2-type responses[135]. Interestingly, variants in the T_H17 cell-associated genes *IL23A*, *IL12B* and *IL23R*[135–137] have been associated with psoriasis susceptibility, supporting experimental and clinical data linking T_H17 cells to psoriasis pathogenesis[91,138]. Current models of immuno-pathogenesis (FIG. 5) focus on a scenario in which pDCs are activated by LL37–self DNA complexes and T_H1 and T_H17 cells interact with skin-resident dermal DCs, contributing to a psoriatic phenotype. In the dermis, IL-12 and IL-23 secreted by dermal DCs can induce the activation of T cells that release pro-inflammatory T_H1- and T_H17-type cytokines. In the epidermis, $VLA1^+CD8^+$ T cells also contribute to disease pathogenesis, for example by producing IFNγ[102]. The resulting cytokine milieu of IFNγ, TNF, IL-17A and IL-22 affects keratinocytes, increasing their proliferation and stimulating the production of pro-inflammatory mediators and AMPs, which in turn sustains and amplifies the chronic inflammatory disease process.

Conclusions and future directions

Studies of skin immune sentinels have made considerable progress since the early days when the skin was considered purely a passive protective shield. Studies of epidermal cells have unveiled unexpected immuno logical sentinel functions of keratinocytes. Essential roles for skin DCs in cross-presentation of pathogen-derived antigens and a new role for tissue-resident T cells in maintaining skin homeostasis are gaining support. Progress in understanding the role of immune sentinels will depend on our ability to answer key questions such as how to transfer insights from mouse model systems into translational research studies focusing on human pathology and ultimately how to develop new therapeutics targeting human skin immune sentinels.

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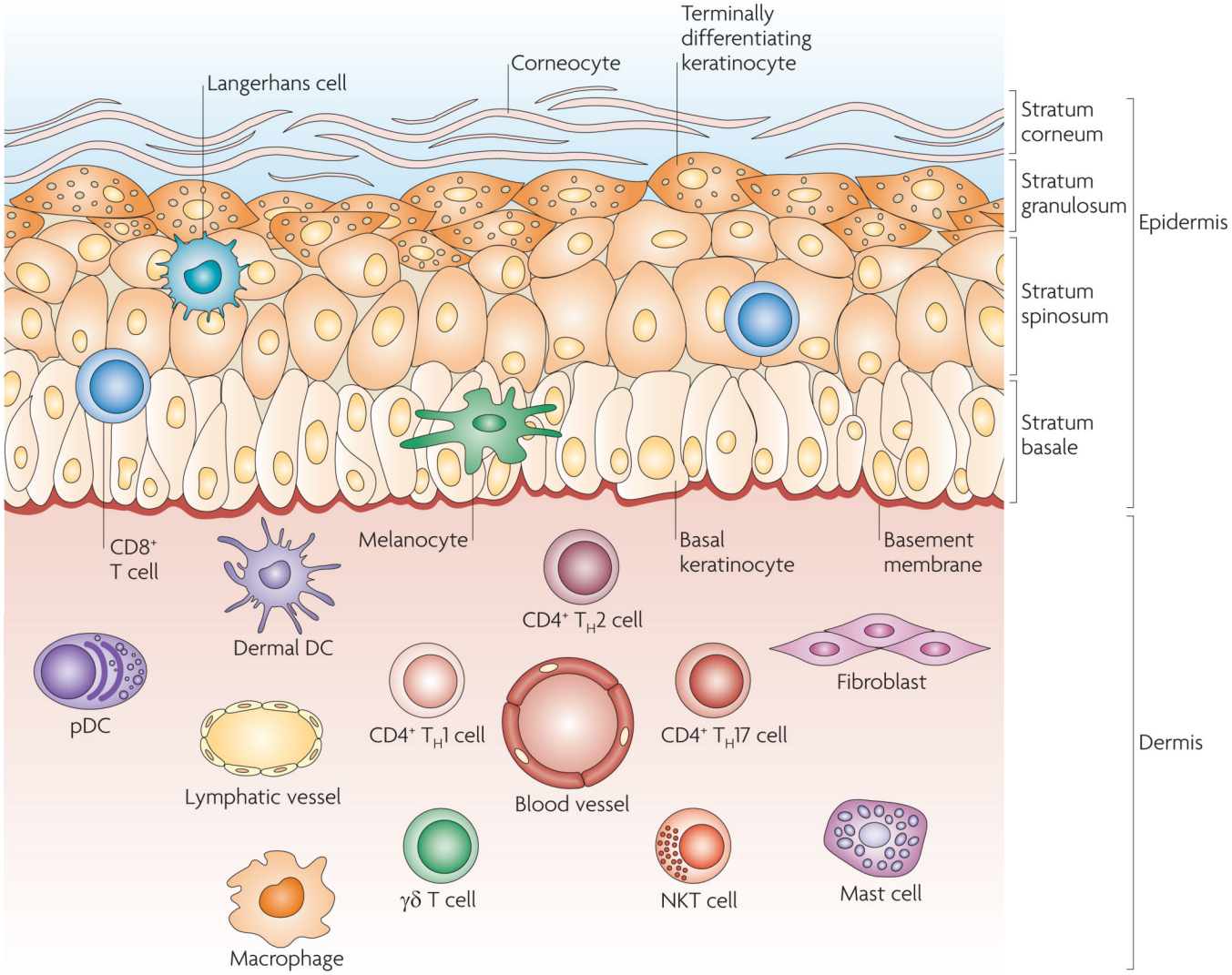

