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# Review: Skin and the Immune System

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**Abstract**

The skin immune system comprises a complex network of cells, functioning both in immunity against invading pathogens but also tolerogenic mechanisms to ensure maintenance of immune homeostasis. The nature of antigens present and interplay between the cutaneous innate and adaptive immune systems determine the type of immune response generated. Dendritic cells are the key players in bridging innate and adaptive immune responses due to their inherent plasticity, direct roles in both type of immune responses, and cross-talk with other immune cells. This review dissects the functional roles of components of both innate and adaptive immune systems in the skin, with a special focus on cutaneous dendritic cells as the only cells capable of inducing primary immune responses, their ability to generate either immunogenic or tolerogenic immune responses, and ability to direct effector cells back to the skin via imprinting of skin-homing properties on T-cells. Finally the reciprocal interactions between the skin microbiota and immune system and their role in host defence and disease have been discussed.

## Introduction

The skin is the largest organ in the body. Its primary function is to serve as a barrier protecting the internal organs from physical and chemical attack, invasion of pathogens and excessive water loss. As the primary immunological barrier to the external environment, the skin is rich in immune cells, forming a complex network called the "skin immune system" [1] comprising both innate and adaptive immune cells [2]. The skin is colonized by a diverse milieu of microorganisms [3,4]; reciprocal interactions between the skin microbiota and immune system play a role in determining the nature of immune responses generated in the skin [5-8]. This review highlights recent insights into cells of the skin immune system and interplay between the skin microbiome, the immune system, and cutaneous inflammatory disease.

## The Innate Immune System

The skin has constitutive innate immune mechanisms that help to protect against pathogens. The uppermost layer of the epidermis, the corneal layer, is a unique layer not present in other epithelia exposed to the external environment (such as the gut and lung epithelia) [2,9]. The corneal layer is comprised of dead keratinocytes that provide a physical barrier to the skin [2,9]. Keratinocytes produce antimicrobial peptides (AMPs) in response to infection, including human β-defensins, cathelicidins and RNases [10,11], which can be found in the corneal layer.

Beneath the corneal layer of the epidermis are the granular, spinous and basal layers. These layers consist of keratinocytes expressing pattern recognition receptors (PRRs) which can detect invading microorganisms via pathogen-associated molecular patterns (PAMPs) expressed on the invading microorganism cell surface; this interaction initiates early immune responses in the skin [12]. Dendritic cells (DC) of the epidermis, known as Langerhans' cells (LC) also express PRRs to initiate early immune responses. The underlying dermis is anatomically more complicated, with greater cell diversity. Immune cells present in the dermis also express PRRs for detection of invading pathogens and include DC, macrophages, mast cells, B and T-cells, plasma cells, natural killer (NK) cells, fibroblasts and innate lymphocytes γδ T-cells and invariant natural killer T-cells (iNKT-cells) [2,9]. Although a crucial function of these cells is detection of invading microorganisms via PRRs, another important function is to maintain the balance between the host and the skin microbiome. It has been hypothesised that, perhaps like commensal microbes found in the gastro-intestinal (GI) tract, these skin microbes have a beneficial role in preventing pathogenic microbes from occupying these unique microenvironments [8].

Interaction of innate immune cells or their products influences their function. However for the purpose of this review, for this section we will focus on the functional roles of innate immune cells and their interactions with DC specifically. Although DC have specific innate properties, they are unique in their potency at generating T-cell mediated immune responses and can therefore be thought of as a link between the innate and the adaptive immune systems.

## Dendritic cells

Dendritic cells (DC) are professional antigen-presenting cells, and the main gate-keepers of the immune system. However, in this section we will focus on the innate properties of DC only (see section 3 for adaptive properties of skin DC). DC are mononuclear phagocytes, and act as immune sentinels, patrolling the peripheral tissues for antigens. DC recognize antigen via a diverse array of PRRs that can sense PAMPs on invading pathogens [13,14]. These PRRs recognize a wide range of PAMPs which leads to DC activation [14-16].

In addition to recognizing a wide range of microbial products, innate DC receptors also recognize so-called endogenous ligands from host cellular debris, in particular from injured or dying tissue, termed DAMPs (damage-associated molecular patterns) [17-19]. Therefore, as well as recognizing invading pathogens, DC can also recognize

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a wide range of self-antigens that are released during tissue damage, inflammation, or necrosis, leading to inappropriate activation resulting in sterile inflammation or autoimmune responses [17-20].

DC recognise whether to initiate an immunogenic immune response (to pathogenic antigens) or tolerogenic immune response (to self antigen or commensal microbiota) via antigen recognition involving PAMP recognitions by PRRs and presence of cytokines or other inflammatory/non-inflammatory mediators. There are three subsets of human skin DC in the steady state; Langerhans' cells (LC), dermal DC (dDC) and plasmacytoid DC (pDC) [21].

**Langerhans' cells:** LC are interspersed throughout the epidermis, where they mediate immune surveillance of substances in the external environment that come into contact with the skin. LC are a unique subset of DC, originally identified by their characteristic organelle, the Birbeck granule. The function of the Birbeck granule is unclear, but is likely to include receptor-mediated endocytosis and transport of cellular materials into the extracellular space [22]. LC are now defined by their location in the epidermis, combined with expression of CD207 (langerin) and CD1a [23]. Langerin is a membrane-bound C-type lectin receptor (CLR) [24] that recognises mannosylated ligands (PAMPs) on the surface of a wide range of pathogens, including viruses, bacteria, fungi and protozoa [25]. Upon antigen encounter, receptor-mediated endocytosis by the LC occurs, followed by trafficking of CD1a and langerin to the Birbeck granule where they play a role in antigen processing [26].

Due to their location in the epidermis, LC are in intimate contact with keratinocytes, and are the first DC to come into contact with microbial antigens in the skin. Studies of skin biopsies from atopic dermatitis (AD) patients have demonstrated the presence of DC expressing the high affinity surface receptor for IgE (FcεRI). Engagement of FcεRI on LC promotes the release of chemokines CCL2, CCL17 and CCL22, attracting cells expressing chemokine receptors, and perhaps enhancing allergen presentation to T-cells and supporting Th2 differentiation [27]. However, LC have also been implicated in immune tolerance in the skin. This is partly due to the expression of surface molecules involved in inhibition of T-cell responses such as inducible co-stimulatory molecule ligand ICOS-L or the production of immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO) [28]. There is still significant debate regarding the functional role of LC in humans which will be discussed in further detail in section 3.2.

**Dermal dendritic cells (dDC): myeloid:** Dermal DC (dDC) are considered analogous to interstitial DC found in connective tissue and the stroma of other organs [29-31]. Various DC subsets reside in the dermis in humans; CD1c (BDCA-1) is often used to describe dermis based myeloid DC (mDC) [29,30,32]. dDC can exist in an immature state with cytoplasmic ruffles and express various PRRs [33]. More mature dDC (post-antigen stimulation) have cytoplasmic veils and express higher levels of co-stimulatory molecules such as CD83, and lower levels of PRRs [34] (limiting their involvement in innate immune responses).

