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Innate Lymphocyte Mechanisms in Skin Diseases

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Abstract

Innate lymphocyte populations are emerging as key effectors in tissue homeostasis, microbial defense, and inflammatory skin disease. The cells are evolutionarily ancient and carry conserved principles of function, which can be achieved through shared or unique specific mechanisms. Recent technological and treatment advances have provided insight into heterogeneity within and between individuals and species. Similar pathways can extend through to adaptive lymphocytes, which softens the margins with innate lymphocyte populations and allows investigation of nonredundant pathways of immunity and inflammation that might be amenable to therapeutic intervention. Here, we review advances in understanding of innate lymphocyte biology with a focus on skin disease and the roles of commensal and pathogen responses and tissue homeostasis.

INTRODUCTION

The skin provides a unique opportunity to understand tissue immunology, with the ability to clinically assess and longitudinally sample during periods of disease induction and resolution. These advantages have provided insights into fundamental biology, disease pathogenesis, and new approaches to treatment. Here we focus on studies of innate lymphocytes as evolutionarily ancient populations of cells for which there have been significant recent advances in our understanding, with broad implications across tissue homeostasis and disease. While recognizing the terminology controversies, we here define innate lymphocytes as those cells derived from the common lymphoid progenitor that are not specific to individual antigens but instead respond rapidly on first exposure to broad environmental cues. It is also recognized that lymphocytes with rearranged antigen-specific receptors can show innate-like responses via T/B cell receptor (TCR/BCR)-dependent mechanisms (1) and TCR/BCR-independent mechanisms, consistent with significant adaptive immune system overlap. In some cases, the cells have been described as unconventional, but it may be that this has rather reflected past and current complexities of study. Nevertheless, roles in diverse inflammatory and defense pathways have been described in the skin, with common themes emerging for bacterial immunity and tissue homeostasis as key evolutionary drivers, which will be focused upon in this review (**Figure 1**).

CUTANEOUS ILCs

Discovery of the innate lymphoid cell (ILC) lineages has provided us with greater understanding of the immunopathology of inflammatory skin disorders including atopic dermatitis (AD) and psoriasis, and additional therapeutic targets (2). ILCs have typical lymphocyte morphology, originate from the common lymphoid progenitor (3), and mirror the T helper subsets in transcription factor dependence and cytokine production (**Supplemental Table 1**). Unlike T cells, ILCs lack antigen-specific rearranged receptors and are primarily activated by innate alarmin-like signals. Upon reassessment (4) of the unified ILC nomenclature (5), cytotoxic natural killer (NK) cells were demarcated from the helper ILC lineages (ILC1/2/3). ILCs are primarily tissue resident (6); ILC2s and ILC3s are enriched at barrier tissues, where they exert their effector functions as professional cytokine producers, whereas ILC1s are more broadly distributed. All three ILC subsets have been described in subcutaneous, dermal, and epidermal layers of healthy and inflamed skin (7). However, ILC surface marker expression dependence on tissue localization can confound characterization (**Supplemental Table 1**), exemplified by the identification of more than 50 ILC subclusters in various tissues (8).

Supplemental Material >

ILC Response to Alarmins and Pattern Recognition

Skin residency and close interactions with both structural and immune cells position ILCs to sense skin barrier compromise and associated infection. Keratinocytes, fibroblasts, and hematopoietic cells secrete mediators that are the prototypic stimuli of ILCs. Among many documented stimuli, human skin ILC1s are primarily activated by IL-12 and IL-15; ILC2s are primarily activated by IL-25, IL-33, thymic stromal lymphopoietin (TSLP), IL-18, prostaglandin D_2 (PGD_2), and leukotrienes; and ILC3s respond to keratinocyte, dendritic cell (DC)- and macrophage-derived IL-23 and IL-1β (**Supplemental Table 1**). In addition to cytokines, ILCs can interpret direct signals of barrier compromise. ILCs express natural cytotoxicity receptor (NCR) genes constitutively or upon induction. Intestinal NCR^+ ILC3s sense bacterial components through NKp46 or NKp44, inducing IL-22 (9) or proinflammatory tumor necrosis factor α (TNF-α) production, respectively (10). In the skin, $NKp30^+$ ILC2s sense

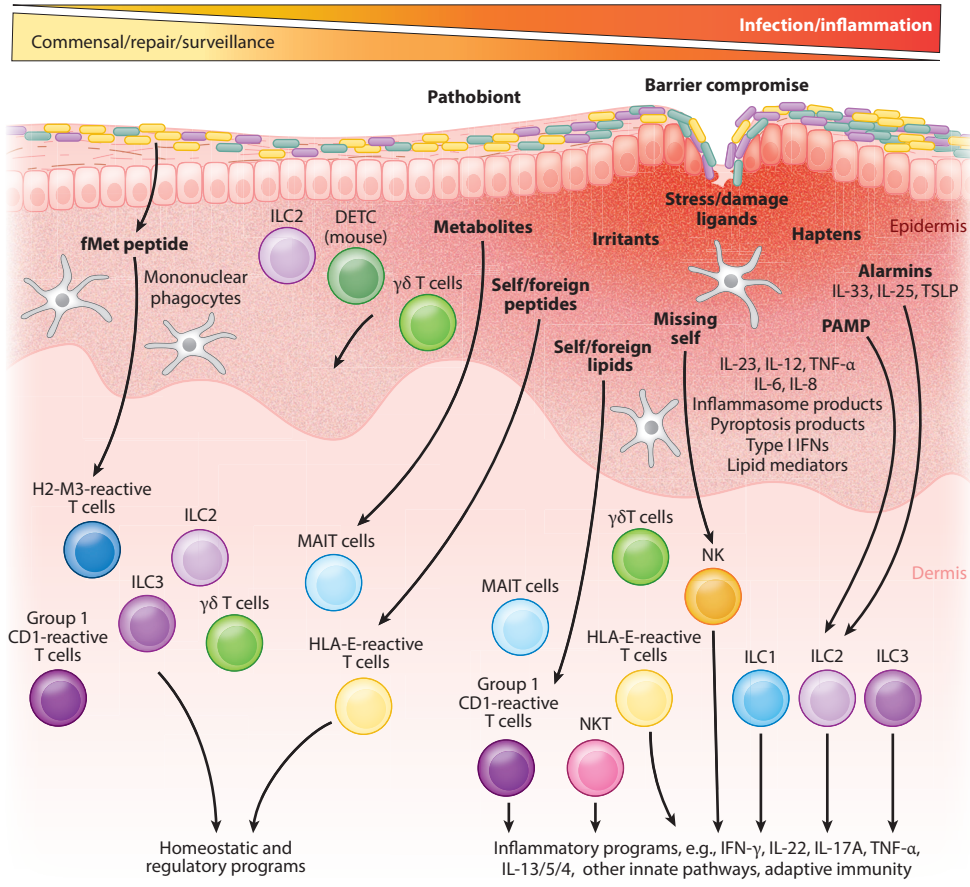

Figure 1

Innate lymphocyte populations in the skin during homeostasis and inflammation. Commensal, pathobiont, and pathogenic organisms include bacteria and fungi, which can be associated with disease under certain circumstances, such as during barrier dysfunction or innate immune defects. Abbreviations: DETC, dendritic epidermal T cell; fMet, *N*-formylmethionine; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; NK, natural killer cell; NKT, natural killer T cell; PAMP, pathogen-associated molecular pattern; TNF-α, tumor necrosis factor α.

increased expression of B7-H6 in AD lesions and tumors, resulting in type 2 cytokine production (11). The aryl hydrocarbon receptor (AHR), expressed by ILC3s, is an important modulator of IL-22 production and necessary for ILC3 development and maintenance and immunity to pathogens (12, 13) and commensal intestinal bacteria (14). This may have implications for ILC interaction with skin microbiota, as AHR^+ ILC3s have been found in healthy skin and are enriched in AD skin, a hallmark of the latter being *Staphylococcus aureus* colonization (8). ILCs are reported to express a variety of Toll-like receptors (TLRs) (15–17), and the resulting effector cytokine production may in part depend on a cytokine costimulus (18). TLR signaling has effects beyond cytokine production; for example, TLR2 and TLR4 stimulation of ILC2s can induce PLA2G4A phospholipase A_2 activity, which was suggested to contribute to ILC2 antigen presentation in the skin (19), and can promote apoptosis of ILC3s during chronic microbial exposure (17). TLR2 engagement might contribute to ILC3 activation during *Candida* infection (20), and it is likely that further pathways will be discovered.