Figure 1. Skin anatomy and cellular effectors

The structure of the skin reflects the complexity of its functions as a protective barrier, in maintaining the body temperature, in gathering sensory information from the environment and in having an active role in the immune system. The epidermis contains the stratum basale, the stratum spinosum, the stratum granulosum and the outermost layer, the stratum corneum, which is responsible for the vital barrier function of the skin. Specialized cells in the epidermis include melanocytes, which produce pigment (melanin), and Langerhans cells. Rare T cells, mainly $CD8^+$ cytotoxic T cells, can be found in the stratum basale and stratum spinosum. The dermis is composed of collagen, elastic tissue and reticular fibres. It contains many specialized cells, such as dendritic cell (DC) subsets, including dermal DCs and plasmacytoid DCs (pDCs), and T cell subsets, including $CD4^+$ T helper 1 (T_H1), T_H2 and T_H17 cells, γδ T cells and natural killer T (NKT) cells. In addition, macrophages, mast cells and fibroblasts are present. Blood and lymphatic vessels and nerves (not shown) are also present throughout the dermis.

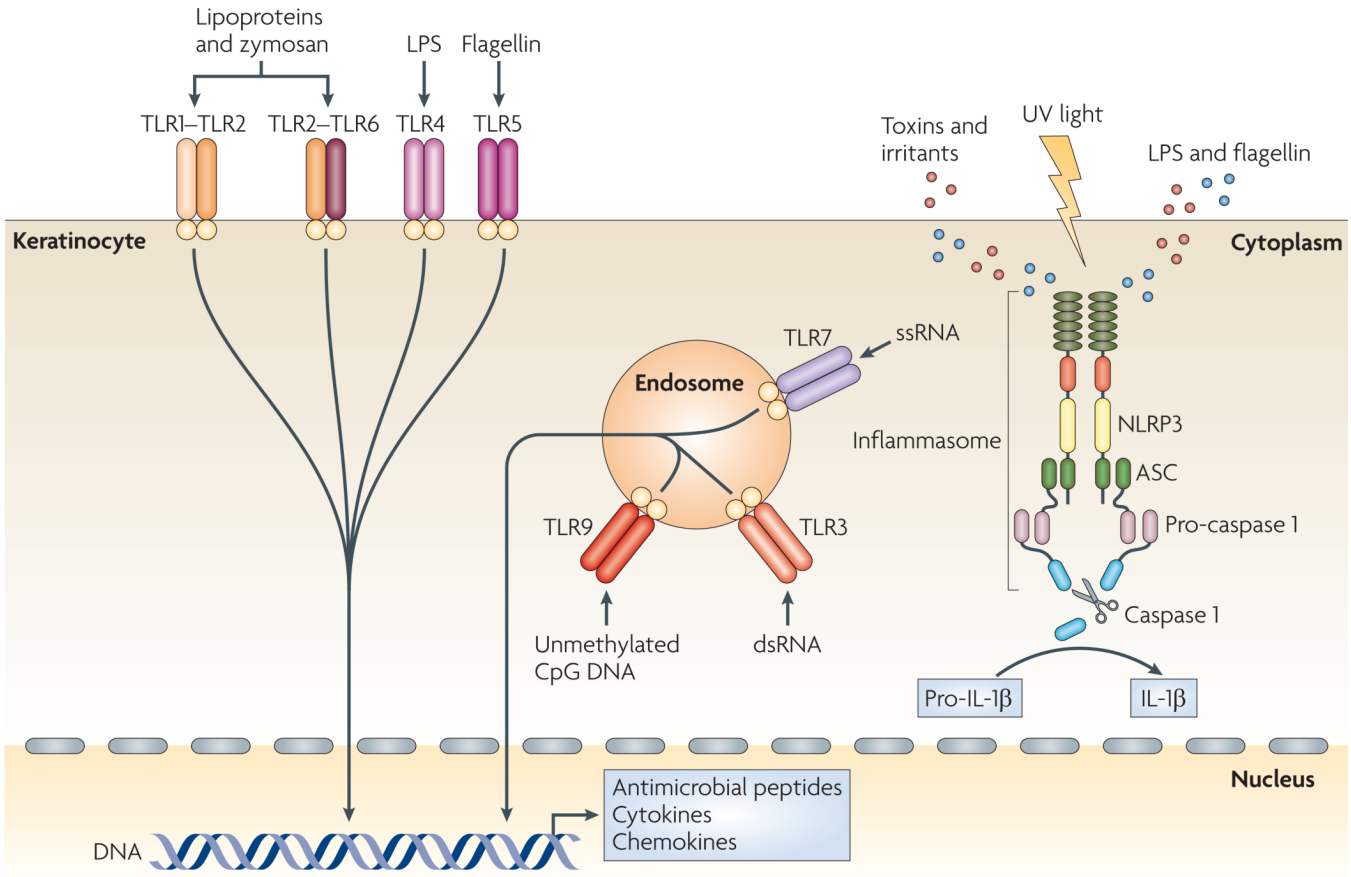

Figure 2. Keratinocytes as sensors of danger

Keratinocytes are central skin sentinels and can recognize foreign and dangerous agents, for example pathogen-associated molecular patterns (PAMPs) of microbial origin and danger-associated molecular pattern (DAMPs), such as irritants and toxins, through Toll-like receptors (TLRs) and the inflammasome machinery. TLRs are transmembrane receptors that are present on the cell surface or on the surface of endosomal compartments. Lipopolysaccharide (LPS) stimulates TLR4; bacterial lipoproteins and fungal zymosan stimulate TLR1–TLR2 and TLR2–TLR6 heterodimers; bacterial flagellin activates TLR5; unmethylated CpG motifs present in DNA function as stimulators of endosomal TLR9; double-stranded RNA (dsRNA) activates endosomal TLR3; and single-stranded RNA (ssRNA) activates TLR7, the expression of which is induced by TLR3 triggering (not shown). PAMP recognition by TLRs leads to activation of host cell signalling pathways and subsequent innate and adaptive immune responses with antimicrobial peptide, cytokine and chemokine production. Keratinocytes also express NLR family, pyrin domain containing 3 (NLRP3), which belongs to the newly identified class of proteins encoded by the nucleotide-binding domain, leucine-rich repeat-containing (NLR) gene family. These proteins can recognize PAMPs that are in the cytoplasm (such as LPS and flagellin), DAMPs and ultraviolet (UV) light, and activate the inflammasome complex. This multimeric complex is formed by an NLR, an adaptor protein termed ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and pro-caspase 1, and its assembly leads to the activation of caspase 1, which processes pro-interleukin-1β (pro-IL-1β) into biologically active IL-1β.