Mature dermal mDC rapidly migrate to the skin-draining lymph nodes, to prime T-cell responses [35,36], but activated dDC also participate in the innate immune response by secretion of cytokines and chemokines [37]. Chemokine and cytokine production can be beneficial when responding towards invading pathogens, but can also underlie persistent inflammation in chronic inflammatory disease. Tumour necrosis factor (TNF) and inducible nitric oxide synthase (iNOS) are produced by a subset of dDC called TIP-DC (TNF and iNOS-producing DC) [38,39], and exhibit pro-inflammatory effects in psoriasis [39].

**Dermal dendritic cells: plasmacytoid:** Plasmacytoid DC (pDC) are rare in human skin, but are mainly found in the dermis. pDC express CD123 and BDCA-2, and are $CD11c^-$ [40]. They are mainly characterised by their ability to produce large amounts of type 1 IFN during viral infections, 10,000x more than any other cell type [40,41]. Early activation of pDC triggers an innate immune response via crosstalk with keratinocytes (discussed in more detail in section 2.2) leading to ligation of TLR9 on pDC with resulting IFN-α production [42]. This pathway has been implicated in the pathogenesis of systemic lupus erythematosus and psoriasis [43,44].

## Keratinocytes

Epidermal keratinocytes are pro-inflammatory effector cells strategically positioned at the outermost layer of the body to respond to invading pathogens by coordinated production of anti-microbial peptides (AMPs), proinflammatory cytokines and chemokines. Keratinocytes in the skin are an important source of β-defensins and cathelicidins; local production of AMPs during skin infections can be increased by T-cell derived cytokines, in particular IL-17A and IL-22, which are produced by Th17 cells [45]. Keratinocytes express several PRRs including TLRs [46,47]. TLR expression by keratinocytes may be crucial for promoting skin immune responses; strong TLR activation of keratinocytes leads to polarisation of Th1 responses and production of inflammatory type I interferons (IFNs) [48].

AMPs are expressed at high levels in the skin of psoriasis patients, and thought to be responsible for lack of skin infections in these patients [49]. Keratinocytes can also contribute to loss of immune tolerance to self-antigens in psoriasis patients via production of a cathelicidin AMP called LL37 [42]. In addition to AMPs, keratinocytes constitutively produce numerous cytokines [50] including IL-1, which has a broad range of biological effects [51]. A role for IL-1α in skin disease was suggested by a transgenic mouse model [52], with overexpression of IL-1F6 by keratinocytes leading to skin inflammation [53]. Expression of IL-1F6 was also increased in psoriatic epithelium. Other studies have shown epidermal keratinocytes can instigate cutaneous inflammation [54-57] and that dysregulation of keratinocyte function can trigger systemic autoimmune responses by lymphocytes [58,59].

Keratinocytes also express chemokines and can therefore modulate immune responses by attracting different cell types into the skin e.g. recruitment of effector T-cells during disease characterised by T-cell infiltration such as psoriasis and T-cell lymphoma [50]. Keratinocytes can also recruit neutrophils to the inflamed epidermis, but this property will be discussed in further detail in section 2.2.

**Keratinocyte: DC crosstalk:** Keratinocytes of the skin produce cytokines including IL-1 which has a broad range of biological effects, including DC activation [51]. Keratinocytes may also condition DC to promote a dysregulated immune response, for example, through secretion of thymic stromal lymphopoietin (TSL) in allergic inflammation [60]. Another important function of keratinocytes is their role in the activation and migration of Langerhans' cells (LC). Keratinocytes constitutively express TGFβ, a cytokine indispensable for immigration of LC precursors in the epidermis; the epidermis of TGFβ knockout mice does not contain LC [61]. Immigration of LC precursors into the epidermis induces keratinocytes to secrete MCP-1/CCL2, which constitutively recruits LC (and other DC) to the skin [62]. MCP-1/CCL2 production is increased in psoriatic skin

[9]. Acute upregulation of retinoic acid early transcript 1 (RAE1), expressed on keratinocytes in the skin, leads to inflammation involving redistribution of LC (and γδ T-cells) within the epidermal compartment (via interaction with RAE1 receptor natural killer group 2, member D known as NKG2D on LC), followed by an influx of innate αβ T-cells [63].

Keratinocytes also interact with pDC in the skin; early activation of pDC triggers increased expression of AMP LL37 (cathelicidin) by keratinocytes [64]. Cathelicidin LL37 bound to self-DNA fragments are released from dead/dying keratinocytes and in turn trigger TLR9 activation in pDC, resulting in IFN-α production and activation of adaptive immune responses [42]. Studies have raised the possibility that high levels of cathelicidins expressed by keratinocytes in psoriatic skin can break tolerance to self DNA, leading to sustained activation of pDC and type I IFN production [42].

## Neutrophils

Neutrophils express a variety of PRRs and are a key component of innate immunity and are essential for protection from bacterial infections due to their ability to recognize, phagocytose and ultimately destroy pathogenic organisms [65-68]. The protective role of neutrophils is associated with rapid recruitment to sites of tissue damage and pathogen entry; neutrophil recruitment from the circulation to the skin is mediated by multiple factors, including pro-inflammatory cytokines such as IL-1α, IL-1β, tumour necrosis factor (TNF) and IL-6, and chemokines. Chemokines produced by activated keratinocytes recruit neutrophils to inflamed areas of the skin (e.g. the inflamed epidermis in patients with psoriasis [50]. Adhesion molecules are also required for neutrophil recruitment to the skin; these molecules promote neutrophil rolling, adhesion and diapedesis [69]. Chemokines and adhesion molecules involved in neutrophil recruitment to the skin are summarised in Table 1.

Once neutrophils encounter pathogens in the skin, they use multiple mechanisms to facilitate bacterial killing, including phagocytosis to engulf the bacteria and oxidative burst to generate reactive oxygen species that mediate bacterial killing. They also produce AMPs (such as cathelicidins, lysozyme and α-defensins) that have direct microbicidal activity, and proteinases (such as cathepsin G, neutrophil elastase and proteinase 3/myeloblastin) with acid hydrolases that degrade bacterial components. Neutrophils also express proteins that sequester essential nutrients to limit bacterial growth, including lactoferrin, transcobalamin II, neutrophil gelatinase-associated lipocalin (NGAL) and calpotectin [66,70,71]. Subsequent clearance of recruited neutrophils is then carried out by macrophage/monocyte populations.

A hallmark of *Staphylococcus aureus* infections in the skin is neutrophil abscess formation, which is required for bacterial clearance [72]. Impaired neutrophil function in humans leads to uncontrolled dermal infections caused by group A *Streptococcus* or *Staphylococcus aureus* [73-75], highlighting the importance of neutrophils for immunity in the skin.

