nature immunology

The skin-resident and migratory immune system in steady state and memory: innate lymphocytes, dendritic cells and T cells

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The skin is a highly complex organ interspersed with a variety of smaller organ-like structures and a plethora of cell types that together perform essential functions such as physical sensing, temperature control, barrier maintenance and immunity. In this Review, we outline many of the innate and adaptive immune cell types associated with the skin, focusing on the steady state in mice and men, and include a broad update of dendritic cell function and T cell surveillance.

The skin is composed of the epidermis, attached to a basement membrane, underlain by the dermis and a subcutaneous fatty region. Each layer is highly complex and is peppered with an array of structures, such as hair follicles, sweat glands (in humans but not in mice), sebaceous glands, nerves, blood vessels and lymphatics. The epidermis and dermis are, in turn, populated by a variety of cell types that together form an orchestrated defense against invading pathogens. These first two layers provide most of the protection against infection, though mounting evidence also points to a defensive role for the microbial flora that also populate this tissue[1–4]. As an organ, the skin is a formidable barrier to infection. To ensure successful control of pathogens, contributions to surveillance and effector function must be provided by many different cell types, from keratinocytes that form the infrastructure of the skin to the many resident and migratory leukocyte populations that specialize in immunity or are multifaceted in their regulation of skin homeostasis. In this Review, we examine the role of some of the important contributors to skin immunity.

Immunity in the skin

The structure of the epidermis is largely dictated by keratinocytes[5], which form an outer enucleated, cornified layer referred to as the stratum corneum (**Fig. 1**). This is followed by the stratum granulosum containing tight junctions[6], then the stratum spinosum and finally the basal layer attached to a complex basement membrane. The stratum corneum and tight junctions within the stratum granulosum ensure an effective physical barrier to the environment and its associated pathogens, whereas the cornified layer also acts as a scaffold for microflora. Recent studies have revealed a vast skin microbiome consisting of bacteria, fungi, viruses and parasites[1]. This normal flora benefits many aspects of host physiology including wound healing[2,3], protection against pathogens[3] (**Fig. 1**) and normal development of the immune system[4].

Keratinocytes have a key innate role in detection of pathogens and defense[7], expressing many pattern recognition receptors, including Toll-like receptors (TLRs) that recognize a wide variety of pathogen components and self components, Nod-like receptors (NLRs) Nod1 and Nod2, which respond to bacterial peptidoglycan and NLR pyrin domain–containing proteins that respond to viral, fungal and self constituents. Expression of RIG-I–like receptors (RLRs) enables response to viral RNA, whereas C-type lectins, such as dectin-1, detect fungal infections. Together, these and other pathogen recognition systems make keratinocytes a formidable barrier for frontline detection of pathogen invasions. In direct response to microbial detection or through indirect activation by cytokines such as interleukin 22 (IL-22), keratinocytes can produce a vast array of microbiocides including antimicrobial peptides such as LL-37 and β-defensins, as well as RNases and S100 family members. The epidermis is also bathed in other proteins that have microbiocidal activity such as dermicidin, produced by eccrine glands (one of the two types of sweat glands present in human but not mouse skin), sebum, a lubricating agent produced by sebaceous glands, and filaggrin, a keratinocyte-derived moisture-retention agent, which can also be cleaved into acids that are capable of slowing pathogen growth[1,7,8].

Keratinocytes can also produce chemokines and cytokines in response to pathogenic stimuli, including CXCL9, CXCL10, CXCL11, CCL20, tumor necrosis factor (TNF), IL-1α and IL-1β, IL-6, IL-10, IL-18 and IL-33 (refs. 5,9). Chemokines can be critical in recruiting T cell and innate effectors such as monocytes to the skin[10], whereas cytokines arm effectors and direct the immune response to ensure appropriate effector mechanisms[11].

In the epidermis there are several specialized cell types that have distinct roles in immunity, including memory αβ T cells[12–14] and Langerhans cells (epidermal dendritic cells (DCs); **Fig. 2**). The epidermis also contains γδ T cells, which make up the vast bulk of

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Received 29 May; accepted 2 July; published online 18 September 2013; doi:10.1038/ni.2680