Cutaneous ILC Interactions

Keratinocytes can express several pattern recognition receptors (PRRs) and cytokine receptors, and activation of keratinocytes induces a variety of ILC-activation cytokines, including TSLP, IL-33, IL-25, and IL-18. TLR sensing of AD skin-colonizing *S. aureus* by keratinocytes induces production of TSLP (21). Further dermal DC-derived IL-25 inhibits keratinocyte filaggrin production, potentiating AD inflammation (22). ILC interaction with structural cells of the skin not only mediates activation but also maintains tissue residency. Keratinocyte-derived CCL27 recruits ILCs into the skin from skin-draining lymph nodes (sLNs), and TNF-α-induced keratinocyte CCL20 expression promotes maintenance of $CCR6^+$ skin ILCs (23, 24). In addition, IL-7 and TSLP produced by hair follicles were shown to be vital for presence of epidermal and dermal ILCs (25).

ILCs reside in close proximity to neurons, but the interaction has mainly been studied in the lung and gut. Allergens and helminth infection induce secretion of neuronal vasoactive intestinal peptide (VIP) (26) and neuromedin U (27), which activate ILC2s, leading to rapid and potent cytokine- and tissue-protective amphiregulin production. Neuroregulatory receptor RET^+ ILC3s secrete IL-22 in response to glial cell–derived neurotrophic factors following microbial and stress signals (28). Conversely helminth-induced β_2AR signaling negatively regulates ILC2-driven immunity (29). The skin is highly innervated, suggesting neuropeptides may orchestrate cutaneous ILC responses. Indeed, upon chemical irritation or fungal infection, sensory neurons in the skin induce dermal DCs to secrete ILC3-activating IL-23 (30). Reciprocally, ILC2-derived cytokines can induce pruritus via direct sensory neuron activation (31).

ILCs interact with multiple immune and nonimmune lineages within barrier tissues. ILCs contribute to adaptive skin immunity, promoting T helper type 2 (Th2) cell differentiation through IL-13 and IL-4 secretion (32), cell-cell contact (33, 34), and OX40/OX40-L signaling (35). ILC2-derived IL-13 is critical for inducing DCs to produce Th2 cell chemokine CCL17. Indeed, ILC2 depletion impairs Th2 cell skin localization after allergen rechallenge (36). Interestingly in the absence of total ILCs, murine skin T cells are biased toward Th17 and Th2, with reduced Th1 and regulatory T cells (Tregs) (24). Therefore, sLN ILCs, upon migration to the skin, can regulate Th subsets in homeostasis, and cutaneous ILC establishment requires T cells. A functional dialogue with T cells has been described. ILCs can process and present peptide antigens with MHC class II molecules (MHC-II) (33, 34), modulating antigen-specific T cell IL-2 production, which promotes ILC2 proliferation and IL-13 production. $MHC\text{-}II^+$ ILC2s and ILC3s are found in the skin and sLNs. $MHC\text{-}II^+$ ILC3 effector function, whether suppressive (37) or activating (38), may be microenvironment dependent, and the role of skin $MHC\text{-}II^+$ ILC3s remains of interest. Furthermore, human skin ILC2s can express CD1a and are capable of presenting lipid antigens. This pathway may be used to sense *S. aureus* by promoting TLR-dependent CD1a-reactive T cell responses to endogenous ligands liberated by the phospholipase action of PLA2G4A (19). Although not described in the skin, murine NCR^- ILC3s can express lipid-presenting CD1d, with engagement inducing invariant natural killer T (iNKT) cell IL-4 and IFN-γ, and ILC3 IL-22 production (39). ILC2 production of type 2 cytokines and antigen presentation function have been shown to be amplified in the presence of the complement factor C3a (40).

Beyond T cell orchestration, ILCs interact with innate immune cells. Basophil-derived IL-4 promotes ILC2 proliferation during murine skin inflammation (41) and increases ILC2 production of cytokines and eosinophil attractant CCL11 (42). Basophil depletion results in reduced ILC2 expansion and reduced AD histopathology. ILC2s colocalize with mast cells during homeostasis (43) where skin ILC2–derived IL-13 suppresses mast cell function, suggesting a regulatory role for skin ILC2s (44). Mast cell production of PGD_2 potently induces ILC2 chemotaxis

and cytokine production (45). Moreover, upon activation, mast cells release leukotrienes (46), and also proteases that cleave IL-33 into hyperactive isoforms to further activate ILC2s (47). It is highly likely that soluble and cell contact mechanisms underlying cutaneous ILC function will continue to emerge.

ILC EFFECTOR FUNCTIONS IN SKIN HOMEOSTASIS AND DISEASE

ILCs are epigenetically poised to react rapidly to tissue-specific stimuli during homeostasis, stress or disease. ILCs possess open chromatin landscapes and are primed prior to activation during lineage differentiation. In contrast, subsets of $CD4^+$ T cells undergo significant chromatin remodeling on activation (48).

ILCs and Wound Healing and Homeostasis

Increased numbers of all three groups of ILCs are detected at wound sites. ILC2s contribute to wound healing through production of amphiregulin (49), and ILC3-derived IL-22 is an important keratinocyte growth factor (50). ILC3s are the dominant source of IL-17F following skin wounding, in addition to expressing IL-17A and IL-22 (51, 52). IL-33 is an important inducer of ILC2 responses in cutaneous injury (53), while ILC3s are recruited into wounded dermis by damage-induced epidermal Notch1. Notch1 signaling in the epidermis, without barrier damage, is sufficient to drive TNF-α, CXCL13, and CCL20 expression in the skin and recruit ILC3s. Delayed macrophage infiltration is implicated in the wound healing delay due to loss of ILC3-derived IL-17F and CCL3 (52).

ILC interaction with the microbiome has been documented in a reciprocal dialogue within skin follicles. Skin ILC-derived TNF and lymphotoxins act on sebaceous glands to negatively regulate the quantity and quality of sebum, regulating production of antimicrobial palmitoleic acid and modulating bacterial commensalism (25).

ILC1s and Skin Inflammation

ILC1s are a rare population in the skin (54, 55); indeed, understanding the role of skin ILC1s may be hampered by the heterogeneity of the ILC1 lineage, including intraepithelial ILC1s (56), noncytotoxic T-bet$^+$Eomes$^-$CD127$^+$ IL-15–dependent ILC1s (57), and IFN-γ-expressing ex-ILC3s (57–60). However, there is evidence that hapten sensitization of the skin initiates CXCR3-dependent migration of IL-7Rα$^+$ ILC1s into sLNs, to undergo priming and gain memory potential. Hapten sensitization induces ear swelling and ILC1-derived TNF and IFN-γ. When the skin reencounters hapten, memory ILC1s accumulate in the skin and mediate inflammation (61). In allergic contact dermatitis patients, IFN-γ- and TNF-producing CD3$^-$CD56^{high}CD16$^-$ cells accumulate in the skin (62, 63), and increased numbers of ILC1s and ILC3s are observed in psoriatic skin (8).