**Neutrophil: DC crosstalk:** Neutrophils can induce maturation of DC through contact-dependent interactions involving CD18 and CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) on neutrophils [76-78] and DC-SIGN (DC-specific ICAM3-grabbing non integrin) on DC [77,78]. Neutrophil-matured DC acquire potential to induce T-cell proliferation and polarization towards Th1 responses [76,78], implicating a role for neutrophil: DC crosstalk in inflammatory skin disorders with increased DC-SIGN expression on skin DC, such as psoriasis [79].

## Macrophages

Macrophages are mononuclear phagocytes and are also deemed professional antigen-presenting cells due to their ability to present antigen to T-cells; however, macrophages do not possess the potency of DC to initiate primary immune responses [80-82]. The innate functions of macrophages play a crucial role in human host defence via phagocytosis and clearance of infectious agents by secretion of cytokines and chemokines. Resident macrophages in the skin maintain tissue homeostasis and dampen initiation of inflammation by clearance of allergens, whilst bone marrow-derived monocytes leave the circulation and migrate towards sites of inflammation in the skin where they differentiate into mature macrophages [83].

**Classically activated macrophages:** The biological functions of activated macrophages involve migration to sites of inflammation to encounter pathogens and degrade them; activated macrophages display no enhanced phagocytosis compared to resting cells [84] but they do possess a markedly enhanced ability to kill and degrade intracellular microorganisms via production of toxic intermediates (nitric oxide NO and reactive oxygen intermediates ROI). Macrophages are activated through ligation of PRRs such as TLRs via microbial PAMPs [85,86]; in the classically activated macrophage this involves production of pro-inflammatory cytokines that induce inflammatory cytokine production by T-cells (Table 1) which in turn acts on the macrophage to enhance cytokine secretion, antigen-presentation and bactericidal activity [87,88]. Such cytokine activity is critical for establishment of effective host defence against intracellular pathogens [89]. Classical macrophage activation is characterized by a heightened ability to produce IL-12 and IL-23 [90] and toxic intermediates; these cells are commonly referred to as M1 macrophages (mirroring Th1 nomenclature) [91].

Classically activated macrophages in the dermis display enhanced production of inflammatory cytokines IL-12 and IL-23 in psoriasis (Fuentes- Duculan J; Zaba LC J Invest Dermatol 2010), likely to contribute to the pathogenic inflammation in this disease. However, the pro-inflammatory properties of classically activated macrophages are useful in wound healing; during the short inflammatory stage, classically activated macrophages exert functions like antigen-presentation, phagocytosis and production of inflammatory cytokines and growth factors that facilitate the wound healing process [92].

**Alternatively activated macrophages:** Th2 cytokines IL-4 and IL-13 induce a distinct activation program in macrophages, referred to as "alternately activated macrophages" [93,94]. Alternatively activated macrophages are sometimes referred to as "type II activated macrophages" due to their ability to preferentially induce Th2 responses [95], and are generated upon exposure to *two* signals; a macrophage stimulatory signal which may include TLR signalling or signalling via CD40 or CD44, *and* FcγR ligation by immune complexes (IC) [95,96]. Alternatively activated macrophages exert potent anti-inflammatory effects due to their production of IL-10 [96] and lack of IL-12 production [97]; they have a suppressive effect on T-cell proliferation [98] and inflammatory responses [99]. These cells fail to make toxic intermediates [100] and are therefore compromised in their ability to kill intracellular microbes.

Recent studies on alternatively activated macrophages have focused on their potential to mediate wound-healing, angiogenesis and ECM deposition; these cells produce high levels of fibronectin and matrix-associated protein βIG-H3 [101], promote fibrogenesis from fibroblastoid cells [102] and induction of arginine in these cells may lead to polyamine and proline biosynthesis, promoting cell growth, collagen formation and tissue repair [103]. However, alternatively activated

| Innate cell | PRRs/activating receptors | Products/molecules | Innate function |
|---|---|---|---|
| **DC (general)** | TLRs, CLRs, RLRs, NLRs | Various | Immune sentinels; proinflammatory or anti-inflammatory effects |
| **LC** | Langerin/CD207 (CLR)<br>FcγR and FcεR<br>DEC205 | Chemokines CCL2, CCL17 and CCL22 | Attraction of other leukocytes to sites of inflammation |
| | | Surface molecules ICOS-L | Inhibition of T-cell responses (immune tolerance) |
| | | Enzyme IDO | Immunoregulatory activity |
| **dDC (mDC)** | TLR2, TLR4, CD206, DC-SIGN (CD209) | CCL17, CCL22 | Attraction of other leukocytes to sites of inflammation |
| | | TNF and iNOS | Proinflammatory effects |
| **dDC (pDC)** | TLR7, TLR9 | Type 1 IFNs | Immunity against viral infections and promote function of T-cells, B-cells, NK cells |
| **Keratinocyte** | TLR1, TLR2, TLR4, TLR5, TLR6 (cell surface) and TLR3, TLR9 (endosomes) | AMPs: β-defensins and cathelicidin | Anti-microbial defence |
| | | AMP: LL37 | Loss of immune tolerance |
| | | IL-1, IL-6, IL-10, TNF, TGFβ | Broad range of effects |
| | | CXCL1, CXCL8 | Mediate attraction of neutrophils and other immune cells to inflamed skin via CXCR2 expression |
| **Neutrophil** | TLRs (excluding TLR3 and TLR7) | IL-1α, IL-1β, TNF, IL-6 | Host defence |
| | | Chemokine CXCR2 | Migration towards CXCL1- and CXCL8-expressing keratinocytes in inflamed skin |
| | | Adhesion molecules L-selectin and LFA-1 (αLβ2) | Promote neutrophil rolling, adhesion and diapedesis for recruitment to skin |
| | | AMPs: cathelicidins, lysozyme, α-defensins | Direct microbicidal activity |
| | | Proteinases: cathepsin G, neutrphil elastase and proteinase 3/myeloblastin | Contain acid hydrolases to degrade bacterial components |
| | | Proteins: lactoferrin, transcobalamin II, NGAL and calpotectin | Sequester essential nutrients to limit bacterial growth |
| **Classically activated macrophage** | TLRs (T-cell/NK cell-derived IFNγ and macrophage-derived TNF needed in combination with TLR ligation for macrophage activation) | IL-12 | Induces IFNγ production from T-cells and NK cells |
| | | TNF | Activates macrophage (second signal) |
| | | IL-23 | Promotes inflammatory immune responses |
| | | Toxic intermediates (NO and ROI) | Bactericidal activity |
| **Alternatively activated macrophage** | TLRs (CD40/CD44 signalling can occur instead of TLR ligation). FcγR ligation by IC required in combination with TLR ligation for activation | IL-10/no IL-12/no toxic intermediates | Potent anti-inflammatory effects |
| | | G-CSF | Anti-inflammatory effects via DC modulation |
| | | Fibronectin, βIG-H3 | Fibrogenesis promoting tissue repair and collagen formation |
| | | Arginine | Polyamine and proline synthesis promoting cell growth and tissue repair |
| **Mast cell** | TLRs (murine skin MC express TLR3, TLR7, TLR9) | TNFα, IL-1, IL-6, IL-10, lipid mediators (PG and LT) | Contribute to allergic and inflammatory responses |
| | | Chemokines | Recruitment to skin |
| **NK cell** | NKG2A, NKG2D (stressed/dying cells) TLR3, TLR9 (exogenous microbes) | IFNγ, TNFα | Cytotoxicity and inflammation |
| | | IL-22 (in response to IL-23) | AMP production, host defence, constraint of inflammation |
| | | IL-17 (in response to zymosan) | AMP production and host defence |
| | | Chemokines CXCR3, CCR5 and CCR6 | Migration towards CXCL10, CCL5 and CCL20 on keratinocytes of inflamed skin |
| **NKT cell** | Invariant TCRα chain combined with limited set of TCRβ chains | IFNγ, IL-4, IL-2, IL-5, IL-10, IL-13, TNFα | Inflammatory and allergic responses |
| | | Perforin, granzymes, FasL, TRAIL, granulysin | Cytotoxicity |
| **γδ T-cell** | TLRs (microbial recognition)<br>Vδ1 receptor (stressed/dying cells and tumour cells)<br>NKG2D (stressed/dying cells and tumour cells) | IL-2, IFNγ, TNFα | Inflammation |
| | | CCL3, CCL4, CCL5, XCL1 | Chemotaxis to recruit cells to site of damage |
| | | KGF | Tissue repair/wound healing |
| | | IGF-1, IL-2 | Epidermal maintenance and development |
| | | IL-17 | Host defence |