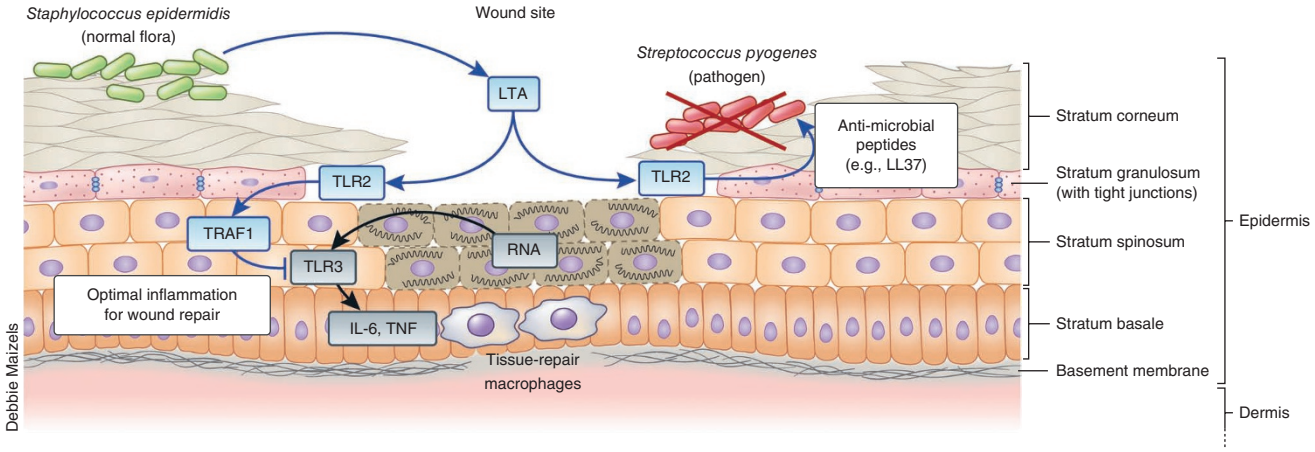

Figure 1 Resident microbiota in the skin contribute to immunity and wound repair. The epidermis comprises several layers of keratinocytes, including two that seal against the outer environment: the stratum corneum composed of corneocytes (which are terminally differentiated from keratinocytes) and the stratum granulosum, a living layer of cells that generate tight junctions between adjacent cells. The skin microflora benefits many aspects of host physiology, including wound healing and protection against pathogens, the latter as a consequence of direct production of antimicrobials, induction of host-cell antimicrobials, conversion of host cell products into antimicrobials or by altering the nature of the adaptive immune response. After skin wounding, for example, keratinocytes can be activated via TLR3 to induce inflammation in response to endogenous RNA released by necrotic cells[2,3]. Although inflammation is needed for wound healing, overt inflammation can slow the repair process and be harmful. To balance the strong inflammatory response induced via TLR3, lipoteichoic acid produced by *Staphylococcus epidermidis*, a prominent member of the normal flora, can signal TLR2 to induce TRAF1, which impairs TLR3-dependent production of IL-6 and TNF and limits inflammation and leukocyte recruitment[3]. Activation of TLR2 by *S. epidermidis* can also increase production of antimicrobial molecules that defend against pathogens like group A *Streptococcus pyogenes*[115], ensuring both steady-state protection and providing potential defense at wound sites.

all epidermal T cells in mice, where they are known as dendritic epidermal T cells (DETCs)[15], but only represent a minor subset in the human epidermis[16]. This region of the skin also contains sparsely dispersed cell types such as Merkel cells, which serve the nervous system[17], and melanocytes, which are responsible for protection against ultraviolet light damage.

The dermis is not as densely packed with cells as the epidermis, and is instead extensively composed of elastin fibers, collagen fibers and other extracellular matrix largely produced by fibroblasts. It is interspersed with a number of structures and many different cell types. Blood vessels and capillary beds are spread throughout the dermis, as are nerves that access the dermis and epidermis. Draining lymphatics begin in the dermis and traverse the deeper layers of the skin to eventually access the lymph nodes. Some of the important immunologically relevant cell types in the dermis include mast cells, macrophages, various DC subsets, innate lymphoid cells (ILCs), γδ T cells and αβ T cells (**Fig. 2**). In the human, the dermis abuts the epidermis in a ridge-like manner, termed glandular ridges, whereas the dermal-epidermal junction in mice is fairly flat except where its many hair follicles form involutions.

Hair follicles consist mainly of keratinocytes and are highly complex structures, continuous with the epidermis, penetrating deep into the dermis[18,19]. They are formed for life, though some *de novo* generation has been demonstrated at wound sites[20]. Hair follicles perform several tasks[18,19], the most obvious of which is production of hairs, which can contribute to thermoregulation, sensory activity, camouflage, physical protection and dispersion of sweat, sebum and pheromones. The relative importance of hair follicles in skin immunity is yet to be fully elucidated, but these structures harbor a large proportion of the microbiome, with distinct microbial constituents[1], implicating them in the immune system–microbiome cross-talk. Recent evidence shows that different regions of the follicle can express a variety of chemokines in a regulated manner that influences trafficking of immune cells[10]. Hair follicles are implicated in controlling access of monocytes and Langerhans cells to the epidermis during periods of repopulation, acting as a 'gateway' to the epidermis. Hair follicle–associated expression of chemokines may also control the accumulation of perifollicular cells such as macrophages, mast cells and DCs[19].

The skin has a vast range of cell types that contribute to adaptive and innate immune functions. Below we will explore the role of various subsets of lymphocytes and DCs associated with this tissue.