ILC2s and Atopic Dermatitis

ILC2s are abundant in AD lesional skin and cutaneous mouse models of house dust mite (HDM)- and MC903-induced dermatitis (41, 49, 64), producing IL-4, IL-5, and IL-13, key effector cytokines of AD pathogenesis. Strikingly, ILC2 production of IL-5 and IL-13 is necessary and sufficient for the development of experimental AD-like disease (44, 65). Notably, ILC2s of AD lesional skin demonstrate elevated IL-25R, IL-33R, and TSLPR. Models using multiple mouse strains

have shown variable dependence and redundancy of IL-25, IL-33, and TSLP in inducing ILC2 AD responses (49). Transgenic keratinocyte IL-33 overexpression is sufficient to induce accumulation of ILC2s and AD-like disease (64). Yet another study reported that TSLP was the primary activating cytokine of skin ILC2s, independent of IL-33 (65). Recently it was shown that IL-18-deficient mice exhibit decreased ILC2 accumulation in the skin and IL-5 and IL-13 production, with consequent decrease in eosinophilia during MC903-induced experimental dermatitis (66). Importantly transgenic keratinocyte overexpression of IL-18 results in severe dermatitis (67), and elevated IL-18 correlates with human AD severity (68). Indeed, IL-18R1 and IL-33R genes share a genome locus with risk for allergic disease (69). Beyond cytokine-mediated regulation, E-cadherin directly inhibits effector functions of human skin ILC2s, possibly via KLRG1 engagement (49). Null mutations in the gene encoding filaggrin are strongly associated with AD and confer altered barrier function (70). E-cadherin is downregulated in lesional AD skin, potentially linked to the loss of filaggrin (49, 71), and may contribute to ILC2 dysregulation in AD.

ILC3s and Psoriasis

It has been shown that RORγt$^+$ ILC3s and γδ T cells, rather than αβ Th17 cells, are the dominant IL-17A and IL-22 cellular sources in psoriaform inflammation (72). IL-17- and IL-22-producing NKp44$^+$ ILC3s are enriched in the blood and lesional skin of psoriasis patients (54, 55) and correlate with disease severity. Importantly NKp44$^-$ ILC3s gain NKp44 expression following IL-1β and IL-23 stimulation (54). Engagement of NKp44 increases cytokine secretion potential and induces a functional switch from homeostasis to proinflammatory IFN-γ and TNF-α production (10). NKG2D$^+$ ILC3 frequency is elevated in both lesional and nonlesional psoriatic skin (73), suggesting NKG2D may activate skin ILC3s. In support of a role for ILC3s in psoriasis pathogenesis, an anti-TNF-α therapy demonstrated correlation between disease amelioration and ILC3 reduction (55). Interestingly, substantial numbers of AHR$^+$ ILC3s and IL-22 are found in AD skin (74). Moreover, IL-22-producing ILC3s can contribute to inflammation and lichenification (8, 75).

NATURAL KILLER CELLS AND THE SKIN

NK cells are distinguished from helper ILC1s by often carrying machinery to directly lyse target cells, including virus-infected cells and tumor cells (4). NK cell functions are modulated by signals transmitted through germ line–encoded receptors, which render NK cells with nonredundant roles in the immune system (see **Supplemental References**). Phenotypically, NK cells have been divided based on their CD56 expression: CD56^{bright}CD16$^{+/-}$ and CD56^{dim}CD16$^+$ subsets, with the former exhibiting a helper phenotype that produces proinflammatory cytokines and the latter specialized for cytotoxicity upon stimulation. However, several NK cell subpopulations have since been described, suggesting NK cells are far more heterogeneous, with plasticity when responding to environmental cues (see **Supplemental References**). In addition to traditionally defined innate cells, which respond to pathogens in a nonspecific manner, NK cells have been shown to be capable of some degree of specificity (see **Supplemental References**).

Supplemental Material >

Human NK cells express three classes of inhibitory receptors recognizing MHC-I, including the killer cell immunoglobulin-like receptors (KIRs), the leukocyte immunoglobulin-like receptors (LIRs), and the CD94/NKG2 heterodimer. These inhibitory receptors contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic tail to transduce inhibitory signals. While KIRs recognize classical HLA-A, -B, and -C molecules and LIRs interact with classical HLAs and nonclassical HLA-G molecules, CD94/NKG2 engages nonclassical HLA-E. Notably, KIRs are highly polymorphic, displaying different affinities for HLA, which may

affect the subsequent cytotoxicity outcome. CD94 can couple with different members of the NKG2 family to form heterodimers to provide either inhibitory (NKG2A and NKG2B) or activating (NKG2C) signals. When cells are undergoing cellular transformation or viral infection, a missing-self phenotype can occur where low MHC-I can lead to cell death (see **Supplemental References**).

Supplemental Material >

NCRs represent one of several kinds of activating or inhibitory receptors responsible for inducing NK cell cytotoxic functions and consist of NKp44, NKp46, and NKp30. Under steady-state conditions human NK cells can express both NKp46 and NKp30, which are elevated on activated NK cells, while NKp44 is only expressed on $CD56^{bright}$ NK cells after activation. Several molecules can engage with NCRs, including virus-derived molecules and previously intracellularly localized proteins, which relocate to the cell surface under cellular stress or transformation. NCRs can interact with extracellular ligands as well (76) (see **Supplemental References**).

NK cells are detected in healthy human dermis (77–79); a subpopulation expresses tissue-homing receptors CCR8 and CLA but lacks CCR7 (80). The concept of adaptive NK cell (and ILC) memory or trained immunity is the subject of intense investigation and is reviewed elsewhere (81, 82), but human NK cells show recall responses after varicella zoster virus skin challenge, which may be mediated through epigenetic changes (83).

In atopic skin lesions, NK cells can be found infiltrating both dermis and epidermis, and in close contact with $CD1a^{+}$ DCs, modulating the cytokine production of DCs toward a type 2 profile (84, 85). Circulating NK cell frequency can be reduced in AD patients, with altered cytokine secretion and an elevated apoptosis rate (86, 87). In addition, peripheral NK cell cytotoxic activity is negatively correlated with disease severity (84, 88, 89), while the expression of CD62L, a receptor responsible for the initiation of leukocyte infiltration into inflammatory sites, is increased on peripheral $CD16^{+}$ NK cells (90).

The majority of psoriatic skin NK cells are found to express CD161; the inhibitory receptor NKG2A; activation marker CD69; and an array of chemokine receptors, such as CXCR3, CCR5 and CCR6 (91–94). These NK cells are equipped with the capacity to release IFN-γ plus TNF-α, which activate keratinocytes to express MHC-I, HLA-DR, and ICAM-1, and produce chemokines, including CXCL10, CCL5, and CCL20, to recruit NK cells into the skin (93). Chemerin, which binds to ChemR23 receptor on NK cells, is expressed in early psoriasis lesions, resulting in the recruitment of NK cells (95–98).

Allergic contact dermatitis (ACD) is a delayed type of hypersensitivity reaction in response to repeat exposures of haptens, and other antigenic forms. While T lymphocytes are a major cell type infiltrating into ACD skin, NK cells have also been shown to be essential contributors (62, 99). At the site of nickel-positive patch tests, skin $CD56^{bright}CD16^{-}$ NK cells express homing receptors CXCR3, CCR6, and CCR5 but are negative for lymph node homing receptors CD62L and CCR7, infiltrating both epidermis and dermis within 72 h (62). The NK cells express perforin, NKG2A, and the activating receptors NKG2D, NKp44, and NKp46, produce IFN-γ and TNF-α after IL-2 stimulation, and mediate apoptosis of keratinocytes (62). Monobenzone induces a memory-like, melanocyte-specific immune response that is dependent on NK cells and macrophages, but not T or B cells (100). The MC903 dermatitis model is partially dependent on ILC2s (49) and is controlled by Tregs through the TL1A-DR3 pathway (101).