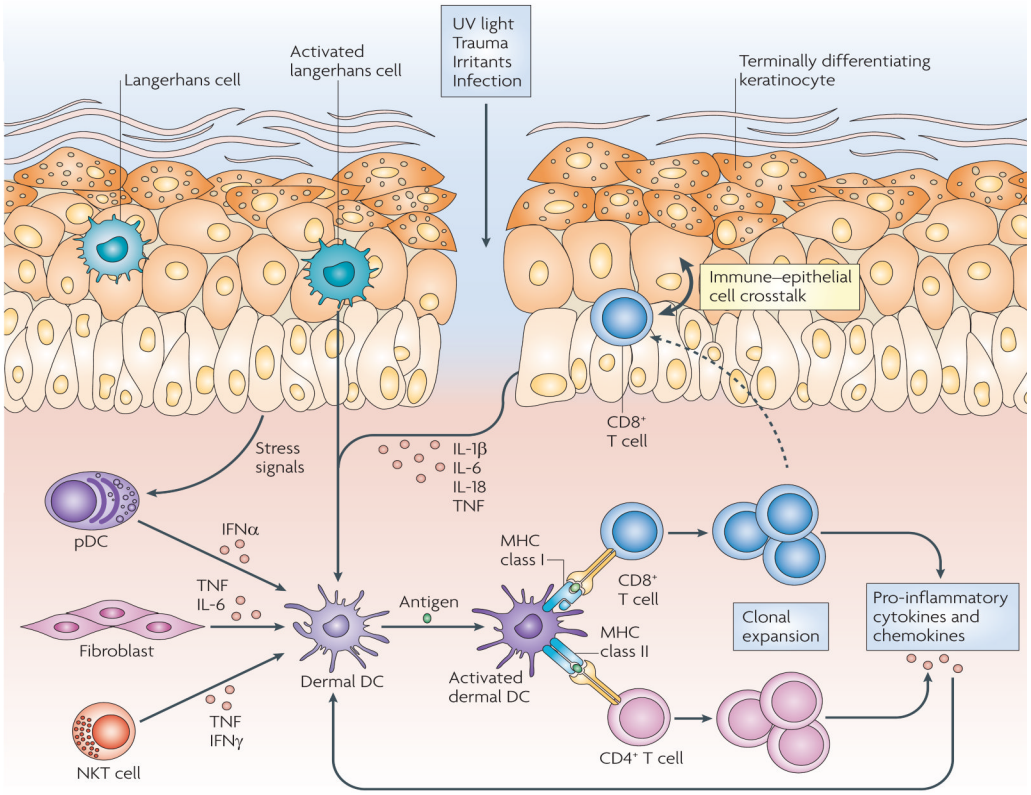

Figure 3. Skin-resident immune sentinels

Ultraviolet (UV) light, trauma, irritants or infection (essentially any type of barrier disruption) triggers a coordinated immune response to maintain skin homeostasis. Skin-resident immune cells are key sentinels for restoring homeostasis but can also be effector cells during tissue pathology. Epidermal Langerhans cells are key immunological sentinels. Keratinocytes sense and react to noxious stimuli by producing pro-inflammatory cytokines (such as interleukin-1β (IL-1β), IL-6, IL-18 and tumour necrosis factor (TNF)), which in turn activate dermal dendritic cells (DCs) in the presence or absence of antigen encounter. Innate immune cells, such as plasmacytoid DCs (pDCs), activated by stress signals derived from keratinocytes, can also contribute to dermal DC activation by releasing interferon-α (IFNα). Fibroblasts can produce TNF and IL-6 and natural killer T (NKT) cells can produce TNF and IFNγ, thereby contributing to the local inflammatory response. Dermal DCs activate and promote the clonal expansion of skin-resident memory $CD4^+$ or $CD8^+$ T cells. T cell-derived pro-inflammatory cytokines and chemokines in turn can further stimulate epithelial and mesenchymal cells, including keratinocytes and fibroblasts, thus amplifying the inflammatory reaction. Moreover, skin-resident T cells can migrate into the epidermis, engaging in an immune–epithelial cell crosstalk.