γδ T cells

The mouse DETC γδ T cell population, which express a conserved $V_{\gamma}5$ $V_{\delta}1$ T cell antigen receptor (TCR), are distributed extensively throughout the epidermis, forming a dense network of dendritic-like cells that are essentially locked in position[15] (**Fig. 2**). Although the ligand of their invariant TCR is unknown, they appear to be signaled by self ligands in the steady state, constitutively clustered on dendrites that form polarized anchors at epithelial tight junctions[21]. This process is likely important for monitoring epidermal integrity. DETCs are radioresistant[22], exibiting slow homeostatic division under steady-state conditions[21] and requiring expression of IL-2Rβ (ref. 23) and access to exogenous IL-15 for proliferation and survival[24]. They use an array of molecules to monitor 'stress' in the epidermis[25]. These molecules include the receptor NKG2D, which detects ligands such as Rae-1, upregulated during viral infection or tumorogenesis[26], TLRs that monitor for foreign ligands as well as self ligands, the junctional adhesion molecule family member JAML, which binds the epithelial coxsackie virus and adenovirus receptor (CAR)[27] that is potentially revealed when integrity of the tight junction is compromised, and CD100 (ref. 28), which recognizes plexin β2, upregulated on keratinocytes after wounding. DETCs have primarily been shown to participate in wound healing[29] but can contribute to inflammation (also essential for wound healing) and tumor surveillance[26], and may participate in contact hypersensitivity and antibacterial responses[15]. Without DETCs, wounds show impaired keratinocyte proliferation, reduced inflammation and slower closure[29]. How DETCs exert their

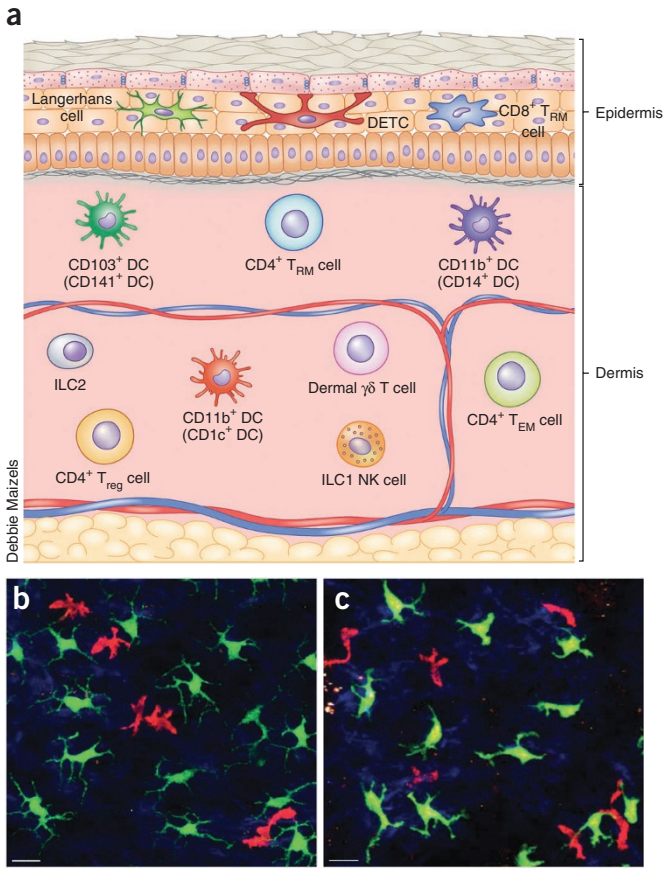

Figure 2 Lymphocytes and DCs of the skin. (**a**) The mouse epidermis is interspersed with three important immune cell types, Langerhans cells, γδ T cells termed DETCs and $CD8^+$ T_{RM} cells. The dermis contains cells of the immune system including T_{reg} cells, $CD4^+$ T_{RM} cells, $CD4^+$ T effector memory cells (T_{EM} cells), other γδ T cells, ILCs and several populations of DCs. In mice, dermal DCs can be divided into $CD11b^+$ DCs and $CD103^+$ DCs, but data collected in humans suggests that the mouse $CD11b^+$ DCs might contain both a monocyte-derived counterpart ($CD14^+$ DCs in humans) and a pre-DC–derived counterpart ($CD1c^+$ DCs in humans). NK cells are a type of ILC1. (**b**) Langerhans cells (green) and $CD8^+$ T_{RM} cells (red) in the skin of mice 44 d after infection with HSV-1. (**c**) DETCs (green) and HSV-1–specific $CD8^+$ T_{RM} cells (red) in the epidermis of mice 30 d after infection with HSV-1. Images in **b** and **c** were provided by A. Zaid and S. Mueller.

repair function is not fully elucidated, but they can induce keratinocyte deposition of hyaluronan, which recruits wound-repair macrophages[30], and they produce keratinocyte growth factors such as insulin-like growth factors. Activated DETCs can express a variety of chemokines and cytokines including CCL3, CCL4, CCL5 and XCL1 (ref. 31), IFN-γ and IL-2 (ref. 32) and IL-13 (ref. 33), which potentially contribute to inflammation and recruitment of innate and adaptive immune cell types as well as to eliciting production of IgE[33]. Like mouse DETCs, γδ T cells present in human epidermis appear to contribute to wound healing[16].

