REVIEW

Skin barrier immunology from early life to adulthood

Aurélien Trompette and Niki D. Ubags ✉

Our skin has a unique barrier function, which is imperative for the body's protection against external pathogens and environmental insults. Although interacting closely and sharing many similarities with key mucosal barrier sites, such as the gut and the lung, the skin also provides protection for internal tissues and organs and has a distinct lipid and chemical composition. Skin immunity develops over time and is influenced by a multiplicity of different factors, including lifestyle, genetics, and environmental exposures. Alterations in early life skin immune and structural development may have long-term consequences for skin health. In this review, we summarize the current knowledge on cutaneous barrier and immune development from early life to adulthood, with an overview of skin physiology and immune responses. We specifically highlight the influence of the skin microenvironment and other host intrinsic, host extrinsic (e.g. skin microbiome), and environmental factors on early life cutaneous immunity.

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The skin is an active immune-rich barrier tissue, which also acts as the outermost barrier of the human body and is thus one of the first lines of defense against exogenous threats. The physical, chemical, microbial, and immune barrier components of the skin form an interactive system, which contributes to cutaneous host defense and skin homeostasis as a whole. Skin barrier immunology has been well-defined and described in the adult setting. However, limited knowledge is available on the development of skin barrier immunity in early life due to technical challenges and ethical concerns related to early life skin sampling (Box 1). Here, we provide an overview of the current knowledge on skin immune and structural development from early life to adulthood, with a focus on the timing of immune cell seeding and their localization, and alterations in physical, chemical, and microbial properties. We highlight the similarities or differences between human and rodent skin.

Box 1 Sampling techniques for assessment of skin immunological responses

The pathophysiology of skin diseases, including atopic dermatitis (AD), has been extensively studied using skin biopsies. Due to the invasive nature of skin biopsy sampling and associated ethical issues, skin biopsies for diagnostic and research purposes in healthy infants and children and those with a skin disease are very limited. Hence, skin immune profiling in healthy subjects or in children with a skin disease is very limited. In addition, sampling limitations may bias our knowledge of skin immune responses as only localized sampling can be done in case of biopsies, and gene expression and lipid composition analysis of tape strips may only reflect the upper layers of the skin[176–180]. However, side-by-side comparison of skin tape stripping and skin biopsies of taped skin and adjacent non-taped skin in adult healthy controls and subjects with AD, indicated that consecutive skin tape stripping removed the stratum corneum and the upper part of the granular layer[181]. Moreover, gene expression levels of epidermal differentiation markers (filaggrin, corneodesmosin, loricrin, involucrin, and keratin-1) from skin tape stripping samples positively correlated with staining intensities of these markers in matching skin biopsies following immunostaining, suggesting that skin tape stripping is reliable for the evaluation of epidermal differentiation markers[181]. Analysis of stratum corneum biomarkers in skin tape strips from children were performed using proteomic, transcriptomic and quantitative real-time polymerase chain reaction (qRT-PCR) analysis[182–186]. The latter provided strong evidence that qRT-PCR analysis of minimally invasive skin tape strips across pediatric age groups can be used for identification of biomarkers associated with AD. In addition, this method may benefit clinical trials in which repeated measures are required to predict for example the course of the disease.

SKIN PHYSIOLOGY AND DEVELOPMENT OF IMMUNE RESPONSES

Skin physiology and physical and chemical barrier development

The development of skin immunity starts *in utero* alongside its structural development[1,2] and continues to mature and expand throughout early life and into adulthood. Adequate immune development in early life is imperative for establishing cutaneous homeostasis, which sets the tone for long-term skin health. In early life, the skin contains a diverse range of immune cell populations, despite having significantly fewer in total than mature adult skin[3], an observation made both in mice[4] and in humans[5]. The two main skin layers, the epidermis, a stratified structure composed of 90%–95% keratinocytes (KCs)[6], and the dermis, which lies underneath the latter, develop throughout

Faculty of Biology and Medicine, University of Lausanne, Service de Pneumologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland. ✉ email: Niki.ubags@chuv.ch

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multiple gestational stages[7,8]. The epidermis layer is maintained through continuous proliferation and differentiation of epidermal KCs in the basal layers and desquamation of corneocytes (dead, terminally-differentiated KCs) on the skin surface. Tight junctions hold these cells together, and degradation of these tight junctions is required during the termination of this dynamic process (i.e. exfoliation of dead skin cells)[9]. While undergoing terminal differentiation, KCs produce two key components: (i) structural proteins [e.g. filaggrin (FLG)] and (ii) lipids (mainly ceramides) that are equally essential for the formation of the stratum corneum (SC), the uppermost layer of the epidermis[10]. This process is often described as a brick-and-mortar model, where the corneocytes represent the bricks and the intercellular lipid matrix, in which the corneocytes are embedded, symbolizes the mortar[11,12]. The SC, which allows tightly-controlled permeability, is the cornerstone of skin barrier function[13].