While emerging evidence supports the involvement of NK cells in skin inflammatory disease, the complexity of these diseases and the variety of clinical patient cohorts render contradictory results. Moreover, recent advances in the finer definition of NK cell heterogeneity prompt the reevaluation of NK cells' role in skin disease progression, and further investigation of the underlying mechanisms is required.

MUCOSAL-ASSOCIATED INVARIANT T CELLS AND THE SKIN

Supplemental Material >

Human mucosal-associated invariant T (MAIT) cells are innate-like immune T cells and express semi-invariant TCRs with high expression of CD161 (102). MAIT cells are activated after recognizing specific bacterial metabolites presented by nonclassical monomorphic MHC-related protein 1 (MR1) molecules, and/or after IL-12/IL-18 incubation. They secrete proinflammatory cytokines, including IFN-γ, TNF-α, IL-4, IL-13, IL-17A, and IL-22, which contribute to the pathology of inflammatory diseases. MAIT cells are also capable of releasing granzyme and perforin, which kill infected host cells (see **Supplemental References**). MAIT cells can be found in human blood and both mucosal and nonmucosal barrier sites, such as lamina propriae of the small intestine and liver, lung, female genital mucosa, and skin (103–106). Peripheral blood MAIT cells can express skin-tropic chemokine receptors, including CLA, CCR6, CD49a, and CD103, suggesting their involvement in human skin (107, 108), and CCR2, which promotes their migration to inflammatory sites (109). Despite unaltered frequency compared to normal skin, MAIT cells are considered a source of IL-17A in psoriatic lesions, potentially leading to the exacerbation of disease (107, 110, 111). By contrast, increased abundance of MAIT cells can be detected in skin of patients with dermatitis herpetiformis, a vesicular disease associated with gluten hypersensitivity (108). Together, these findings suggest that MAIT cells can play a role in skin inflammatory conditions and warrant further investigation.

CD1-REACTIVE T CELLS AND THE SKIN

The CD1 family comprises nonclassical MHC molecules that present lipid antigens to T cells. Structurally, CD1 proteins are similar to MHC-I and consist of an α chain that is noncovalently bound to β_2-microglobulin. The CD1 family can be further divided into three groups, group 1 consisting of CD1a, b, c, group 2 consisting of CD1d, and group 3 consisting of CD1e. Group 1 and group 2 CD1 proteins have antigen presentation functions and are the focus of this section. CD1 proteins differ in the nature of the lipids they bind, their interaction with specific TCRs, and the subcellular compartments they survey (112). The group 1 CD1 proteins present endogenous and exogenous lipid antigens to αβ and γδ T cells largely bearing a diverse TCR repertoire, with some subsets expressing specific TCR variable regions (113, 114). In contrast, CD1d can present glycolipids and other lipids to iNKT cells, which express a semi-invariant TCR α protein (Vα24) paired with a limited repertoire of TCR β chains (in humans, Vβ11 being the most common), but other CD1d-reactive T cells can have a diverse TCR repertoire.

Lipids in the skin help to maintain the barrier function with keratinocytes, and sebocytes contribute to the unique lipid environment. A breach in the skin barrier may expose immune sentinels to these lipids; and thus, lipid sensing may provide an opportunity for a tissue-specific adaptation of immune surveillance in the skin. CD1a can bind several skin lipids including squalene, lysophospholipids, wax esters, free fatty acids, triacylglycerides, phospholipids, and sphingomyelins (115). CD1a is constitutively expressed by Langerhans cells (LCs) and can be induced on dermal DCs and other cells including skin ILCs (19, 116). Although the TCR repertoire of CD1a-reactive T cells appears diverse, the same TCR can interact with CD1a bound to different lipid antigens (115, 117), explained by absence of TCR engagement with the bound lipid (117). In this model, skin lipids that lack a polar head group (permissive ligands) do not interfere with this interaction and subsequent T cell activation. In contrast, lipids with a polar head group (nonpermissive ligands), such as sphingomyelins, disrupt the TCR-CD1a interaction and inhibit T cell activation (115, 117). Conformational change in other CD1 molecules upon lipid binding may also contribute to their TCR engagement. Furthermore, our understanding of other models of TCR-CD1a engagement and non-TCR ligands for CD1 molecules is likely to develop (118).

CD1 molecules sample distinct environments; for example, CD1a is found in early recycling endosomes, while CD1c samples early and late recycling endocytic compartments (119, 120). As they survey different intracellular compartments, polyspecific CD1a- and CD1c-reactive T cells could help in broad immune surveillance of the skin. Healthy individuals have both CD1a-reactive and CD1c-reactive T cells in the blood, many of which express skin homing markers (121–123). Functionally, CD1a-reactive T cells in healthy skin appear to predominantly produce IL-22, a cytokine implicated in early antimicrobial defense and wound-healing responses (115, 121). It is plausible that a subset of CD1-reactive T cells are functional counterparts of the dendritic epidermal T cells (DETCs) in mice. However, low CD1a expression has not been reported to be associated with susceptibility to skin diseases, suggesting functional redundancy (124, 125). However, elevated CD1-reactive responses may represent therapeutic targets.

CD1 and Dermatitis

Under homeostatic conditions, CD1-autoreactive responses may be kept in check by specific lipids in the tissue, and by interactions with other regulatory cell populations, and also by physical separation of lipids from the responding cells. Thus, in diseases such as AD, altered skin lipids in concert with barrier defects may lead to the activation of CD1-reactive T cells and exacerbation of inflammation. CD1 may contribute to inflammation directly by presenting allergen-derived lipids or indirectly by presenting neolipid antigens generated by the enzymatic activity of the allergen, activated immune cells, or microbial communities. HDM, a common household allergen, can generate neolipid antigens via HDM-derived PLA2, which can be inhibited by filaggrin (126). Similarly, bee and wasp venom–derived PLA2 can also generate neolipid antigens that activate CD1a-reactive T cells (127, 128).

Among the group 1 CD1 proteins, CD1a is most widely studied in the context of dermatitis. Pentadecylcatechol (C15:2) found in poison ivy can bind to CD1a, and patients with poison ivy dermatitis show CD1a-dependent production of inflammatory cytokines IL-22 and IL-17A (129). Furthermore, a transgenic mouse model showed that CD1a plays a role in allergen sensitization (129). Phospholipids present on the surface of cypress pollen can also bind to CD1a as well as CD1d and trigger cytokine production by T cells in allergic individuals (130). Betts et al. (131) have reported that a broad array of contact sensitizers, including dinitrochlorobenzene,1,4-benzoquinone, resorcinol, isoeugenol, and cinnamaldehyde, can activate CD1a- or CD1d-mediated responses. These responses are dependent on the presentation of endogenous lipids and suggest a common mechanism for how different sensitizers may amplify inflammation by targeting CD1-autoreactive T cells.

Changes in the skin microbiome are causally linked to chronic inflammation in AD (132–134). These might directly or indirectly affect the local lipid antigen presentation by regulating CD1 expression on antigen-presenting cells (APCs) (135), by producing bacterial lipid antigens that can be presented by CD1, by infection-induced production of endogenous lipids, or by producing enzymes that can produce neolipid antigens. De Libero and colleagues (136) have shown that bacterial infection increases the synthesis of self-glycolipids, which can stimulate CD1a and CD1b self-reactive T cells. As above, ILC2s from AD patients exhibit increased PLA2 activity upon stimulation with bacteria, for example *S. aureus* (19). LCs are specialized in uptake and loading of bacterial antigens from *Mycobacterium leprae* (137), and the mycobacterial lipopeptide dideoxymycobactin is a known CD1a ligand (138).