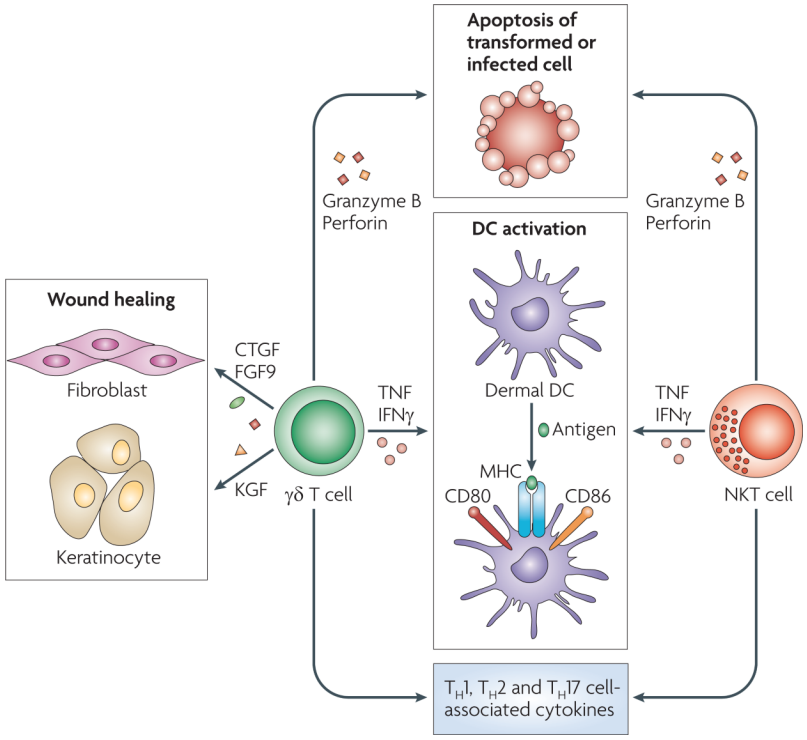

Figure 4. Unconventional T cells in the skin

Unconventional T cells, such as γδ T cells and natural killer T (NKT) cells, are involved in skin immunosurveillance. Both γδ T cells and NKT cells are cytolytic and release granzyme B and perforin and cause apoptosis of transformed or infected cells. They activate dermal dendritic cells (DCs) by producing tumour necrosis factor (TNF) and interferon-γ (IFNγ). Moreover, γδ T cells produce growth factors that are essential for wound healing, such as connective tissue growth factor (CTGF), fibroblast growth factor 9 (FGF9; also known as GAF) and keratinocyte growth factor (KGF). Finally, both γδ T cells and NKT cells produce cytokines that are usually associated with T helper 1 (T_H1), T_H2 and T_H17 cells.