In addition to the presence of DETCs in the epidermis, mice have a largely $V_\gamma5^-V_\gamma4^+$ population of γδ T cells in the dermis[22]. Expression of eGFP under the *Cxcr6* promoter in mice deficient of αβ T cells allowed the visualization of DETCs in the epidermis but also revealed a separate population of γδ T cells in the dermis, often associated with major histocompatibility complex (MHC) class II^+ cells. Unlike DETCs, the dermal γδ T cell population was not dependent on IL-15 for survival but required IL-7. γδ T cells had been reported to enhance $CD4^+$ T cell immunity to some infections, such as with Bacillius Calmette-Guerin (BCG)[25], and this appears to be facilitated by the production of IL-17 by dermal γδ T cells, leading to neutrophil recruitment, which may contribute by delivering antigen to the draining lymph node[22]. Notably, mice lacking this population of γδ T cells showed reduced dermatitis associated with application of imiquimod[34,35], whereas psoriasis patients showed increased numbers of IL-17–producing γδ T cells in their skin[36].

Innate lymphoid cells

Despite extensive characterization of ILCs in tissues such as the spleen, mesenteric lymph nodes and lungs[37], ILCs other than NK cells have only recently been identified in the skin[35,38,39]. In other organs, three major classes of ILCs have been distinguished, referred to as ILC1, ILC2 and ILC3 (ref. 37). ILC1 populations express the transcription factor T-bet, make IFN-γ and consist of conventional NK cells as well as nonlytic populations. This group of ILCs participate in viral immunity and are triggered by the cytokines IL-12 and IL-18. ILC2 populations, which include members referred to as nuocytes and natural helper cells, express the transcription factor GATA-3, respond to the cytokines IL-25 and IL-33 and produce the T_H2 cell–type cytokines IL-5, IL-9 and IL-13 and amphiregulin. They have roles in tissue repair, asthma and responses to helminths. ILC3 populations include lymphoid-tissue-inducer lymphocytes, express the transcription factor RORγt and produce cytokines such as IL-22, IL-17A and some IFN-γ, responding to IL-1β and IL-23 and participating in responses to bacteria, tissue repair and development of lymphoid tissue[37].

Of the ILC1 subset, only NK cells have so far been detected in healthy skin, usually in small numbers that are increased in conditions such as psoriasis[40–42]. ILC2 populations in other (non-skin) tissues are defined as lineage-negative cells that express CD45, CD90, CD127 and ICOS, with variable expression of c-Kit, Sca-1 and the IL-33 receptor ST2. IL-13, produced by the ILC2 population, can function by suppressing monocyte synthesis of inflammatory cytokines (for example, IL-6, IL-1β and TNF)[43], by inducing mucous production by globlet cells (not relevant to the skin)[44] and by recruiting eosinophils indirectly via eliciting eotaxin and IL-5 from other cell types such as epithelial cells[45]. ILC2-like cells, recently recognized in mouse and human skin[38,39], express CD25 and ST2, constitutively produce IL-13, require IL-7 for survival and are activated by thymic stromal lymphopoietin (TSLP), which increases their production of IL-13 and induces IL-4. ILC2 cells were found to accumulate in patients with atopic dermatitis, a T_H2 cell–like allergic disease, whereas in T cell–deficient mice, depletion of the ILC2 population with anti-CD25 monoclonal antibody reduced inflammation associated with T_H2 cell–type cytokines in a dermatitis model[38]. In the steady state, the skin ILC2 population was often found to associate with mast cells as they trafficked through the dermis[39]. Constitutive production of IL-13 by this ILC2 population suppressed the function of mast cells. However, in inflammatory conditions in which mice were injected with an IL-2 complex that stimulated CD25 receptors, these innate lymphocytes were more frequent and increased their production of IL-5 and IL-13 and the recruitment of eosinophils. These findings suggest that ILC2 can have both suppressive or inflammatory effects depending on the conditions and cellular targets[39]. Finally, ILC3-like cells have been identified in mouse skin under inflammatory conditions and might contribute to an experimental psoriatic skin condition induced by administration of imiquimod[35].