The structural maturation of the skin, and particularly that of the epidermis, is achieved by 34 weeks of gestational age[14], whereas functional maturation [e.g. hydration, skin surface pH, and transepidermal water loss (TEWL)] starts *in utero* and continues into adult life[15–17] (see Table 1). Visscher and colleagues recently reported on the transcriptomics analysis of human newborn (6–10 weeks old), adult (20–24 years old), and elderly (60–65 years old) skin. Gene ontology analysis revealed differences in genes associated with epidermal development, keratinocyte differentiation, and immune function (antigen processing and presentation of exogenous antigen) with higher expression in adults than in infants[18]. Interestingly, similar findings have been reported comparing neonatal and adult murine skin[4]. This age-dependent maturation process is critical for establishing the physical and functional barrier properties of the skin. The cross talk between these different barriers is fundamental for their own development and maintenance but is also pivotal for the establishment of the so-called immune barrier and ultimately contribute to adequate maturation of the cutaneous immune system.

The physical barrier

Innate immunity is of paramount importance to protect the body from environmental aggression and infection, particularly at birth when the newborn emerges from the womb. Hence, achieving adequate epidermal barrier formation at birth is pivotal for the newborn, an event that is attained by 34 weeks of gestational age[14]. Despite having a thin epidermis[19], the skin from term newborns is characterized by low TEWL, indicative of low skin permeability, which is similar to that of adults[20,21]. However, TEWL in premature babies (25–32 weeks of gestational age) is elevated[22,23].

KCs, the predominant cell type in the epidermal layer, play a critical role in innate immunity and act as *bona fide* immune sentinels. KCs produce antimicrobial peptides and are equipped with Toll-like receptors (TLRs). Moreover, they not only participate in the regulation of the skin microbiota but can also recognize microbial components and initiate cascades of immune responses both in infants and adults[24–27]. KCs are also important mediators of skin immune homeostasis in early life. Using an experimental mouse model, Tamoutounour and colleagues demonstrated that by elevating their major histocompatibility complex (MHC) class II expression, KCs selectively control the accumulation of commensal-induced T helper (Th)1 cells in the skin after skin neocolonization[28]. In another study, Kobayashi *et al.* demonstrated that by secreting interleukin (IL)-7, thymic stromal lymphopoietin protein (TSLP), and the chemokine CCL20, adult murine KCs can regulate the development and localization of cutaneous innate lymphoid cells (ILCs)[29]. KCs also produce kallikreins (KLKs), which are essential for skin desquamation. KLK5 and KLK7 regulate skin innate immunity by controlling the activity of the antimicrobial peptide LL-37 both in humans (*in vitro*) and in mice (*in vivo*)[30]. The dysregulation of KLK proteases can cause skin inflammatory disorders, such as atopic dermatitis or psoriasis, underlining their role in skin immune homeostasis[31]. Furthermore, in mouse skin, KCs control the migration of skin-resident antigen-presenting cells toward draining lymph nodes and subsequent immune priming by releasing glucocorticoids, thereby modulating the skin physiological immune responses[32].

Cutaneous lipids are equally important for skin innate immunity. KCs and sebaceous glands are responsible for the production of skin lipids (e.g. ceramides, wax esters, and cholesterol esters) and sebum. Newborn skin contains high levels of skin surface lipids, particularly sebum[33]. Subsequently, sebum levels diminish within the first 6 months of life before increasing again during pre-adolescence and reaching adult levels[33–35]. Notably, it was shown that keratinocyte-derived lipids promote the survival of skin-resident memory T cells in both mouse and human settings[36], whereas human sebocytes produce lipids with immunomodulatory properties promoting the differentiation of monocytes into alternatively activated macrophages *in vitro*[37]. However, modulation of skin immunity by lipids warrants further investigation. Interestingly, using targeted proteomic analysis of human skin, Visscher and colleagues demonstrated that new-

Table 1. Evolution of the main structural and functional factors of human skin over time.