More correlations suggest an inflammatory role for CD1 in AD. LCs that express CD1a are increased in the lesions of AD patients (139). One study also found an unusually high expression of CD1b on lesional epidermal LCs from AD patients (140). CD1d expression and the frequency

of iNKT cells are increased in lesional AD skin (141). An inflammatory role for iNKT cells is further supported in vivo through models of contact hypersensitivity, while other studies suggest a regulatory role of iNKT cells in contact hypersensitivity to the hapten DNFB (142).

CD1 and Psoriasis

There is evidence for a role of both group 1 and group 2 CD1 molecules in psoriasis pathogenesis. Psoriatic patients have increased numbers of CD1a-reactive T cells in circulation as compared to healthy controls, and their responses are amplified in the presence of a mast cell–derived phospholipase (PLA2G4D) (129, 143). Kim et al. (129) also observed a CD1a-dependent exacerbated inflammation in a CD1a-transgenic mouse model of imiquimod-induced psoriasis. CD1b-autoreactive cells are enriched in the blood of psoriatic patients (144). Furthermore, in the context of hyperlipidemia, CD1-autoreactive T cells can drive disease through IL-17A production (145).

Group 2 Vα24$^+$ cells are elevated in psoriatic lesions, and their numbers correlate with disease severity (146). CD1d expression is also enhanced in keratinocytes within psoriatic plaques (147). Injection of a human iNKT line into SCID mice engrafted with prepsoriatic skin resulted in the development of a psoriatic plaque (148).

In contrast, in a mouse model of delayed-type hypersensitivity (DTH), iNKT cells were shown to suppress a DTH response to UV exposure (149). Although UV treatment is used to suppress inflammation in psoriasis, subsequent effects on iNKT cell function have not been extensively studied. Overall, the role of the CD1 system in psoriasis pathogenesis and treatment is emerging and will likely offer new targets for therapeutic intervention.

CD1 and Melanoma

Though the metabolic reprogramming in melanomas entails an altered production of lipids, their immunogenicity is understudied. It is conceivable that skin lipids serve as surrogates of tissue health and indicate cellular stress in transformed cells. Interestingly, LCs in skin tumors express low levels of CD1a, and supernatants from melanoma cell lines suppress CD1a expression by DCs (150–152). In some cancers, CD1a is a favorable prognostic marker, and a higher density of CD1a expression is linked to increased survival and reduced tumor recurrence (153, 154). Thus, established tumors may have developed strategies to escape CD1-lipid-mediated immune surveillance.

There is some evidence for the role of CD1d in antitumor immunity, mostly correlative in humans but more compelling in mouse models (155–160). iNKT cells may act directly on tumors bearing CD1d-lipid or augment antitumor CD8$^+$ T cell responses (161). However, in human studies, iNKT cell therapies may require additional factors to enhance antitumor effects in vivo (161).

HLA-E and the Skin

HLA-E is a nonclassical MHC-I molecule that can bind a diverse array of self-peptides derived from leader sequences of classical MHC molecules or HLA-G, stress proteins, and nonself peptides derived from viruses and bacteria, some of which may be posttranslationally modified (see **Supplemental References**). Although it can be expressed at low levels by keratinocytes, melanocytes, and LCs, its role in skin homeostasis is unclear (**https://www.proteinatlas.org/ENSG00000204592-HLA-E/tissue**). Compounding the complexity of HLA-E function in host immunity is its ability to engage multiple receptors including innate receptors such as CD94/NKG2A and CD94/NKG2C on NK cells and T cells, as well as specific $\alpha\beta$ TCRs (162–164).

Supplemental Material >

HLA-E and Inflammatory Skin Diseases

Deficiency of NKG2C and increase in the frequency of the HLA-E*01:01 allele has been associated with psoriasis (165). The HLA-E*01:01 allele exhibits a lower surface expression and weaker peptide binding, but how this may contribute to disease is unclear. The lower surface expression of the HLA-E*01:01 allele may favor binding by the inhibitory CD94/NKG2A receptor, which has a higher affinity (166), further impairing NK cell–mediated inhibition of autoreactive T cells. Activated NKG2C-expressing NK cells have been shown to eliminate HLA-E-expressing keratinocytes (167). In this way, the deficiency of NKG2C may also be linked with the hyperproliferation of keratinocytes seen in psoriatic patients. A signal peptide derived from the stress-induced protein Hsp60 can bind HLA-E and prevent its recognition by NKG2A (168). Although the expression of Hsp60 is elevated in psoriatic plaques as compared to healthy skin, whether it can contribute to disease through HLA-E is unknown (169). It is possible that disruption of HLA-E NKG2C and NKG2A interactions may contribute similarly to other inflammatory skin conditions such as AD.

HLA-E and Skin Tumor Immunity

HLA-E bound to peptides from leader sequences of MHC molecules can inhibit killing by NK cells by engaging the innate receptors CD94/NKG2A on NK cells. Thus, in homeostasis, the surface expression of HLA-E could be an indicator of tissue health. There is some evidence that skin tumors can exploit this pathway to evade antitumor immunity. HLA-E is overexpressed in melanoma cells, and melanoma patients have higher levels of secreted HLA-E in serum compared to healthy donors (170, 171). In line with this, blocking the NKG2A receptor in vitro can enhance melanoma killing by NK cells (170, 172). As $CD8^+$ T cells can also express CD94/NKG2A, a similar inhibition of their cytolytic function by HLA-E can be expected.

There are conflicting reports for the functional equivalent for HLA-E in mice, Qa-1, supporting a role in tumor immune evasion as well as antitumor immunity. Wang et al. (173) showed that activated $CD4^+$ T cells can facilitate melanoma metastasis by suppressing NK function through Qa-1:NKG2A interaction. Conversely, tumors with impaired antigen-processing machinery presented neoantigens through Qa-1, activating specific cytotoxic $CD8^+$ T cells (174). TAP-deficient environments generate a different peptide repertoire for HLA-E (175). Blocking the inhibitory receptor, NKG2A, may still enhance broad antitumor activity by both NK cells and $CD8^+$ T cells, and this certainly warrants further investigation as a therapeutic target (176). Antibodies that block NKG2A have been shown to have a therapeutic benefit in a mouse model of HPV16-induced carcinoma and in human head-and-neck squamous cell carcinoma (177, 178).

Thus, HLA-E can provide rheostat-like regulation by engaging inhibitory or activating germ line–encoded receptors and specifically interacts with distinctive rearranged receptors on T cells. Hence, this complexity makes examining the function of HLA-E in host immunity and tissue homeostasis challenging.