**Table 1:** Innate immune cells of the skin

macrophages also infiltrate fibrotic areas of the skin in the connective tissue disorder localized scleroderma [104]; their potential to produce fibrosis-inducing cytokines and ability to promote fibrogenesis and collagen formation is likely to play a crucial role in the pathogenesis of this disease.

**Macrophage: DC crosstalk:** Although data is limited regarding direct crosstalk of macrophages with DC via cell contact, the local cytokine milieu produced by macrophages may affect DC activation and in turn, skew T-cell responses towards Th1, Th2, Th17 or tolerogenic T-cell responses, depending on the cytokines present. For example, the ability of classically activated macrophages to produce IL-12 and IL-23 [90] is enhanced in the psoriatic dermis [105]. IL-12 and IL-23 can alter DC activation and skew T-cell responses towards inflammatory Th1/Th17 responses, likely to contribute to disease pathogenesis in psoriasis.

Granulocyte colony stimulating factor (G-CSF) is produced by macrophages under certain conditions e.g. conditioning with probiotic bacteria [106]; G-CSF elicits anti-inflammatory effects mediated through modulation of DC [107], highlighting the relevance of the skin microbiome in maintaining the balance between immunity and immune tolerance in the skin (discussed in section 4). Reciprocally, DC-produced cytokines can affect the function of macrophages e.g. DC production of IL-15 (in response to IFN-α) controls the responsiveness of macrophages to TLR4 ligands [108] suggesting a role for crosstalk between skin macrophages and DC in bacterial skin infections and/or response to commensal bacteria.

## Mast cells

Mast cells (MC) are innate immune cells involved in clearing bacterial [109-113] and parasitic [114-117] infections but are also thought to contribute to allergic and inflammatory responses via release of cytokines, chemokines, lipid mediators, proteases and biogenic amines upon cross-linking of cell-bound IgE by allergens. MC originate from bone marrow stem cells [118-120] and circulate as immature MC progenitor cells, completing their maturation upon recruitment into the peripheral tissues [121,122] e.g. the skin.

Human MC can be categorized into two different subtypes depending on the presence of different protease granules [123,124]. Cells containing tryptase alone are called $MC_T$, whereas MC with only chymase are called $MC_C$; MC with both tryptase and chymase are called $MC_{TC}$, and it is this subset that is present in large amounts in the skin [125-127]. MC express different types of TLRs depending on the type and location of the MC; MC in murine skin specifically express TLRs 3,7 and 9 and upon stimulation via these TLRs, produce inflammatory mediators TNF-α and IL-6, amongst others [128].

**Mast cell: DC crosstalk:** MC have a direct effect on other immune cells such as DC; MC or MC products can induce cutaneous DC maturation and migration [129-131]. However, the action of MC on DC in the onset of inflammation is dependent on the context, as prostaglandin (PG) is produced by MC in response to allergens [132] which inhibits LC (epidermal DC) migration [133]. The functional role of MC in inflammatory responses such as contact hypersensitivity (CHS) in the skin is unclear; murine studies of MC in CHS have provided conflicting results with MC-deficient mice showing attenuated CHS responses in one study but not in another [134]. However more recent studies have demonstrated that activated DC induces MC activation, which in turn triggers migration and maturation of DC via cell-cell contact. This DC-MC interaction plays an essential role in the sensitization phase of CHS [135].

MC crosstalk with DC also plays an important role in regulation of protective adaptive immune responses against pathogens in the skin; recent murine studies have shown MC directly induce DC maturation resulting in a release of Th1 and Th17 polarising cytokines and such MC-primed DC stimulated efficient $CD4^+$ Th1 and Th17 responses. Enhanced disease progression of MC-deficient mice in *Leishmania major* infection in the skin correlated with impaired induction of both Th1 and Th17 cells [136].

## Innate immune lymphocytes

There are several lymphocyte classes that participate in innate immune responses in the skin; these include natural killer (NK) cells, natural killer T-cells (NKT-cells), invariant NKT-cells (iNKT-cells) and γδ T-cells.

**Natural killer cells:** Natural killer (NK) cells are able to kill cells that are virally infected, as well as cancer cells; however, they also produce a range of cytokines [137]. In humans, NK cells are defined as $CD3^-CD56^+$ or $CD3^-CD16^+$ lymphocytes. NK cells express several TLRs [138]; ligation by TLR ligands induces IFN-γ production and enhances cytotoxicity. However activating NK receptors also include those recognizing stress-induced self ligands e.g. NK cell receptor NKG2D recognizes human ULBP and MIC molecules expressed on stressed or dying cells [139,140]. Although the primary function of NK cells is cytotoxicity towards virally infected cells and cancer cells, NK cells have become increasingly recognized as contributors to pathophysiological situations such as psoriasis and AD. NK cells are recruited to the skin in inflammatory conditions via expression of chemokine receptors corresponding to ligands (chemoattractants) expressed on cutaneous keratinocytes (Table 1) [141,142].

Two distinct NK cell populations exist in the human skin which have the capacity to produce either IL-22 or both IL-22 and IL-17; these cutaneous NK cells are therefore likely to play a role in skin-mediated inflammatory diseases mediated by these cytokines, including atopic dermatitis (AD) and psoriasis. Both IL-17 and IL-22 induce synthesis of AMPs including cathelicidins and β-defensins from keratinocytes, demonstrating their participation in the host innate immune defence in the skin [143-147].