	Newborn	Infant (<1 y)	Adult
TEWL (g/m^2/h)[18,187]	8.7	15.9	10
Surface lipid - abundance[34]	++	+	++
Surface lipid - main source	Sebaceous glands	Sebaceous glands	epidermis
pH[21,188]	6.6-7.5	5.45-6.6	4.5-6.7
Hydration[187,189]	+	+++	++
NMF component levels[18]	+	+++	++
Microbiome composition (predominant genera)[115]	Natural birth: *Lactobacillus*	*1.Staphylococcus* *2.Corynebacterium* *3.Cutibacterium*	*1.Cutibacterium* *2.Staphylococcus* 3.*Corynebacterium*
	C-section: *Streptococcus and Cutibacterium*		

NMF = natural moisturizing factor; TEWL = transepidermal water loss.

born and infant skin contains elevated keratinocyte-derived biomarkers related to skin barrier function and innate immunity (e.g. antimicrobial peptides) compared with adult skin[1], confirming the age-dependent differences in epidermal maturation and the necessity for an accelerated differentiation status and effector function of epidermal KCs in early life.

The chemical barrier

Newborn skin has an alkaline pH at birth[21,38], which progressively decreases to adult levels[39] (pH of 5.4–5.9) during the first 2–3 months of life[40] (Table 1). This acidification of the skin surface is crucial for the establishment and physiological desquamation of the aforementioned physical barrier[41]. Indeed, many enzymes (e.g. β-glucocerebrosidase) involved in these processes are pH-dependent and function optimally at an acidic pH[39,42,43]. The acidification of the skin surface leads to the formation of the so-called acid mantle. This chemical, acidic barrier is paramount, particularly in neonates whose immature cellular immune system forces them to rely on innate immunity to mitigate the increased risk of infection in early life. Indeed, an acidic pH allows (i) the maintenance of a normal cutaneous microbiota, inhibiting pathogens, such as *Staphylococcus aureus*, while promoting the growth of the beneficial commensals, such as *Staphylococcus epidermis* and Corynebacteria[44,45] and (ii) the efficacious antimicrobial defenses (e.g. β-defensin 2, dermcidin, LL-37) against invading pathogens in human and murine skin[25,46–48].

The hydration levels of newborn skin reach adult levels a few months after birth[18]. One of the main mechanisms to retain skin hydration is the generation of a complex of water-binding molecules known as the natural moisturizing factor (NMF)[49]. Comprised mostly of amino acids derived from *FLG* proteolysis, along with lactate, urea, and electrolytes, the NMF helps maintain the acid mantle of the SC[50] and also participate in skin immunity. Using an *in vitro* system, uronic acid and 2-pyrrolidone-5-acid, both constituents of NMF, were shown to reduce the growth of skin pathogenic *S. aureus*, as well as its ability to express colonization and immune evasion factors[51].

A rather important yet poorly studied "chemical" barrier for the newborn skin is the vernix caseosa, a waxy mixture of water, cells, and lipids that coats the neonatal skin *in utero* and at birth. This lipid-base layer protects the baby from dehydration and allows the cornification of the fetal epidermis *in utero*. Due to the presence of antimicrobial compounds[25,52], as well as inflammatory cytokines and chemokines (e.g. tumor necrosis factor-α (TNFα), IL-8, IL-6, monocyte chemoattractant protein (MCP)-1)[18], the vernix acts as a crucial first line of defense by providing innate immunity to the newborn both *in utero* and at birth[1,53]. Vernix lipids also exhibit anti-inflammatory effects[54]. Qiao *et al.* demonstrated *in vitro* that vernix lipids from infants downregulate the production of TSLP and TNFα by human KCs exposed to polyinosinic:polycytidylic acid[54].

Immune development

Immune cell seeding of the skin occurs during the late stages of gestation and after birth. The epidermis and dermis contain a variety of resident immune cells, and we will describe their localization and maturation, plus the similarities or differences between human and rodent skin (Figs. 1 and 2, and Table 2).