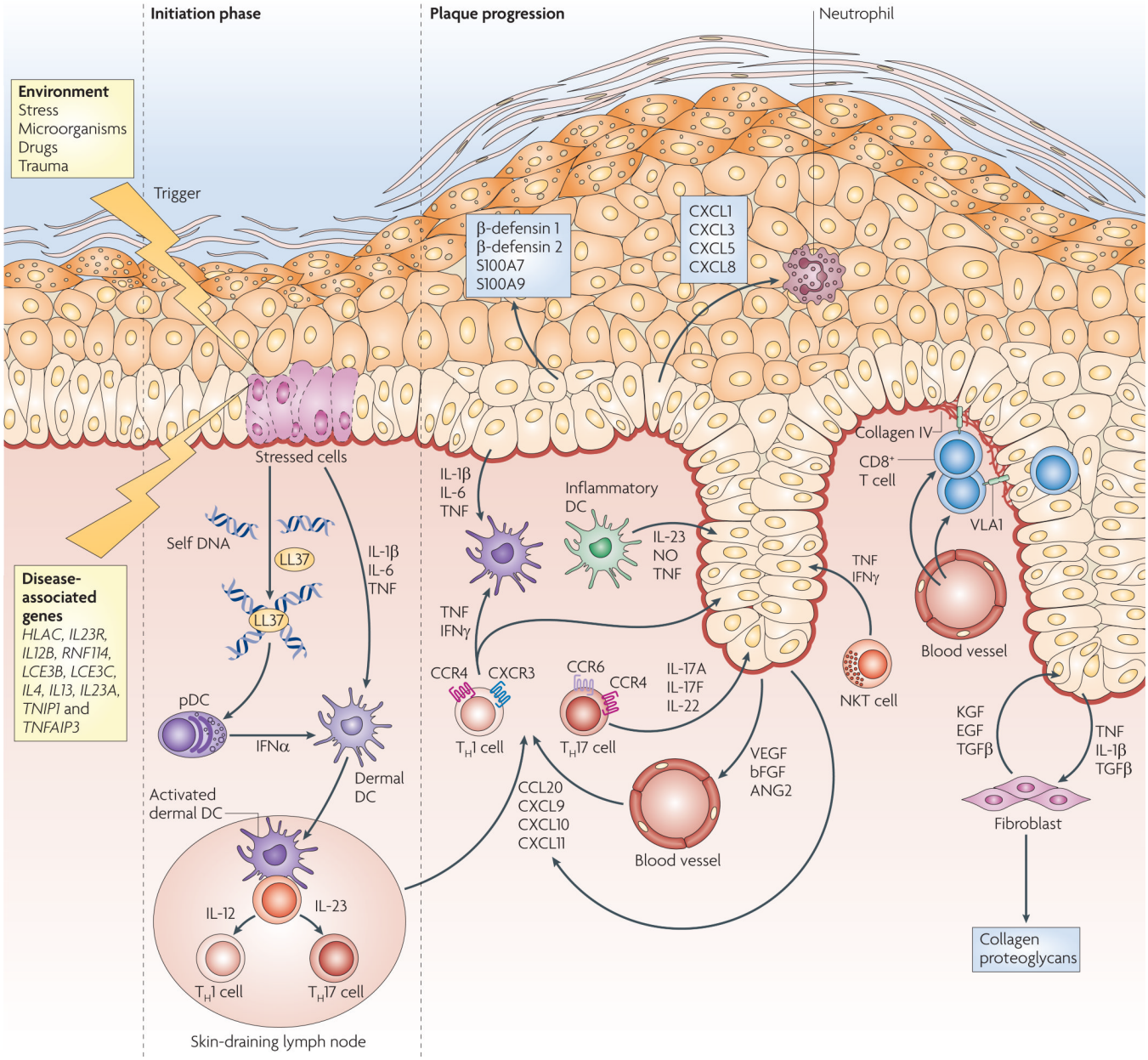

Figure 5. Psoriasis immunopathogenesis

Environmental factors trigger psoriasis in genetically predisposed individuals carrying susceptibility alleles of disease-associated genes. In the initiation phase, stressed keratinocytes release self DNA that forms complexes with the cathelicidin antimicrobial peptide LL37, which in turn activates plasmacytoid dendritic cells (pDCs) to produce interferon-α (IFNα). Keratinocyte-derived interleukin-1β (IL-1β), IL-6 and tumour necrosis factor (TNF) and pDC-derived IFNα activate dermal DCs. Activated dermal DCs then migrate to the skin-draining lymph nodes to present an as yet unknown antigen (either of self or of microbial origin) to naive T cells and promote their differentiation into T helper 1 (T_H1) and/or T_H17 cells. T_H1 cells (expressing cutaneous leukocyte antigen (CLA; not shown), CXC-chemokine receptor 3 (CXCR3) and CC-chemokine receptor 4 (CCR4)) and T_H17 cells (expressing CLA and chemokine receptors CCR4 and CCR6) migrate via lymphatic and blood vessels into psoriatic dermis, attracted by the keratinocyte-derived chemokines CCL20, CXCL9, CXCL10 and

CXCL11, which ultimately leads to the formation of a psoriatic plaque. T_H17 cells secrete IL-17A, IL-17F and IL-22, which stimulate keratinocyte proliferation and the release of β-defensin 1, β-defensin 2, S100A7 and S100A9 and the neutrophil-recruiting chemokines CXCL1, CXCL3, CXCL5 and CXCL8. Moreover, inflammatory DCs produce IL-23, nitric oxide (NO) radicals and TNF. At the dermo–epidermal junction, memory $CD8^+$ cells expressing very-late antigen-1 (VLA1) bind