Table 1 Mouse DC subtypes

DC type	Location and migration	Phenotype (mouse)	Function	Origin
Plasmacytoid DCs	Migrate between the blood, spleen and lymph nodes	$CD11c^{int}$ $B220^{+}$	Type I interferon	Bone marrow via CDPs or LMPPs
$CD8^{+}$ DC–like DCs	Spleen and lymph node; nonmigratory, resident cells	$CD8\alpha^{+}$, $CD11b^{lo/-}CD103^{+/-}$, $langerin^{+/-}$ $DEC205^{+}$ $Sirp\alpha^{-}$ $Clec9A^{+}$ $XCR1^{+}$	Cross-presentation, induction of T_H1 cells, uptake of dead cells, production of IL-12, capture of antigen from migratory DCs or from blood	Bone marrow via pre-DCs
	Interstitial (dermis for skin); migrate to lymph node	$CD8\alpha^{-}$ $CD11b^{lo/-}$ $CD103^{+}$ $Sirp\alpha^{-}$ $Langerin^{+/-}$ $DEC205^{+}$ $Clec9A^{+}$ $XCR1^{+}$	Cross-presentation, induction of T_H1 cells, uptake of dead cells, production of IL-12	Bone marrow via pre-DCs
$CD11b^{+}$ DCs	Spleen and lymph nodes; nonmigratory resident cells	$CD4^{+/-}CD8^{-}$ $CD11b^{+}$ $Sirp\alpha^{+}$ $DEC205^{-}$	Presentation of MHC II, capture of soluble antigen from blood or via conduits of lymph node	Bone marrow via pre-DCs
	Interstitial (dermis for skin); migrate to LN	$CD11b^{+}$ $DEC205^{+}$	Presentation of MHC II, induction of T_{reg} and T_H2 cells	Bone marrow via CDP greater than via $Ly6C^{hi}$ monocytes
Langerhans cells	Epidermis; migrate to lymph node	$CD11b^{int}$ $EpCAM^{hi}$ $Langerin^{+}$ $DEC205^{+}$ $CD103^{-}$	Presentation of MHC II, induction of T_H17 and T_H2 cells, deletion of self-reactive T cells, induction of T_{reg} cells	Fetal liver cells greater than via yolk sac cells greater than via bone marrow via $Ly6C^{hi}$ monocytes during inflammation
Monocyte-derived DCs	Anywhere (dermis and epidermis for skin, mainly during inflammation, rare in steady state)	$CD11b^{+}$ $DEC205^{+}$	Presentation tailored to pathogen and probably dictated by inflammatory environment TNF and inducible nitric oxide synthase (iNOS)-producing DCs (TIP DCs)	Bone marrow via $Ly6C^{hi}$ monocytes

Dendritic cells

DCs are present throughout the body and can be divided into at least five broad groups based on phenotypic, functional and developmental analysis (**Table 1**). Such diversity is probably needed to cover the vast array of pathogens encountered by the immune system, a conclusion supported by the differential expression of pathogen recognition receptors on DC subgroups[46–48]. These groups include plasmacytoid DCs, migratory and lymphoid tissue-resident $CD8^{+}$ DC–like DCs, migratory and lymphoid tissue–resident $CD11b^{+}$ DCs, Langerhans cells and monocyte-derived DCs. The different groups of DCs are derived from a range of progenitors[49]. Fetal liver–derived and yolk sac–derived cells generate Langerhans cells during embryonic development[50,51], whereas common DC progenitors (CDPs) seed plasmacytoid DCs and other conventional DC subsets. Pre-DCs, which are downstream of CDPs, have lost plasmacytoid DC generation capacity but generate lymphoid tissue–resident $CD8^{+}$ DCs and $CD11b^{+}$ DCs[52] and probably their migratory counterparts, referred to as respective $CD103^{+}$ and $CD11b^{+}$ DCs, found in many tissues[53,54]. Plasmacytoid DCs can also be derived from lymphoid-primed multipotent progenitors (LMPPs), which are of bone marrow origin[55]. Though their exact contribution to the steady-state pool of DCs is unclear, blood monocytes in adult mice can also generate DCs in various tissues, including the lungs[56], skin[57], gut[58] and spleen[59], usually but not strictly under inflammatory conditions. Such monocyte-derived DCs can contribute to both innate[59] and adaptive immune responses[60].

DC subsets in the skin have been extensively studied in mice and humans[53,54,61,62], and a picture is beginning to form that is relatively similar between species. A very simple view of skin DCs in mice is that there are three distinct subsets[54]: Langerhans cells, found in the epidermis, and two dermal populations corresponding to the $CD11b^{+}$ DCs and $CD103^{+}$ DCs found in other organs[53]. Based on several findings that suggest $CD11b^{+}$ DCs in various tissues, including the skin, are heterogeneous[48,53,58], it is likely that dermal $CD11b^{+}$ DCs consist of two different populations, which are phenotypically similar for most surface markers; one group deriving from pre-DCs and similar to splenic $CD8^{-}$ DCs and the other derived from monocytes. This would match nicely with DCs in human skin, which comprise up to four different subsets: Langerhans cells, $CD1c^{+}$ DCs, $CD14^{+}$ DCs and a recently identified $CD141^{+}$ DC subset[63]. In this scheme, Langerhans cells are found in both species, whereas human $CD141^{+}$ DCs match mouse $CD103^{+}$ dermal DCs and human $CD1c^{+}$ DCs of pre-DC origin and $CD14^{+}$ DCs of monocyte origin would together make up the mouse $CD11b^{+}$ dermal subset (**Fig. 2**). Our rapidly advancing capacity to define common relationships between mouse and human DC subsets will aid clinical application.

$CD103^{+}$ dermal DCs[64–66] and their human equivalents, the $CD141^{+}$ population[63] are members of the broadly represented $CD8^{+}$ DC–like DC group, with properties aligned to mouse splenic $CD8^{+}$ DCs. This group of DCs has a relatively well-defined role in immunity, particularly important for $CD8^{+}$ T cell responses and viral immunity[54]. These DCs are highly adept at capturing dead cells, express molecules directed to recognition of viral or other intracellular pathogens, express IL-12 (at least in mice) to drive T_H1 cell–type immunity and are very efficient at cross-presenting antigens for induction of $CD8^{+}$ T cell responses[67]. CD8-like DCs express molecules such as Clec9A, which recognizes F-actin released from necrotic cells[68,69], and TLR3 (ref. 47), which binds double-stranded RNA, an intermediate associated with most viral infections, indicating a major focus on intracellular, primarily viral, pathogens.