Langerhans cell (LC) precursors are recruited to the epidermis around embryonic day 18 (mouse) and 7 weeks of gestational age (human), acquire a dendritic cell (DC)-like morphology directly after birth, with the expression of MHC class II molecules, CD207 (langerin), and CD11c, and consequently undergo extensive proliferation (10–20 fold expansion) between postnatal days 2 and 7[55–58]. The further differentiation of murine LCs requires transcription factors involved in transforming growth factor-β signaling (Runx3 and ID2) and engagement of colony stimulating factor 1 receptor by KC-derived IL-34[59–63]. The adult LC network is ultimately established by 3 weeks of age in mice, and once developed, these LCs form a self-renewing, radioresistant population within the epidermis[64]. Although LCs were long considered similar to DCs, they have a unique ontogeny, which led to their classification as being related to prenatally established non-lymphoid tissue macrophages[59,65]. Being an important antigen-presenting cell in the skin, LCs can migrate to the lymph nodes in a capacity similar to that of non-lymphoid tissue conventional DCs, whereas tissue macrophages are unable to migrate to lymph nodes[28]. Newborn mouse LCs are capable of antigen uptake and migration to the draining lymph nodes, even though they have differential expression of surface markers compared to adult LCs[4,58] (Table 2).

DCs are located in the dermis and comprise conventional DCs (cDCs), plasmacytoid DCs, and monocyte-derived DCs (moDCs). Conventional DCs, and specifically CD11b$^+$ cDCs, are the most abundant type of DCs in the healthy mouse dermis[66]. At this time, very little is known about the development of cDCs in the skin during early life. Naïve skin from neonatal mice contains fewer CD11b+ cDCs than those found in adults, and a gradual increase was observed with age, with the largest increase between weanling (postnatal day 21) and adult age[4]. Moreover, antigen uptake and processing capacity were reduced in neonatal cDCs[4], suggesting distinct differences between the neonatal and adult skin cDC pools. Interestingly, these differences may not be driven by microbial exposure because no changes were observed in the cDC populations in the skin of mice housed under specific pathogen-free conditions compared with those in a germ-free environment[4]. Fetal human skin DCs develop during gestation and can be recognized by their CD206 and CD1c expression from 9 weeks of estimated gestational age[67]. The frequency of human CD1c leukocytes increases with gestational age and reaches levels similar to those of adult skin by mid-gestation[67,68]. In mice, dermal moDCs are derived from extravasated Ly6C^{hi} monocytes, which acquire a DC transcription profile and ultimately share a partial transcriptional program with CD11b$^+$ cDCs on top of their monocytic signature[66]. Murine moDCs express high levels of IL-10, suggesting that they may have an anti-inflammatory role under homeostatic conditions[66].

Macrophages are located in the dermis and specifically in the perifollicular space[69–71]. After birth, dermal macrophages are the most abundant resident immune cell present in the skin and they rapidly adapt to alterations in the environment by establishing a heterogeneous mature macrophage population. In early life, dermal macrophages have nearly exclusively bone marrow origin[66,72]. Thereafter, the dermal macrophage population (in mice) receives continuous input from circulating Ly6C^{hi} monocytes, and this pool of macrophages of monocytic origin increases over time after repeated episodes of inflammation[66,73]. Kolter and colleagues recently added to this knowledge with the identification of a CX_3CR1^{int} macrophage subset in murine skin, which has a direct monocytic origin and expands during infection and injury[74]. Moreover, they observed that CX_3CR1^{hi} dermal mouse macrophages present in early life could persist beyond the first months of life if in physical contact with nerves, suggest-