IL-23, produced by activated DC and macrophages [148], is crucial in stimulating IL-22 production by NK cells (NK-22 cells). Keratinocytes can also produce IL-23 and expression of IL-23 is enhanced in keratinocytes of psoriatic patients [149]. NK-22 cells have a diminished capacity to degranulate and produce IFN-γ [150,151]; but although IL-22 is necessary for production of antimicrobial molecules in the skin [152], an excessive IL-22 response may contribute to disease pathogenesis in psoriasis [146,153,154].

The other subset of NK cells in human skin are referred to as human lymphoid tissue inducer-like cells (LTi-like cells). LTi-like cells are able to produce both IL-17 and IL-22 [143,155] and the yeast wall product zymosan can elicit Il-17 production by these cells *in vivo* [156]. It is likely that these cells contribute to host defence but the production of IL-17 also implicates LTi-like cells in autoimmunity and inflammation. However, data on Lti-like cells in the skin is currently scarce.

**NK cell: DC crosstalk:** DC can efficiently enhance activation marker expression, proliferation, inflammatory cytokine production, and cytotoxic activity of NK cells, via the action of inflammatory mediators such as IL-12, TNFα and type 1 IFNs [157]. Reciprocally, NK cells promote DC maturation and increase their capacity to produce IL-12 and polarize Th1 responses [158]. NK-mediated effects on DC are dependent on TNFα and IFNγ. A direct contact between DC and NK cells was first demonstrated in skin lesions resulting from fungal (*Malassezia)* infections of the skin and was later highlighted in specific forms of induced dermatitis [159]. It has been hypothesised that dysregulation of LC: NK cell crosstalk may participate in the chronic inflammation observed in malignant Langerhans histiocytosis [160]. The reciprocal activating interaction between DC and NK cells may also play a pivotal role in immune defense against viral infections (and tumours).

**Natural killer T-cells:** Natural killer T-cells (NKT-cells) coexpress T-cell receptor (TCR) and NK lineage markers such as CD16, CD56, CD57, CD94 and CD161, and unlike conventional T-cells, recognize glycolipid antigens in the context of MHC class I-like antigen-presenting molecule CD1d. The most widely studied NKT-cells are

type 1, or classical NKT-cells (also known as invariant NKT-cells; iNKT cells), characterized by their ability to recognise the prototypic CD1d-restricted glycosphingolipid antigen α-GalCer (a marine sponge-derived compound with potent immunoregulatory potential). iNKT-cells have a highly restricted TCR repertoire as they express an invariant Vα24-Jα18 rearranged TCR-α chain, typically coexpressed with Vβ11-containing β chain [161-163]. Type II nonclassical NKT-cells express diverse TCR-α chains, are generally not reactive with αGalCer but are also specific for antigens presented by CD1d [164].

NKT-cells only constitute a small proportion of lymphocytes. These cells can rapidly secrete large amounts of cytokines [165-167], but also exert cytotoxic properties through expression of perforin, granzymes, FasL, TRAIL and granulysin [166]. Some of these elements contribute to the pathogenesis of skin inflammatory disorders such as psoriasis [168-171]. In general, NKT-cells mediate both protective and regulatory immune functions including tumour rejection, protection against infectious microbes, maintenance of transplant tolerance and inhibition of autoimmune disease development [172]. However, in the skin, NKT-cells play an active role in diseases such as psoriasis and contact hypsersensitivity (CHS).

In humans, in the steady state, NKT-cells constitute a small proportion of lymphocytes in the skin but are expanded in psoriasis [173-176], although the exact role played by these cells is yet to be defined. Some results demonstrated a pathogenetic link between psoriatic keratinocytes, which overexpress CD1d and NKT-cells infiltrating psoriatic lesions [177,178]. Experiments in severe combined immunodeficient mice demonstrated that injection of human cells with NKT-cell characteristics into transplanted psoriatic skin could drive lesion development [177]. An increased NKT-cell density in psoriatic lesions in the epidermis compared with healthy skin was also confirmed, and CD1d expression was more extensive in psoriasis than in normal skin [179].

Activation of NKT-cells occurs during early innate stages of CHS, leading to a cascade of events such as complement activation; this generates C5a which in turn activates mast cells and platelets to release TNF-α and serotonin. This cascade results in the activation of endothelial cells to recruit T-cells locally [180]. Inhibition of the CD1d-antigen-presenting pathway to NKT-cells interferes with both initiation and effector phases of CHS [181]. NKT-cells are emerging as an important subset of lymphocytes, with a protective role in host defence and a pathogenic role in certain immune-mediated disease states.

**NKT-cell: DC crosstalk:** As NKT-cells are CD1d-restricted, these cells can be directly activated by CD1d-expressing cells, able to present antigen. Human and mouse CD1d are expressed at detectable levels on most cells of haematopoietic origin with high levels of expression on DC [182,183]. CD1d expression on DC is increased by the presence of inflammatory cytokines [184,185] and TLR ligation [186], but is decreased by immunoregulatory cytokines [187] and various infections of the skin [188,189]. NKT-cells can, in turn, modulate DC differentiation and function. Regulation of myeloid DC by NKT-cells in mice controls both the transition from innate to adaptive immunity and the type of T-cell responses generated [190].

**γδ T-cells:** γδ T-cells with invariant or restricted TCR are preferentially located within epithelial tissues that are points of contact between the body and the external environment. The unique population of γδ T-cells in the mouse epidermis are called Thy-1$^+$ dendritic epidermal T-cells (DETC). DETC monitor epidermal cells and are poised to recognize and respond to non-peptide self-antigens expressed by neighbouring keratinocytes following tissue stress or damage; this process resembles PAMP recognitions by PRRs on DC. One example of such a self-antigen in humans is MHC class I chain-related protein A (MICA) which is expressed on keratinocytes [191], upregulated during inflammation and infection, and recognised by NKG2D receptor expressed on γδ T-cells. Once keratinocyte distress is detected, DETC respond by local secretion of chemokines, cytotoxic effector molecules, growth factors and cytokines that orchestrate skin inflammation, tumour killing and wound-healing responses [192].

Many factors contribute to epidermal homeostasis, including skin-resident γδ T-cells [193,194]. This is partly due to expression of insulin-like growth factor (IGF-1), which mediates epidermal development and maintenance via interaction with keratinocytes [195,196]. The localization of large numbers of γδ T-cells in the skin suggests they form a first line of defence against invading pathogens, as well as contributing to tissue homeostasis. DETC (mouse epidermal γδ T-cells) play a protective role against cutaneous *Staphylococcus aureus* infections [197,198] and may also respond to gram-negative bacteria [199]. γδ T-cells express innate PRRs such as TLRs, enabling them to directly recognize microbial patterns [200]; indeed, DETC upregulate expression of TLR4 during cutaneous inflammation [201].