For herpes simplex virus-1 (HSV) infection of the skin, CD103$^+$ DCs were found to efficiently present viral antigens to both CD4$^+$ T cells and CD8$^+$ T cells, supporting their role in viral immunity[70]. They were also the dominant subset capable of cross-presenting skin-associated self antigens to CD8$^+$ T cells[62,70], indicating a potential role in self tolerance in the steady state. Human dermal CD141$^+$ DCs also efficiently cross-present antigens[63], aligning their function with the mouse CD103$^+$ DC subset and supporting a role for these DCs in viral immunity.

The role of migratory CD11b$^+$ DCs in mouse skin immunity is not as clear, though in other tissues they have been linked to T_H17 cell–mediated immunity[71,72]. After skin infection with HSV, CD11b$^+$ DCs were shown to present antigens preferentially to CD4$^+$ T cells[70], whereas after intradermal injection of protein antigen in adjuvant these DCs stimulated CD4$^+$ T cells in the lymph node (LN)[73] and skin[74], in the latter case also providing antigen for regulatory T cells (T_{reg} cells), which dampened responses by IFN-γ-producing CD4$^+$ T cells[74]. Intradermal infection with *Leishmania major* has also revealed an important role for CD11b$^+$ DCs in antigen presentation[75]. As indicated earlier, the CD11b$^+$ dermal DC group may contain two different subsets. One study divided the CD11b$^+$ dermal DCs based on expression of aldehyde dehydrogenase activity (ALDH), showing that ALDH$^+$ DCs could convert retinol to retinoic acid that could drive T_{reg} cell development[76], mirroring what had already been shown for ALDH$^+$ DCs in the gut[77].

Langerhans cells are positioned in the epidermis above the basal keratinocytes and are able to project their dendrites upward toward the cornified epithelial layer[6]. These dendrites can pass through tight junctions in a regulated manner, enabling sampling of material within the cornified layer without breaching epidermal integrity[6,78]. The function of Langerhans cells has been intensively studied in the last decade, with several reviews comprehensively covering this work[79–81]. These DCs were originally considered the archetypal DCs responsible for priming skin immunity but a few years ago were shown to be of questionable importance for responses to contact allergens or herpes simplex virus[82,83]. More recently it has been shown that Langerhans cells may have a role in contact hypersensitivity when the sensitizing agent is delivered at a very shallow depth, excluding access by deeper dermal DCs[80]. More recently, strong evidence was provided that Langerhans cells contribute to priming immunity to skin pathogens such as yeast (*Candida albicans*) and bacteria (*Staphylococcus aureaus*), favoring induction of T_H17 cell responses important for these pathogens[84,85]. In contrast, Langerhans cells had a poor capacity to induce CD8$^+$ T cell immunity, which was attributed to CD103$^+$ DCs. Langerhans cells can sample bacterial toxins on the apical side of tight junctions, enabling the generation of humoral immunity critical for protection from the damaging effects of this toxin, without requiring free toxin to breach the epithelial barrier[78]. Langerhans cells were also reported to be immunosuppressive, either inducing T cell deletion[86], or activating T_{reg} cells that dampened skin responses[87]. In the presence of the pathogen *C. albicans*, human Langerhans cells stimulated both skin-associated T_{reg} cells and effector T cells, the latter producing IL-17 and IFN-γ (ref. 88). Together, the above findings support a model where Langerhans cells provide important regulatory feedback but can also selectively contribute to effector T cell responses.

Functionally, plasmacytoid DCs are only moderately efficient antigen presenting cells compared to conventional DCs but can be a major source of type I interferons, especially during viral infection[89]. These atypical DCs circulate in the blood and are essentially absent from normal human skin[90]. However, they may be recruited during inflammatory conditions such as viral infection, allergy or autoimmunity. In the autoimmune disease systemic lupus erythematosis (SLE), they have an important role, producing IL-6 and type I interferons in response to autoantibody–nucleic acid complexes, driving autoreactive B cell responses[91]. In psoriasis, they drive disease initiation by producing type I interferon in response to complexes of the antimicrobial peptide LL37 bound to self nucleic acids[92].

Before leaving the discussion of DCs, it is important to emphasize that migratory DCs present in the skin are not the only DCs involved in skin immunity. Resident DC populations in the cutaneous draining LN include a CD11b$^+$ DC population and the CD8α$^+$ DCs, both of which also exist in the spleen. There is limited evidence that LN-resident CD11b$^+$ DCs participate in immunity[93–95], whereas LN-resident CD8α$^+$ DCs have been implicated in responses to various organisms, particularly viruses[67]. In studies examining access of CD8α$^+$ DCs to HSV-1 antigen, migratory dermal DCs were implicated in the transport of antigen eventually passed on to CD8α$^+$ DCs for cross-presentation[96]. Just how extensively LN-resident populations contribute to skin immunity probably depends on the pathogen and may be especially important for those infectious agents that kill migratory DCs.