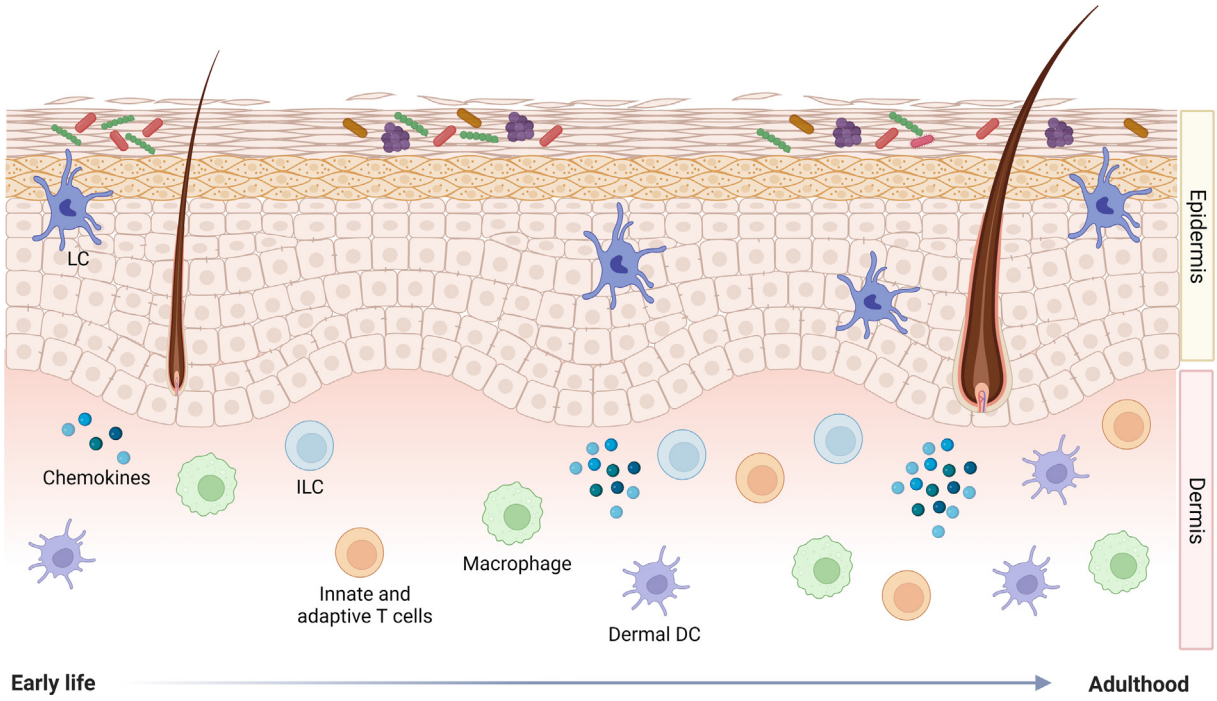

Fig. 1 The skin immunological landscape throughout development. In early life, murine skin has low-frequency antigen-presenting cells and chemokines, which increase during childhood and into adulthood. Under homeostatic conditions, Langerhans cells are located in the epidermis, whereas most other immune cells reside in the dermis. Chemokine seeding and antigen-presenting cell seeding and maturation is, at least in part, driven by the skin microbiome. The skin microbiome is less diverse in early life compared with adulthood and develops during the first weeks of life. DC = dendritic cell; ILC = innate lymphoid cell; LC = Langerhans cell. This figure was created with biorender.com.

ing that under homeostatic conditions, these skin nerve-associated macrophages originated from CX_3CR1^{hi} prenatal progenitors. In early life, high levels of IL-10 expression in mouse dermal macrophages, similar to that seen in moDCs, indicate an anti-inflammatory role and thus involvement in tissue homeostasis and repair under homeostatic conditions[66]. Gene ontology analysis revealed that cutaneous *S. aureus* infection enhanced the terms associated with antigen presentation, response to interferons, and positive regulation of cytokine production in dermal mouse macrophages 3 weeks after infection, suggesting lasting changes in innate memory responses; however, this effect was lost at 6–12 weeks after infection, likely due to replenishment of the dermal macrophage pool[75]. Dermal mouse macrophages have antigen-presenting cell capacities from early life onward[4]; however, these capacities are considered poor compared with conventional and monocyte-derived DCs, which are responsible for most of the antigen uptake and presentation in the skin and associated lymph nodes.

The most abundant resident *T-lymphocyte* subsets in the human skin are αβ T cells, whereas mouse skin is mainly composed of γδ T cells[76,77]. T cells are first detected in the human fetal skin at 17–18 weeks of gestational age, and most conventional αβ T ($CD4^+$ and $CD8^+$) cells have a naïve and proliferative phenotype at this developmental stage[68,78]. However, a subset of memory-like conventional T cells with an enhanced propensity to reduce IFNγ has also been observed in the fetal human skin[78]. The majority of T cells are located in the dermal-epidermal junction. Regulatory T cells develop in close proximity to the hair follicles[78] and accumulate in the skin during the first weeks of life[79]. This accumulation coincides with early life skin colonization by commensals[79]. Murine skin contains a cell type not described in humans, namely the dendritic epidermal T cells (DETCs), which are resident γδ T cells. Only very small numbers of DETCs have been observed in fetal human skin[76]. The first step in the development of DETCs is the adhesion molecule and chemokine-mediated migration of Vγ3+ T cells from the thymus and circulation to the epidermis. Ultimately, once seeded in the epidermis, DETC expansion is mediated by IL-15 produced by adjacent epithelial cells. IL-7 receptor signaling is important for the development, and specifically survival and proliferation, of the DETCs[80,81], whereas IL-15 signaling plays an important part in their maturation and expansion[82,83].