to collagen IV, allowing entry into the epidermis and contributing to disease pathogenesis. Cross-talk between keratinocytes, producing TNF, IL-1β and transforming growth factor-β (TGFβ), and fibroblasts, which in turn release keratinocyte growth factor (KGF), epidermal growth factor (EGF) and TGFβ, contribute to tissue reorganization and deposition of extracellular matrix (for example, collagen and proteoglycans). Figure is modified, with permission, from REF. [127]

Table 1

Skin dendritic cells and macrophages

Cell types	Location	Main surface markers*	Sentinel role
Langerhans cells	Epidermis	CD1a, CD207 (langerin) and MHC class II	Antigen-presenting role during certain infections and possibly tolerance induction
Inflammatory dendritic epidermal cells	Inflamed epidermis	CD11b, CD23 (FcεRII), CD206 (MMR), FcεRI, IgE and MHC class II	Responds to antibody–allergen complexes in atopic dermatitis
Dermal DCs	Dermis	CD1a^{low}, CD1c (BDCA1), CD206 (MMR), CD209 (DC-SIGN) and MHC class II	Antigen presentation and cytokine and chemokine secretion
Inflammatory DCs (also known as TIP DCs)	Inflamed dermis	CD11c	TNF and nitric oxide production
Macrophages	Dermis	CD163, factor XIIIa, CD16, CD32 and CD64	Antimicrobial activity and production of pro-and anti-inflammatory mediators
Plasmacytoid DCs	Dermis	CD45RA, CD123, CD303 (BDCA2) and MHC class II	IFNα production, functional role in psoriasis and recognition of self-DNA–LL37 complexes

* Alternative protein names are given in brackets. DC, dendritic cell; FcεR, Fc receptor for IgE; IFNα, interferon-α; TIP, TNF- and iNOS-producing; TNF, tumour necrosis factor.