DETC can play a regulatory role in some inflammatory skin disorders; TCRδ$^{-/-}$ mice spontaneously develop localized dermatitis which requires the presence of αβ T-cells. Adoptive transfer experiments demonstrated DETC downregulated dermatitis in TCRδ$^{-/-}$ mice [202]. The underlying mechanisms of DETC regulatory function are unknown, but γδ T-cells also play a regulatory role in other inflammatory disorders. γδ T-cells can mediate downregulation of both αβ and γδ effectors in contact hypersensitivity (CHS) *in vivo* and IFN-γ production by the CHS effector cells *in vitro* [203]. γδ T-cells also have the capacity to negatively regulate αβ T-cell driven allergic IgE responses [204]. In the context of infection, γδ T-cells can play a protective role e.g. murine dermal γδ T-cells rapidly produce IL-17 following exposure to IL-1β and IL-23 [205], therefore may be key source of IL-17 following skin infection. However, a novel proinflammatory subset of human circulating IL-17-producing γδ T-cells has been recently identified in psoriasis; these cells are rapidly recruited into perturbed human skin [206].

**γδ T-cell: DC crosstalk:** γδ T-cells can be directly activated by DC as a proportion of γδ T-cells are CD1-restricted. CD1-restricted T-cells can also mediate the maturation of DC. Upon recognition of CD1, CD1-restricted γδ T-cells secrete TNFα and other products that, together with LPS, induce immature DC to mature and produce pro-inflammatory and Th1-polarizing cytokine IL-12 [207]. In human skin, expression of CD1 on DC increased significantly after *Borrelia burgdorferi* (the causative agent of Lyme disease) infection and in disease-specific skin lesions [208] which has implications for DC activation of γδ T-cells and bidirectional crosstalk between γδ T-cells and DC in this disease setting.

## The Adaptive Immune System

The innate immune system uses a combination of PRRs to detect microbes, induce anti-microbial defence mechanisms and maintain host-microbial homeostasis. However, in vertebrates, two types of immunity are used to protect the host from infections: innate and adaptive. The adaptive immune response comprises T- and B-cell responses and employs antigen receptors that are not encoded in the germ line but are generated de novo in each organism; adaptive immune responses are highly specific.

## Dendritic cells drive adaptive immunity: bridging the innate and adaptive immune system

Although the innate properties of dendritic cells (DC) and expression of PRRs allows them to recognise PAMPs on invading pathogens and DAMPs on injured/dying tissue cells, DC also possess the unique ability to initiate primary adaptive cell-mediated immune responses, generating immunological memory. DC can determine whether an active or tolerogenic immune response occurs to a particular antigen, and whether an inflammatory or tolerogenic immune response predominates [80-82,209]. DC play a role in co-stimulation of B-cells in the humoral immune response to generate antibody-secreting plasma cells [210] but, for the purpose of this review we will focus on the role of DC as being unique from other APC in their potency at initiating cell-mediated immunity (T-cell responses), focusing on DC at cutaneous sites.

## T-cell responses initiated by skin dendritic cells

**Epidermal dendritic cells: Langerhans' cells:** Langerhans' cells (LC) are among the first DC to come into contact with microbial antigens; LC take up and process lipid antigens and microbial fragments for presentation to effector T-cells [211]. Human LC can preferentially induce differentiation of Th2 cells and can prime and cross-prime naive $CD8^+$ T-cells [212]. Due to the proximity of LC to the external environment, LC were thought to have a potential role in contact hypersensitivity (CHS) reactions [213]; however removal of LC enhances CHS, suggesting LC may inhibit CHS responses [214].

LC are indeed dispensable for the induction of certain types of cell-mediated immune responses, and may actually generate tolerogenic responses [215,216]. LC express surface molecules involved in the inhibition of T-cell responses such as inducible co-stimulatory molecule ligand ICOS-L (B7-H2) or the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO), both of which function as strong inducers of peripheral tolerance [28]. Our recent data characterising human DC from different tissues supports the theory of a tolerogenic role for epidermal DC, which exhibited a restricted stimulatory capacity for allogeneic T-cells compared with their blood and dermal counterparts. Such restricted stimulatory capacity was also reflected in gut DC. This is likely to be due to high antigenic load in the gut [217].

The role of LC in antimicrobial immunity has been questioned by the finding that LC were unable to generate $CD8^+$ T-cell immunity upon cutaneous infection with herpes simplex virus (HSV) [218]. One explanation of such results was that HSV can induce LC apoptosis and therefore diminish LC function. Indeed, infection of DC with a number of different viruses can block their function e.g. during DC infection with Rauscher leukaemia virus [219], dengue virus [220], rhinoviruses [221], cytomegaloviruses [222] and HIV [223]. The role of LC in generation of T-cell responses has not yet been fully clarified, but it is likely that the immune response generated is dependent on the antigen itself and cross-talk involving other cutaneous immune cells e.g. keratinocytes as well as other LC and dermal DC (dDC).

**Dermal dendritic cells: myeloid:** Several subpopulations of dermal DC (dDC) have been described in humans both in the steady state and in an inflammatory context. In the steady state, the majority of dDC are of myeloid origin and express CD1c (BDCA-1) [30]. Co-expression of CD1c with CD11c is a useful marker *in situ* to distinguish dDC from macrophages [32]. dDC migrate rapidly to the skin-draining lymph nodes (LN) to present antigen to T-cells [29-31]; however $CD1c^+$ dDC can be divided into at least three discrete subsets based on their surface expression of CD1a and CD14 [224].

*Ex vivo* isolated $CD1a^+CD14^-$ dDC have a mature phenotype and are potent inducers of allogeneic naive $CD4^+$ and $CD8^+$ T-cell proliferation [30,212,225,226]. In contrast $CD14^+$ dDC are less mature than $CD1a^+CD14^-$ and display a reduced capacity to prime naive T-cell proliferation [33]. However, IL-23 treatment enhances T-cell stimulatory capacity of $CD14^+$ dDC and IL-23-neutralising antibody inhibits T-cell proliferation induced by $CD14^-$ dDC [227]. These results have implications in inflammatory disease, given the importance of IL-23 in Th17 cell immunity and that dDC produce IL-23 in skin pathology [228], and may partly explain the clinical benefit observed in psoriasis patients treated with an anti-IL-12/23p40 [229;230]. $CD14^+$ dDC are also able to polarize naive $CD4^+$ T-cells into follicular helper T-cells, which in turn promotes naive B-cell differentiation [212].

$Langerin^+CD103^+$ DC also constitute a proportion of $CD1c^+$ DC in the dermis; these cells are distinct from epidermal LC in both their origin and function [23,231,232] and do not represent LC *en route* to skin-draining LN, as previously assumed [233]. $Langerin^+CD103^+$ dDC can cross-present epidermal-derived viral and self antigens to $CD8^+$ T-cells [234], including keratinocyte-derived antigens. Studies on $langerin^+CD103^+$ dDC raised the possibility that this DC subtype may be broadly represented in many tissues, mainly for its function in $CD8^+$ T-cell responses and tolerance. Indeed, $langerin^+$ DC are required for $CD8^+$ T-cell responses to influenza in the lung, despite the presence of other DC subsets [235].