ILCs can reside in subcutaneous, dermal, and epidermal layers of the skin and originate from common lymphoid progenitors present in the fetal liver and bone marrow[84]. Murine skin ILC2s have been shown to peak during the neonatal and infancy period[85], and only a minority of tissue-resident ILC2s during adulthood are replenished from hematopoietic stem cells, indicating that this pool in adult skin is still largely composed of the population formed during the early stages of life. The localization and residency of skin ILCs requires epithelia-derived chemokines and cytokines. Interestingly, dermal ILC2s have been shown to produce IL-13 at steady state, independent of the skin microbiota composition, IL-25, IL-33 or TSLP[86]. Through this capacity to secrete Th2 cytokines, ILC2s present in healthy skin can thus foster cDC2 activation, thereby inducing Th2 priming independently of exposure to allergens[87]. Kobayashi and colleagues observed that ILCs can also regulate commensal bacteria through cross talk with hair follicles and sebaceous glands under homeostatic conditions. Although there have been reports on the influence of microbiome alterations on ILCs in early life (*in utero* and postnatal), most of these studies have

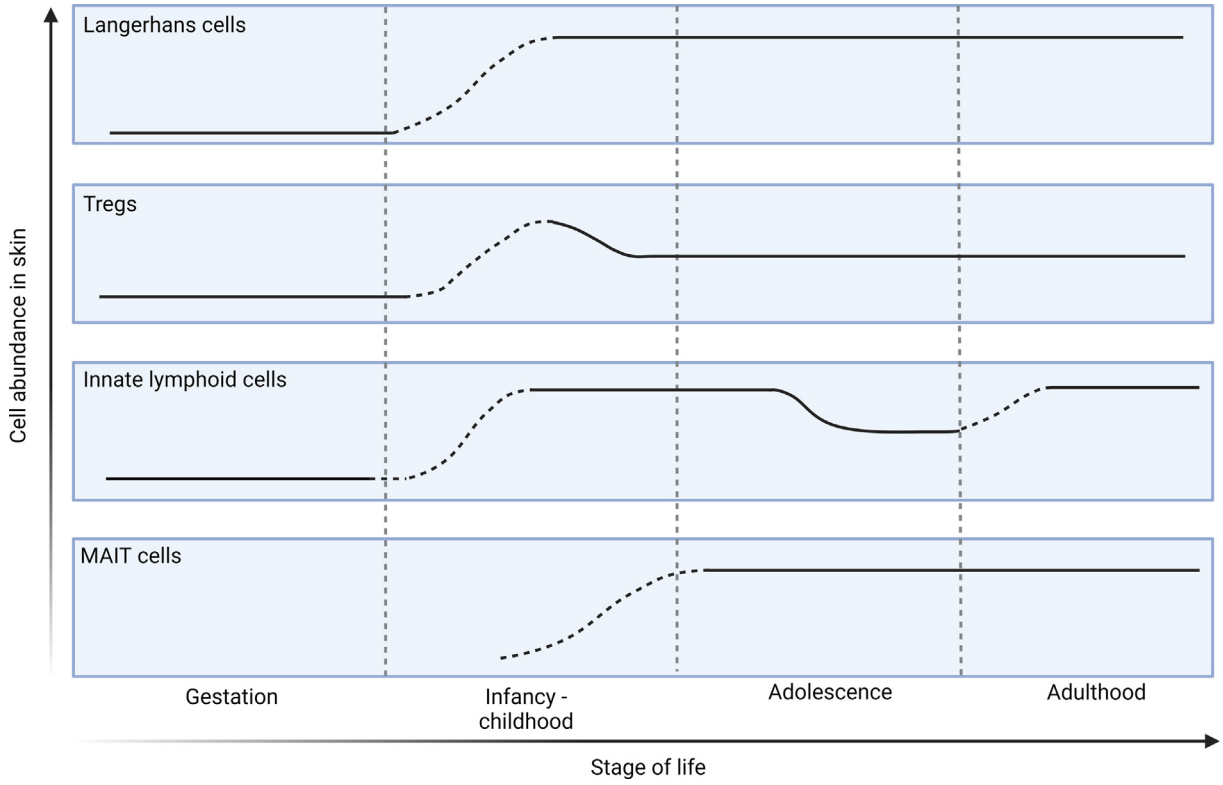

Fig. 2 Murine skin immune cell abundance during development. Developmental trajectories of murine skin immune cells from gestation through to adulthood. Dashed lines indicate expansion of the cell population. This figure reflects the current knowledge and does not include all immune cells due to limited availability of data. MAIT = mucosal-associated invariant T cells; Tregs = regulatory T cells. This figure was created with biorender.com.