αβ T cells

Human skin contains a large number of αβ T cells, essentially all of memory phenotype, and in number nearly twice that found in the blood[13]. These memory T cells consist of both CD4$^+$ and CD8$^+$ subsets, with about 10% of the CD4$^+$ T cells expressing Foxp3, indicative of a T_{reg} cell phenotype[88]. Some researchers have referred to all the T cells in human skin as tissue-resident memory cells, but we prefer to distinguish between those cells simply passing through the tissue (either recirculating memory cells or effector cells) and those that are disconnected from the greater blood circulation, remaining permanently in the tissue as a memory population; these latter cells we call tissue-resident memory cells (T_{RM} cells)[12]. The idea of T_{RM} cells in human skin was suggested by studies of psoriasis, where normal healthy looking 'uninvolved' skin from patients was transplanted onto immunocompromised mice that later developed graft psoriasis because of the presence of passenger T cells[97]. Failure to detect human T cells in the circulation of grafted mice suggested T cells resided permanently in the grafts. Detection of large numbers of T cells in human skin, expressing homing receptors for this tissue, was used as further support for the existence of T_{RM} cells[13]. In the mouse, studies of HSV-1 infection[12,98] demonstrated that skin-associated T cells could exist as a population disconnected from the wider circulation. First, greater numbers of memory CD8$^+$ T cells were detected in areas of previous infections. Second, these memory T cells were maintained in skin grafts. Finally, when virus-specific T cells from male mice were transferred into female mice that were then infected with HSV-1, responding cells from the male mouse were rejected from the circulation by their female hosts but survived in the epidermis. These observations showed that CD8$^+$ T cells could accumulate in the epidermis as a long-term tissue-resident memory cell population and, as an aside, implied that the epidermis was somehow disconnected from the greater circulatory pool; otherwise host T cells would have rejected the transferred virus-specific male CD8$^+$ T cells located there. Following demonstration of T_{RM} cells in skin and neuronal ganglia[12], T cells of a similar phenotype were reported to reside permanently in a wealth of tissues, including the gut, brain, salivary glands, the female reproductive tract, lungs and elsewhere[99–104], supporting earlier studies that described T cells with limited recirculation potential in the brain and gut[105]. In most studies, T_{RM} cells were of the CD8$^+$ T cell lineage and expressed a unique set of markers, including CD69, VLA-1 and CD103 (ref. 12). For skin T_{RM} cells, CD69 was expressed independent of antigen recognition, as was CD103 (ref. 106), though antigen recognition was required

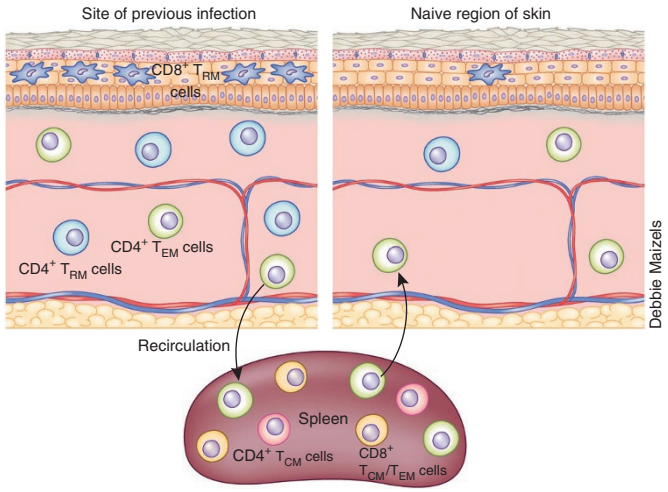

Figure 3 Tissue-resident memory T cells in the skin. After resolution of skin infection, various populations of memory T cells can be recognized in the skin and wider circulation. These include $CD8^+$ T_{RM} cells that are localized to the epidermis at the original site of infection, are rare in distant skin sites and are absent from the circulation. For $CD4^+$ T cells there appear to be skin-resident $CD4^+$ T_{RM} cells in the dermis as well as a circulating memory cell population (traditionally termed T effector memory cells (T_{EM} cells), although they could be a distinct, recirculating memory T cell subset[110]) found in both the dermis and wider circulation. It is yet to be determined whether $CD4^+$ T_{RM} cells are more highly represented at sites of previous infection as speculated in this diagram. Within the lymphoid tissues and blood, there are central memory $CD4^+$ T cells ($CD4^+$ T_{CM} cells), $CD8^+$ T_{CM} cells and $CD8^+$ T_{EM} cells, none of which appear to enter the dermis during memory, and $CD4^+$ T_{EM} cells, which can recirculate to the dermis. Although $CD8^+$ T_{RM} cells can enhance protection against local infection[12], they may recruit circulating memory cells $CD8^+$ T cells (T_{CM} cells and/or T_{EM} cells) to achieve this function[104].

for CD103 expression in tissues such as neuronal ganglia[106] and the brain[107]. T_{RM} cells were also reported to develop from $CD4^+$ T cells, in this case associated with lung infection[99].