γδ T CELLS AND THE SKIN

The specialized subset of γδ T cells termed DETCs populates the murine epidermis. DETCs are thought to represent an innate population, as they are derived from the fetal thymus and are quasi-monoclonal bearing a germ line–encoded invariant Vδ1Vγ5 TCR (179–183). DETCs can respond to antigens from stressed or damaged epithelium and are implicated in the maintenance of skin barrier function, wound healing, and protection against cutaneous malignancies (184–187). However, human skin lacks a DETC counterpart, and γδ T cells are a small proportion of all T cells in

the dermis and even smaller in the epidermis (188–191). Still, it is plausible that human γδ T cells play a role in wound healing and other skin disease; epidermal γδ T cells act synergistically with αβ T cells by producing insulin-like growth factor IGF-1 to aid wound closure in a skin organ model (190). Skin-resident γδ T cells have a distinct repertoire compared to their counterparts in the circulation (192); Vδ2 cells are the predominant γδ T cells found in human circulation; and within the δ2 population, the Vδ2Vγ9 subset exhibits a semi-invariant repertoire that contains public sequences, i.e., identical TCRs shared between individuals (see **Supplemental References**). Vδ2Vγ9 T cells respond to self or microbial pyrophosphate antigens derived from the mevalonate metabolic pathway and are dependent on butyrophilins BTN3A1 and BTN3A2 (193–196). Some studies have linked butyrophilin-like molecules in shaping the tissue-specific γδ T cell repertoire, for example, in the human gut, BTNL3 and BTNL8 expressed by the colonic epithelium, shaping the local γδ T cell repertoire (197). In mice, Skint1, a butyrophilin-like molecule expressed by keratinocytes, functions similarly to drive the maturation of DETCs in the skin (198). However, a human homologue of Skint1 is not yet known.

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Vδ2-negative γδ T cells are fewer in circulation and enriched within tissues. Their expansion in the blood is associated with cytomegalovirus (CMV) (199, 200). The Vδ5Vγ4 LES clone bound to endothelial protein C receptor (EPCR), which was upregulated on tumor cells and CMV-infected cells (201). As the CDR3 loop of the TCR bound to EPCR directly, the specificity of this interaction was independent of direct contacts with the lipid ligand on EPCR. Although EPCR expression by human keratinocytes may aid the wound-healing response (202), the degree of cross talk between γδ T cells and keratinocytes via EPCR is unknown.

The polymorphic MHC-like molecule MICA is another endogenous ligand for γδ T cells bearing Vδ1Vγ4 TCRs (203). MICA is induced upon cellular stress as well as on certain tumors (204). However, the affinity of MICA for the γδ TCR is remarkably lower than its affinity for the activating receptor NKG2D, which is expressed by γδ T cells, $CD8^+$ T cells, and NK cells (203). Hence MICA can transmit TCR-dependent and -independent signals to γδ T cells.

Specific Vδ1Vγ4 cell subsets can also bind to nonclassical MHC molecules including CD1d; for example, the germ line–encoded region of TCRs interacts with CD1d, while the specificity for CD1d-bound sulfatide is conferred by the interaction of the non–germ line–encoded CDR3 loop. Similarly, Vδ1Vγ5 (9C2) binds to CD1d loaded with α-galactosylceramide. Germ line–encoded residues of TCRδ bind CD1d, and the hypervariable CDR3 γ loop interacts with the lipid (see **Supplemental References**).

Besides endogenous antigens, some γδ T cells can also recognize bacterial antigens, and a subset of γδ T cells can be directly activated by cytokines independent of TCR stimulation. A recent study highlighted further how γδ T cells combine innate and adaptive functionalities (205); γδ T cell clones were isolated from human colon, which exhibited dual reactivity. Germ line–encoded hypervariable region 4 interacted with butyrophilin-like molecules, while the clonal-restricted response toward CD1d or EPCR was linked to Vδ1 CDR1–CDR3. A similar response was observed for a CD1c lysophosphatidylcholine-reactive γδ T cell clone (205).

γδ T Cells and Atopic Dermatitis

There is some evidence that γδ T cells play a proinflammatory role in AD. There is an increase in the frequency of Vδ2Vγ9 T cells in AD patients (206). Additionally, in severe disease, the frequency of $CD62L^{lo}CD45RO^+$ cells within the Vδ2Vγ9 subset is increased, suggesting they may be recruited to inflamed tissue. Patients with cutaneous associations of inflammatory bowel disease have elevated CLA expression on circulating γδ T cells, which is reduced upon corticosteroid treatment (207).

Epidermal abrasion releases Rae-1 (one of the mouse MICA homologues), which activates γδ T cells through the NKG2D receptor driving type 2 cytokine induction (208). Moreover, when the epidermal abrasion is combined with allergen sensitization, γδ T cells support allergen-specific IgE production (208). In a model of 2,4-dinitrofluorobenzene-induced contact hypersensitivity, dermal γδ T cells can promote inflammation by producing IL-17 (209).

γδ T Cells and Psoriasis

Dermal γδ T cells in mice have a propensity to produce IL-17A and are implicated in antimicrobial immunity as well as exacerbating cutaneous inflammation (209–211). In many mouse models of psoriasis, IL-17A production by dermal γδ T cells exacerbates the disease (210, 212, 213). γδ T cells have also been shown to be the primary source of IL-17A in an imiquimod-induced model of psoriasis (72). IL-38 has recently been shown to restrain γδ T cell production of IL-17A in the same model (214).

In psoriatic lesions, dermal γδ T cell numbers are elevated, and these γδ T cells can produce IL-17A in response to IL-23 stimulation (215). A distinct subset of Vγ9Vδ2 T cells expressing skin-homing markers CLA and CCR6 has been described in human blood (216). These cells can be recruited to inflamed skin, where they can activate keratinocytes. Interestingly, in the circulation of people with psoriasis their frequency is reduced, while being increased in lesional skin (216). Overall, it is possible that in psoriasis, safeguards that prevent inflammation by autoreactive γδ T cells may be deficient.

γδ T Cells and Antitumor Immunity (Melanoma)

γδ T cells were shown to protect against cutaneous tumors using chemical carcinogenesis or transplantable tumor mouse models (184). Since then several studies have suggested a similar function in humans. As many γδ T cells can recognize several stress-induced self molecules, it is perhaps not surprising that they play a role in immune surveillance against transformed cells, for example, through sensing the metabolic abnormalities of tumor cells, such as overproduction of phosphorylated intermediates of the mevalonate pathway (217).

Melanoma patients have a variable frequency of γδ T cells in circulation (218, 219). Human γδ T cells isolated from the skin can lyse tumor cells in vitro. Cytotoxicity of γδ T cells from melanoma patients is reduced (218), but Vδ1 and Vδ2 γδ T cell subsets may differ in cytotoxic function. Additionally, the tumor microenvironment could impact γδ T cell function. It is also possible that γδ T cells may switch to an immune-suppressive phenotype, which has been reported for other cancers (220).

Many questions regarding γδ T cells in human skin disease remain unanswered. What is the complete nature of skin-specific γδ TCR ligands and receptors, and how are they regulated? How does the skin safeguard against damage by autoreactive T cells? What are the selection pressures for the seeding and maintenance of the γδ T cell repertoire in human skin? It may be beneficial to use human in vivo challenge studies to gain a more comprehensive understanding of γδ T cells in skin health and disease.

COMMENSAL VERSUS PATHOGEN LYMPHOCYTE RESPONSES IN HOMEOSTASIS AND SKIN DISEASE

Skin is colonized by complex microbial communities, including symbiont, pathobiont, or pathogenic microbes. It has recently been recognized that the dialogue between the immune

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system and microbiome shapes both the innate and adaptive immune systems (133). While microbial communities can be found across mucosal and nonmucosal body sites, including skin, gut, respiratory tract, and female genital tract, the diversity and specificity of cutaneous microbiota highlight their roles in maintaining the balance of the skin ecosystem and regulating skin barrier functions (see **Supplemental References**). Moreover, the unique topographical skin niches influence the cutaneous microbiome through the subject's genetic predisposition, lifestyle, antibiotic treatment, and other environmental factors (221). Recent investigations suggest that commensal microbiota–host interaction is necessary for preventing the colonization of pathogenic counterparts (134) (see **Supplemental References**). The majority of studies have focused on bacterial microbiota, and this review accordingly reflects this, but it is recognized that fungi, viruses, and parasites will likely be shown to have major influences on the development and function of innate lymphocytes, with relevance to skin immunity, inflammation, and new approaches to treatment.