A small population of myeloid dDC have been identified that do not overlap with the $CD1c^+$ population in normal skin. These cells constitute approximately 10% of $CD11c^+$ dDC and can be identified by expression of CD141 (BDCA-3) [32]. In blood, these cells are also non-overlapping with the $CD1c^+$ population, and are thought to be the least immunostimulatory myeloid blood DC population. Evidence now suggests that these $CD141^+$ DC may be the human equivalent of mouse $CD8\alpha^+$ DC [236], which take up dead/dying cells, process exogenous antigen on MHC class I molecules to present to $CD8^+$ T-cells [237-239], and induce protective $CD8^+$ responses against cancers, viruses and other pathogenic infections [240-243].

Activated myeloid dDC participate in the inflammatory responses partly by secretion of chemokines and cytokines (as mentioned in earlier sections) but also affect T-cell polarization. Tumour necrosis factor (TNF) and inducible nitric oxide synthase (iNOS)-producing DC (TIP-DC) play a major role in psoriasis [39], partly mediated by activation and differentiation of Th17 cells [21].

**Dermal dendritic cells: plasmacytoid:** Human plasmacytoid DC (pDC) represent a minor population in the blood and the skin and play a major role in anti-viral immunity due to their capacity to rapidly produce large amounts of proinflammatory type I interferons (IFNs) upon viral infection [244,245], thus activating inflammatory adaptive immune responses [246]. pDC have been implicated in the pathogenesis of psoriasis, and also of systemic lupus erythematosus (SLE) [44,247]; early activation of pDC triggers innate immune responses in psoriasis resulting in pDC activation via TLR9. This in turn leads to IFNα production and activation of inflammatory adaptive immune responses [42].

**Inflammatory dendritic epidermal cells:** Inflammatory dendritic epidermal cells (IDEC) can populate both the epidermis and the dermis during an inflammatory immune response [37,248]. IDEC over-express the high affinity Fc receptor for IgE (FcεRI), facilitating their reactivity to IgE-bound allergens, resulting in a pro-inflammatory allergic-specific T-cell response [249].

## Function of T-cells in the skin

$CD4^+$ and $CD8^+$ T-cells are present in approximately equal numbers in the skin, and most are memory T-cells [250]. The three main types of $CD4^+$ Th cells have been found in the skin during various inflammatory diseases; Th1, Th2 and Th17 cells. Th1 cells are present during infections with intracellular organisms and produce IFNγ and lymphotoxin to kill such organisms. Although previously Th1 responses have been associated with autoimmunity (such as psoriasis) and Th2 responses linked with allergic diseases (such as asthma and atopic dermatitis; AD), Th17 cells also play a crucial role in both psoriasis [228] and AD [251].

Th17 cells are essential for first-line defence against various fungal and bacterial infections [45], specifically diseases which are characterised by recurrent and persistent infections of the skin and mucosal membranes [252-254]. A putative mechanism of host defence against microorganisms involving IL-17 and IL-22 in the skin is the upregulation of anti-microbial peptide (AMP) production by keratinocytes [144]. A subset of circulating T-cells with skin-homing potential that produce IL-22 but not IL-17 or IFN-γ (Th22 cells) [255,256] have also been identified in skin cell cultures from patients with AD [257], though their functional role in skin pathology and homeostasis is currently unclear.

It has been proposed that skin-resident T-cells have a role in skin immune homeostasis and pathology [258]; normal skin contains twice as many T-cells as the blood and 98% of $CLA^+$ skin-homing lymphocytes in the body reside in the skin in the steady state [259]. Skin-resident memory T-cells play a key role in skin inflammation e.g. psoriasis [260,261] and can be activated by skin DC resulting in local proliferation of antigen-specific $CD8^+$ T-cells during HSV infection [262]. Skin-resident memory T-cells express CD103 and VLA-1 and undergo homeostatic proliferation, and provide protection from pathogen challenge [263].

## Immune cell homing and migration to the skin

**General principles of T-cell homing to the skin:** Lymphocytes continuously migrate around the body to meet antigens. For T-cells trafficking to lymphoid and extra-lymphoid sites, this migration involves a multi-step process, regulated by co-ordinated interactions between cell surface molecules on T-cells with their respective ligands on the surface of vascular endothelial cells [264]. Transendothelial migration into cutaneous sites is dependent on T-cell adhesion to endothelial cells, and their subsequent migration to and through endothelial cell junctions [264-266].

The trafficking pattern of T-cells changes during their transition from naive to memory T-cells. Naive T-cells constitutively traffic through lymphoid tissue while memory T-cells acquire the ability to infiltrate non-lymphoid sites, such as the skin, at the site of antigen. Upon DC stimulation, T-cells acquire the ability to express homing receptors including tissue-selective integrins and chemokine receptors allowing migration to specific organs, such as the skin.

T-cells localizing to the skin express cutaneous lymphocyte-associated antigen (CLA). CLA arises from specialized glycosylation of P-selectin glycoprotein ligand-1 (CD162) [267], thought to be involved in tissue-specific localization of cutaneous T-cells within the skin [268,269]. CLA mediates tethering and rolling of T-cells through interaction with its endothelial receptor E-selectin, constitutively expressed on skin post-capillary venules. However, interactions of P- and E-selectin with their T-cell expressed ligands are not skin-specific, suggesting a role for other skin-homing molecules.

The interaction between chemokine receptor CCR4 and its ligand CCL17 (TARC) has been implicated in skin-homing of immune cells; CCR4 is involved in vascular recognition by cutaneous but not intestinal memory T-cells [270], and is necessary for antigen-driven cutaneous accumulation of $CD4^+$ T-cells under physiological conditions [271]. Interactions between chemokine receptor CCR10 and its ligand CCL27 (CTACK) has also been implicated in skin-homing [272]. The ligands for CCR4 and CCR10, CCL17 (TARC) and CCL27 (CTACK), have been found on inflamed and non-inflamed skin endothelium [270,273]. CCL27 (CTACK) is preferentially produced by epidermal keratinocytes [273].

**Cutaneous dendritic cells imprint skin-homing properties on T-cells:** DC not only activate naive T-cells to generate antigen-specific T-cell proliferation and expansion, but they also direct the T-cells to the site where antigen is most likely to be encountered, by imprinting tissue specificity. DC from skin-draining lymph nodes specifically induce expression of skin-homing markers on activated T-cells [274]. Likewise, mouse LC (epidermal DC) are specialized to target T-cells to inflamed skin [275] and our recent studies demonstrate human freshly isolated epidermal and dermal DC specifically imprint a skin-homing profile on stimulated T-cells [217]. In contrast, murine DC from secondary lymphoid tissue in the gut specifically induce gut-homing molecules $\alpha_4\beta_7$ and CCR9 on activated T-cells [276-278], supported by our studies demonstrating fresh human gut DC specifically imprint a gut-homing profile on T-cells [217].