In a study of HSV-1 infection of the skin[98], memory $CD4^+$ T cells and $CD8^+$ T cells showed different tissue locations and recirculation patterns, with $CD8^+$ T_{RM} cells found resident in the epidermis and memory $CD4^+$ T cells preferentially found in the dermis but capable of recirculating through the blood (**Fig. 3**). Evidence for both $CD4^+$ skin T_{RM} cells and $CD8^+$ skin T_{RM} cells came from examination of humans treated with the T cell–depleting monoclonal antibody alemtuzumab (anti-CD52), which revealed a major cohort of T cells in patients' skin, despite depletion of essentially all T cells from the peripheral blood circulation[108]. This not only demonstrated the existence of human $CD4^+$ T_{RM} cells and $CD8^+$ T_{RM} cells as well as tissue-resident $Foxp3^+$ T_{reg} cells, but hinted that the surviving T_{RM} cells provided functional immunity, as patients showed no increase in susceptibility to infections. Such capacity of T_{RM} cells to control infections is consistent with other studies showing that $CD8^+$ T_{RM} cells protect mice against skin infection with viruses[12,109]. Further support for skin $CD4^+$ T_{RM} cells was provided by a study that used T cells expressing the photoconvertible fluorescent protein Kaede to track migration[110]. By using ultraviolet light to convert skin-associated T cells expressing Kaede from green to red, a proportion of $CD4^+$ T cells were shown to migrate into the circulation, while many remained in the skin and expressed markers of T_{RM} cells, i.e., CD103 and CD69. Consistent with this report, about half the skin-associated $CD4^+$ T cells in mice[110] and humans[13] lack expression of CCR7, a chemokine receptor required for migration to the draining LN[111,112].

Although within mouse skin $CD4^+$ T cells appear to exist as both recirculating and resident populations located primarily in the dermis, memory $CD8^+$ T cells are predominantly resident and restricted to the epidermis[14,97,98,110] (**Fig. 3**). A few $CD8^+$ T cells can be found in the dermis in both humans and mice, but many of these are likely to be effector-type populations. The latter persist for about a month after the resolution of local infection in mice, after which they are confined to the epidermis around the site of their original recruitment[12,98]. Similarly, $CD8^+$ T cells were recently shown to vanish from the dermis 2 weeks after resolution of HSV-2 infection in humans, retreating to the dermal-epidermal junction[14]. The surviving cells had T_{RM} cell hallmarks: persisting for long periods in a highly localized pattern, expressing effector molecules associated with cytotoxicity and downregulating CCR7 and a G protein–coupled receptor $S1P_1$ required for tissue egress. Notably, they also carried the αα form of the CD8 molecule[14]. Given that HSV-2 infections in humans are often associated with continuous virus reactivation[113], the possibility that ongoing antigen stimulation drives this form of CD8 expression requires further investigation.

Infection with vaccinia virus showed that protective T_{RM} cells were also focused around the original site of infection as well as revealing a level of seeding throughout the broader noninfected areas of the skin[109]. This is similar to T_{RM} cell lodgment in the gut after systemic virus infection[101]. The detectable but relatively poor seeding away from sites of active infection probably reflects low inflammatory chemokine expression in the steady state because localized inflammation or chemokine administration efficiently seeds T_{RM} cells into the skin and mucosal tissues in the absence of antigen[106,114]. Although the frequency of T_{RM} cells at sites distant from the initial infection can be relatively low[12,109], their numbers in the skin increase dramatically after repeated immunization[109]. Use of parabiotic mice demonstrated efficient protection by T_{RM} cells compared to circulating memory $CD8^+$ T cells[109]. Finally, T_{RM} cells may protect in part by recruiting circulating memory cells to sites of virus reactivation or reinfection[104], though they also have direct effector capabilities[14,107].

Concluding remarks

The skin is rich in immune cells and infrastructure to ensure our fragile underbodies are well protected from an otherwise hostile environment. The last few years have seen a rapid increase in our knowledge of the cell types associated with the skin and have led to the identification of an ever-expanding array of cytokines, chemokines, antimicrobial peptides and other players that can be added to the immune arsenal. The exciting interplay between the host's immune system and normal flora and the influence this has on pathogen control is just beginning to be elucidated. It is evident that DCs are much more diverse than was first anticipated and that environmental cues as well as subset-specific genetic programs ensure the right DC is available to tailor immunity to each invading pathogen and to ensure rigorous control of self tolerance. Keratinocytes have a major role in pathogen detection, as do ILCs, γδ T cells, DCs and mast cells. Together, these cells direct and drive the appropriate T helper cell responses to mediate pathogen control and the development of memory T cells that control recurrent infections. Although circulating memory T cells are important immune mediators, it is the newly recognized tissue-resident memory T cells that provide premium protection and offer new strategies for vaccination. Knowing how these cells develop and expand within the

skin and how we can preferentially draft them via vaccination will be important for controlling skin-associated pathogens.

ACKNOWLEDGMENTS

We thank S. Mueller and A. Zaid for the immunohistology in **Figure 2b,c**. Supported by the Australian Research Council (W.R.H.) and the National Health and Medical Research Council of Australia (W.R.H. and F.R.C.).

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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