Bacterial superantigens have long been associated with inflammatory skin disease, including Kawasaki disease, AD, and psoriasis (222, 223). Through binding directly to germ line–encoded regions of the TCR, often with HLA cross-linking, superantigens can drive lymphocyte activation and skin homing. The degree to which such lymphocyte activation contributes to disease in relation to conventional antigen-driven TCR-mediated activation is debated (191) and reviewed elsewhere (224, 225).

Bacterium-derived ligands, including glycolipids, glycosphingolipid, and their analogues can directly activate iNKT cells through CD1d presentation. Furthermore, pathogen-triggered TLR signaling in APCs allows the generation of self-lipids for CD1d presentation. Additional pathways exist where iNKT cells can respond to microorganisms through a ligand-independent manner, activated directly by inflammatory cytokines produced by activated APCs (see **Supplemental References**). Accumulation of iNKT cells can be found during the early phase of certain skin-relevant bacterial infections, coupling with efficient cytokine production and bacterial clearance (226). For example, in humans, *Mycobacterium tuberculosis*–related glycolipids and self-lipids are presented to iNKT cells (227). In patients infected with *M. tuberculosis*, iNKT cell number and functions are negatively regulated (228, 229). At the infection site, iNKT cells assist B cells to promote humoral immunity against *M. tuberculosis* (230). Nevertheless, further investigations are required for understanding iNKT cells and their interaction with the skin microbiome.

The interrelationships between microbiome and skin immune system can shape the function of γδ T cells (231). Mice raised in germ-free conditions display aberrant γδ T cells, whereas commensal skin microbiota influence the number of skin IL-17A-producing γδ T cells (232, 233). Resident commensals are indispensable for maintaining skin integrity, in coordinating with local environmental cues. Pre-associating *Staphylococcus epidermidis* onto murine skin before infecting with the protozoan parasite *Leishmania major* augments IL-1 signaling, consequently regulating IFN-γ and IL-17A effector T cell function (134). γδ T cell–deficient mice have been reported to exhibit compromising defects in wound healing and cutaneous *S. aureus* clearance (190, 234, 235). Intradermal *S. aureus* challenge of these mice resulted in the accumulation of bacteria in the skin, with less T cell infiltration into the challenge site and lower IL-6 concentration in the serum (235). In addition, larger and chronic skin lesions developed in response to cutaneous challenge with *S. aureus*. Administration of IL-17A to γδ T cell–deficient mice rescues wound repair and reduces the bacterial loads, indicating the indispensable function of IL-17A in bacterial clearance (236). DETCs, which also express γδ TCRs, recruit neutrophils to the skin upon *S. aureus* infection; mice deficient in DETCs exhibit compromising defects in skin wound healing and cutaneous *S. aureus* clearance (236). Interestingly, germ-free mice exhibit more rapid wound repair, raising the possibility that the density and composition of skin microbiota are key factors in regulating wound healing (237).

Corynebacterium spp. can be abundant microbes on human and mouse skin (238, 239). An increased abundance of γδ T cells and their IL-17A production are described in the skin and sLNs of mice infected with *Corynebacterium*, which can be sustained up to 3 months after infection. Successful colonization of *Corynebacterium* selectively activates a subset of Vγ4$^+$ γδ T cells and alters the diversity of endogenous skin-resident microbiota in mouse skin. Interestingly, associating mice with *S. epidermidis* encourages Vγ4$^-$ γδ T cells instead, suggesting that distinct regulatory pathways are in place for different commensal species. Infection models using mycobacteria suggest that skin γδ T cells can regulate downstream CD4$^+$ T cell expansion (240, 241). Peripheral γδ T cell frequencies of patients with various bacterial infection are elevated and shown to be specialized in intracellular bacterial defense (242–244). However, much remains to be learned about the interactions between cutaneous microbiota and γδ T cells in shaping human skin integrity.

MAIT cells have been shown to recognize a variety of pathogen-derived antigens through MRI-presentation of APCs (245). The range of microorganisms includes bacteria and fungi, including several cutaneous species (see **Supplemental References**). MAIT cells are absent in germ-free mice, suggesting a critical role of bacteria in MAIT cell development (104, 246). MAIT cells can be activated in vitro by skin commensals including *S. epidermidis*, *S. aureus*, *Candida albicans*, and *Candida glabrata*, but not by *Streptococcus pyogenes* (247). Interestingly, TCR diversity analysis revealed that the *C. albicans*–reactive MAIT cell TCR repertoire displays lesser variation compared to *Mycobacterium smegmatis*–reactive or *Salmonella* Typhimurium–reactive MAIT cells (247). To date, the clinical relevance of MAIT cells in skin commensal or pathogenic microbiome-mediated immune responses is still underappreciated.

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As above, Qa-1 and Qa-2 are nonclassical MHC-Ib molecules and are predominantly found in the hair follicles of mice (248, 249); however, their roles in skin immunity are unclear. In addition to self-peptides, Qa-1 and Qa-2 present *Mycobacterium* peptides to CD8$^+$ T cells (250, 251). Human analogues of Qa-1 and Qa-2 are HLA-E and HLA-G, respectively (252). HLA-G is absent in healthy skin but is detectable under inflammatory conditions (253–257). As well as self-peptides, HLA-E also presents *Mycobacterium*- and *Salmonella*-derived and virus-derived peptides to CD8$^+$ T cells.

Another MHC-1b molecule, H2-M3, presents maternally transmitted N-formylated mitochondrial peptides and N-formylated bacterial peptides. H2-M3 has been reported to play an indispensable role in the clearance of pathogenic *Listeria monocytogenes* (see **Supplemental References**). Recent advances have demonstrated that a subset of commensal-specific H2-M3-restricted CD8$^+$ T cells drives the wound-healing process. The study showed that *S. epidermidis*–specific CD8$^+$ T cells recognized *N*-formyl methionine–containing peptide through H2-M3, accelerating wound healing in vivo (258). It is unclear how non-TCR signals are potentially integrated, for example, through Ly49A, which is also known to bind H2-M3 (259). However, how this specificity for commensals avoids cross-reaction with pathogenic microbes and how immune cells distinguish between commensals and pathogens using H2-M3 remain unclear. Furthermore, H2-M3 can be found in mice but is absent in humans, and the potential human analogues and ligands have not yet been determined (260).

Aberrant skin inflammatory conditions are associated with the dysregulation of host-bacteria immune interactions (221, 261). Most skin injuries heal well in healthy individuals; however, patients who suffer from diabetes, vascular insufficiency, chronic inflammation, and malignancy can experience impaired skin wound healing. Using a mouse diabetic model, a selective shift in the diversity of cutaneous bacterial species in the chronic skin wound is observed, and negatively correlates with skin re-epithelialization rate. A prolonged immune response occurs during barrier restoration, caused by the host's defense against the potentially pathogenic microorganisms (262). Anaerobic bacteria are thought to have a critical role in the pathogenesis of chronic wounds, but

little is known about the underlying mechanisms (263). Both *S. aureus* and *S. epidermidis* biofilms contribute to delayed re-epithelialization in mouse skin wounds (264). However, several studies have described *S. epidermidis* being capable of blocking *S. aureus* biofilm formation by secreting proteases, and preventing *S. aureus* survival through releasing antibiotics (265–267). Moreover, the interaction between *S. epidermidis* and human keratinocytes results in the production of antimicrobial peptides from keratinocytes, abrogating the colonization of pathogenic species (268). *S. aureus* and *S. pyogenes* have been shown to be clinically associated with AD and psoriasis, respectively, in the context of disease progression and therapeutic relevance (269–273). Shifts in the diversity of the microbiome have been reported in the setting of skin disease with recovery on treatment (221, 274–277). Bacterium-derived short-chain fatty acids delivered locally or from other sites can impact models of skin disease, for example, through effects on Treg function (278).