Vitamin D may promote development of DC that stimulates T-cells to express skin-homing markers. In humans, *in vitro* studies show vitamin D3, a pre-vitamin produced by sunlight in the skin, is itself inactive but efficiently processed to DC to its active form, $1,25(OH)_2D_3$, which induces surface expression of the skin T-cell associated chemokine receptor CCR10. Expression of CCR10 confers an attraction to the epidermal chemokine CCL27 [272]. However, the role of vitamin D in leucocyte migration to the skin is unclear as it also downregulates CLA expression [279]. Although vitamin D can confer expression of particular skin-homing markers on T-cells, it also induces tolerogenic properties on DC [280-282]; $1,25(OH)_2D_3$-treated DC stimulate hyporesponsive T-cell responses and generate regulatory T-cell populations ($T_{regs}$) [281-283]. These properties are likely to contribute to the immunosuppressive effects of UV light (specifically UVB) [284-286] and efficacy of UV-light therapy for inflammatory disorders such as psoriasis [287].

**Migratory properties of skin dendritic cells:** DC themselves must also exhibit tissue-specific properties since they control trafficking of lymphocytes (that they stimulate) and deal with different microenvironments at different sites. However, information about expression of tissue-homing markers on DC themselves is scarce, particularly in humans, primarily due to the methodological difficulties in studying human tissue.

Antigen encounter causes DC maturation and subsequent migration of DC to the peripheral LN to generate a T-cell mediated immune response [288-291]. Most models of DC migration are based on epidermal LC migration following administration of skin-sensitising agents [292], carcinogens, or upon infection [293,294]. Human studies demonstrate a dramatic change in chemokine receptor expression on DC can be induced by TLR-mediated stimulation and maturation of DC [295]. This includes up-regulation of LN-homing marker CCR7, enabling migration to secondary lymphoid organs [296].

Little information was previously available regarding the homing

profile of tissue-resident DC in humans, in the steady state. However, we recently demonstrated that fresh human DC express tissue-specific homing profiles, with the ability to induce specific homing properties on T-cells. Both epidermal and dermal DC lacked expression of gut-homing markers β7 integrin and CCR9 but expressed skin-homing markers CLA and CCR4, and skin-associated homing marker CCR10. The opposite was true of gut DC which expressed gut-homing markers only [217]. However, there were skin DC present that did not express skin-homing markers, suggesting skin-homing marker expression may not be essential for retention of DC within cutaneous compartments.

Epidermal LC display some unique characteristics compared with other DC. LC express particular proteinases allowing them to pass through the basement membrane, including metalloproteinases (MMPs) [297]. MMP-9 is expressed by LC and up-regulated by inflammatory cytokines TNF-α and IL-1β [298]. Migration of both LC and dermal DC (dDC) can be prevented by MMP inhibitors, MMP-9 and MMP-2 antibodies, and by natural tissue inhibitors of MMPs (TIMPs) [299].

## The Skin Microbiome

The skin is in constant contact with the external environment and hosts an ecosystem colonized by a diverse collection of microorganisms, including bacteria, fungi, viruses and mites [3-8]. Many of these microorganisms are harmless and can provide vital immunological functions; symbiotic microorganisms protect against host invasion by more pathogenic organisms. The perception of the skin as an ecosystem comprised of diverse microorganisms can be compared to the gastrointestinal (GI) tract; the GI tract is in contact with numerous commensal microbiota and diverse pathogens, and therefore a balance needs to be maintained between immunogenic or tolerogenic immune responses. Disruption of this balance at either site can result in skin disorders or infections, or inflammatory bowel diseases, infections or even cancer.

### Modulation of cutaneous immune responses by the skin microbiome

The skin can discriminate between commensal microorganisms and harmful pathogenic microorganisms; mechanisms of this discrimination are not fully clear but are likely to involve DC modulation. DC in the gut are central to maintaining the balance between immunogenic or tolerogenic immune responses [300]; alterations in gut DC occur in inflammatory bowel diseases [300,301]. DC influence peripheral tolerance by promoting negative selection in the thymus [302] and generation of T-cells with regulatory properties [303].

*Staphylococcus epidermidis*, a commensal bacterium, has recently been demonstrated to modulate the host innate immune response. *S. epidermidis* products can selectively inhibit skin pathogens such as *Staphylococcus aureus* and Group A *Streptococcus*, and even co-operate with host anti-microbial peptides (AMPs) to enhance pathogen killing [304,305]. Commensal bacterial-induced TLR signalling may be necessary for cell survival and repair during infection. Lipoteichoic acid produced by *S. epidermidis* can inhibit skin inflammation through a TLR2 and TLR3-mediated crosstalk mechanism [306]. *S. Epidermidis* also triggers keratinocyte expression of AMPs through a TLR2-dependent mechanism [307].

### The skin microbiome and disease

Skin diseases can be associated with a specific organism within the skin microbiome via three different mechanisms: skin disorders with a correlation to microbiota, skin disorders with a currently unidentified microbial component or a skin commensal microorganism that can become invasive to cause infection [308]. More than 90% of atopic dermatitis (AD) lesions are colonized with *S. aureus* on both lesional and non-lesional skin, compared with under 5% in skin samples from healthy individuals [309,310]. The most common treatments for AD include antibiotics and steroids. Dilute bleach baths to lower the bacterial load are also effective in reducing clinical severity [311].

Some skin disorders are linked with unidentified microbial components; commensal skin organisms can invade and become pathogenic in cases such as chronic wounds affecting diabetic, elderly and immobile individuals. Although these organisms do not cause the initial wound, they are thought to contribute to the lack of healing and persistent inflammation that is associated with chronic wounds [312-315]. Slow-healing diabetic mouse models demonstrate correlation between the commensal microbiota and aberrant expression of skin defence and inflammatory genes [316], likely to contribute to wound failure.

Some skin commensal microorganisms can become invasive and cause infection; *S. epidermidis* is a very common commensal microorganism on the skin, but is also the most frequent cause of hospital-acquired infection during administration of intrusive medical devices such as catheters or heart valves [317]. Once commensal microorganisms breach the skin barrier, virulent strains of these organisms can form biofilms, protecting them from the host immune system and antibiotics [318].

## Conclusions

The skin immune system comprises a complex network of cells that all contribute not only to immunity against invading pathogens but also to homeostasis in the skin. The nature of immune responses generated in the skin depends on the types of antigen present, effects of environmental and genetic factors, and the interplay between components of the innate and adaptive immune systems. DC with their inherent plasticity play crucial roles in initiating and modulating immune responses, and are arguably the driving force bridging the innate and adaptive immune systems. This is due to their direct roles in both types of immune responses; however, the cross-talk between the complex network of DC subsets, skin-resident innate and adaptive immune sentinels, and accessory epidermal and dermal components also contribute to homeostasis and pathology. The role of the skin microbiome in modulating immune responses in the skin has started to be investigated; cutaneous DC are likely to play a crucial role in maintaining the balance between tolerance to harmless commensal microorganisms and immunity against harmful invading pathogens in the skin, as gut DC are known to, in the GI tract. Recent advances in the knowledge of skin DC in health and disease has led to development of therapies harnessing skin DC with specialized properties to control immunity; several therapeutic interventions targeting skin DC have proved beneficial to psoriasis patients [39,319]. However, further studies are required to fully understand the contribution of skin DC subsets in immunity and tolerance.

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