INNATE LYMPHOCYTES AND AUTOINFLAMMATORY DISEASE OF THE SKIN

Autoinflammatory diseases, including periodic fevers, are characterized by either systemic or localized inflammatory conditions that are partly driven by endogenous factors (279, 280). Several major pathways have been identified, and, here in this review, we focus on those with particular skin relevance, although it is recognized that wider pathways are involved: IL-1 and inflammasome pathway, type I interferon (IFN-I) pathway, and TNF pathway (see **Supplemental References**). Variants in the genes involved in these pathways can lead to intrinsic hyperactivity of the intracellular PRRs, excessive generation and accumulation of endogenous stressors, enhanced inflammatory signaling cascades, and the loss of negative mediators of these pathways. In addition, the genetics underlying severe and early forms of atopy are often linked to innate lymphocyte pathways [for example caspase recruitment domain family member 11 (CARD11)] and are well reviewed by Milner (281).

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The inflammasome is often a key element in the pathogenesis of autoinflammatory diseases. Infectious agents and danger signals stimulate specialized cytoplasmic receptors, such as the NOD-like receptor (NLR) family of receptors: NLRP3, NLRP1, AIM2, and MEFV, which initiate the assembly of inflammasome complex with adaptor proteins and caspase-1. Activation of caspase-1 results in the processing of pro-IL-1β and pro-IL-18, producing the active forms. Inflammasome activation is tightly regulated; therefore, single-nucleotide polymorphisms (SNPs) in the genes encoding components of the inflammasome may result in dysregulated proinflammatory responses (see **Supplemental References**). IL-1β can be released by human keratinocytes, macrophages, and DCs, and it activates neutrophils, macrophages, and ILC3s. IL-1 receptor antagonist (IL-1Ra) is a decoy inhibitor that competes the binding of IL-1 to its receptor, which downregulates the subsequent signaling.

Human type I interferons include 13 IFN-αs, IFN-β, IFN-ω, IFN-κ, and IFN-ε. They function as essential immune modulators during infections and autoimmune diseases, regulating cell survival, enhancing antitumor activities, and modulating functions of the adaptive immune system. Cells produce IFN-I upon sensing of microbial derivatives or autologous nucleic acids through PRRs, including TLRs or cytosolic nucleic acid sensors, such as melanoma differentiation–associated protein 5 (MDA5), retinoic acid–inducible gene 1 (RIG-I), and stimulator of interferon genes (STING). Engaging of the type I IFN receptors (IFNARs), which are composed of IFNAR1 and IFNAR2, triggers the activation of downstream signaling molecules, including Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2), signal transducers and activators of transcription (STATs), and interferon-regulatory factors (IRFs), and induces the upregulation of interferon-stimulated genes (ISGs), which contain loci encoding antiviral proteins, chemokines, and antigen-presenting

molecules. Negative regulatory mechanisms are in place to prevent the adverse effects caused by prolonged IFNAR activation; for example, after IFN-I binding, the IFNAR is internalized and undergoes ubiquitination and rapid degradation, abrogating further activation. Interferon-inducible proteins can suppress TYK2-mediated signal cascade, as well as interfere with the recruitment of IFNAR subunits to disrupt the IFNAR complex formation. Type I interferonopathy fits the definition of autoinflammatory diseases, as genetic defects occur in components of the IFN-I pathway, resulting in subsequently uncontrolled immune cascades (see **Supplemental References**).

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Type III interferons include a family of cytokines (IFN-λ1–4, IL-28, IL-29) that bind to the heterodimeric receptor IFNLR (IFNLR1 and IL10Rβ), known to be expressed by epithelial cells (282). Psoriatic lesions express higher levels of IFN-λ1 than AD sites (283), and a SNP in the 3′ untranslated region of IFNLR1 is associated with psoriasis disease outcome (284, 285). Th17 cells are thought to be one source of IFN-λ in psoriatic skin, which inhibits type 2 cytokine production and may contribute to antiviral defense. However, the role of type III interferons in skin disease remains to be fully investigated.

TNF-α is a proinflammatory cytokine that regulates innate immune functions and governs cell survival. The classical nuclear factor-κB (NF-κB) signaling pathway is activated upon TNF receptor 1 (TNFR1) and TNFR2 ligation. Posttranslational ubiquitination in TNF-α signaling is essential for mediating the formation of specific intracellular signaling complexes, determining cell fates. Several deubiquitinases, including A20, OTULIN, cylindromatosis, and Cezanne, are negative modulators of the TNF and NF-κB pathways. Dysregulation of the deubiquitination process and components of the NF-κB pathway are linked with several autoinflammatory disorders (see **Supplemental References**). TNFSF15, encoding a member of the TNF superfamily cytokines, was reported to associate with psoriasis susceptibility (286). Variants of TNF-α and its pathway members are associated with an altered risk of psoriasis phenotypes (287–289), and anti-TNF-α shows effectiveness in treatment.

Many autoinflammatory diseases clinically present in the skin, displaying constitutive activation of proinflammatory signaling (290). Inflammasome components NLRP3, NLRP1, and AIM2 have been found expressed in human keratinocytes; NLRP3 can sense bacterial derivatives and is involved in the sensitization phase of contact hypersensitivity (291). SNPs are reported in genes encoding inflammasome components NLRP1 and NLRP3 in individuals with psoriasis susceptibility (292). Furthermore, polymorphisms in the gene encoding CARD14, a regulator of the NF-κB pathway, are linked with psoriasis (293). Generalized pustular psoriasis (GPP), albeit less common, is a potentially lethal form of psoriasis, characterized by a widespread pustular rash accompanied with repeated episodes of fever (294, 295). Mutations of genes encoding anti-inflammatory mediators IL-1Ra and IL-36 receptor antagonist (IL-36Ra) associate with GPP (294–298). Treatment with IL-1 blockade has shown positive clinical responses in some patients (299). Research in classic psoriatic individuals with active disease also suggests the IL-36 pathway is relevant for the pathogenesis of the disease, raising the possibility of further therapeutic targeting (300).

IFN-I is an essential initiator of immune responses in psoriatic lesions (301), and, in humans, the IFN-I pathway is highly activated (302). Variants in genes involved in IFN-I signaling and production, including *IFIH1* and genes encoding MDA5 and TYK2, showed protective effects (286, 303). IFN-I can act on ILCs and T cells, regulating their survival and cytokine production (304, 305). Several strategies have been suggested to modulate the IFN-I/IFNAR signaling pathway in psoriasis where IFN-I is believed to exacerbate the pathology (306–308). However, the interferon signature profile in psoriatic skin remains uninhibited with drugs targeting IFN-I pathways, suggesting functional redundancy (307, 308; **Supplemental References**). Inhibitors targeting the downstream molecules of the IFN-I signaling pathway, such as JAK1 and TYK2,

have been reported to be effective. A recent study showed clinical benefit in targeting BDCA-2 in the setting of systemic lupus erythematosus (309).

Overall, these studies show that innate lymphocyte pathways are tightly linked to skin disease. Significant heterogeneity is emerging among innate lymphocyte populations with sometimes striking differences between human and model systems. Furthermore, there are significant differences between circulating and tissue innate lymphocytes. Such heterogeneity will be challenging to interpret and place into context and treatment relevance. However, the mechanisms underlying innate lymphocyte function and the sensing and repair of the microbial and physical skin barrier will likely generate insights into disease and into new approaches for therapeutic intervention. Furthermore, the mechanisms co-opted by microbes and tumors will provide further context to our understanding of fundamental biology and how this might be exploited for patient benefit.

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