been performed on lymphoid tissue ILCs, and the effects in non-lymphoid tissues, such as the skin, remain to be determined.

Mucosal-associated invariant T (MAIT) cells are present and enriched in the skin of both human (~2% of $CD3^+$ T cells) and mice (20%–40% of αβ-T cells)[88,89] and are localized at the interface of the dermis and epidermis, in close proximity to the basal layer. It was recently described that MAIT cells accumulate in barrier tissues of mice, including the skin, between 2 and 3 weeks of age, thereby strengthening the idea that MAIT cells develop during a very specific temporal window in early life and in response to defined microbial exposures[88]. Skin MAIT cells are tissue resident and require IL-23 for homeostasis. MAIT cells represent a dominant Th17 effector subset in the murine skin and are associated with tissue repair based on their gene expression profile. Similarly, human MAIT cells depend on IL-23 for acquiring a strong Th17 phenotype after antigen stimulation[90].

FACTORS INFLUENCING SKIN IMMUNITY AND ITS AGE-DEPENDENT DEVELOPMENT

Genetic

Genes involved in skin structure are pivotal for skin health, and abnormalities in such genes can promote skin inflammation and disease. Over the last decades, epidermal barrier dysfunction has received much attention and has been associated with a variety of immune diseases, such as Netherton disease[91], ichthyosis vulgaris (IV)[92], and particularly atopic dermatitis (AD)[93]. The filament aggregating protein *FLG* plays an important role in the formation of the epidermal barrier by (i) binding to keratin fibers in KCs and (ii) forming most of the NMF, once degraded by proteolysis in the SC. *FLG* mutations are strong predisposing factors for AD in children[94]. After this work, the association between *FLG* mutations and increased risk for AD or IV has been reproducibly reported[95–97]. Particularly, heterozygous loss-of-function mutations in *FLG* are associated with type 2 allergic disorders, such as AD and allergic asthma[95], whereas homozygous loss-of-function mutations cause onset of IV[98]. Experimental mouse models have contributed to deciphering how mutations in the *FLG* gene influence immune responses. *FLG*-deficient mice exhibit a Th17-dominated skin inflammation and eczematous changes with age and are permissive to epicutaneous sensitization with protein antigen[99]. Interestingly, in flaky tail (ft/ft) mice (which have a spontaneously arising autosomal recessive mutation located at chromosome 3 within the mouse epidermal differentiation complex), no visible skin lesions were observed at 4, 8, and 16 weeks of age, but skin lesions appeared at 28 weeks of age. However, the high expression of IL-17 and IL-17-promoting cytokines IL-6 and IL-23 was observed in the skin of 8-week-old ft/ft mice[100], suggesting that although no overt skin inflammation was observed, an enhanced Th17 inflammatory response was present at baseline. In addition, peripheral Th17 cell frequencies are increased in adult *FLG* mutation carriers and similar results were observed in adult ft/ft mice[109]. Circulating Th17 cell frequencies were not altered in 2-week-old ft/ft mice compared with controls, suggesting that this exaggerated T_H17 phenotype is acquired over time and other exogenous factors are involved. *FLG* deficiency is also associated with an increased SC IL-1 cytokine profile[101]. Indeed, patients with AD with an *FLG* null muta-

Table 2. Cutaneous immune development over time.

Immune cell	Properties	Origin	Location in skin	Timing of skin appearance	Key differences between human and mouse skin	Differences in cell function between neonates and adults	Interactions with microbes
LCs	Antigen presentation Migration to lymph nodes	Yolk sac-derived myeloid precursors Fetal liver-derived monocytes	Interfollicular epidermis Hair follicles	Found in the epidermis at approximately embryonic day 18 (mouse) Proliferation between postnatal day 2-7 (mouse) Adult LCs present in skin by 3 weeks of age (mouse) Human LC precursors found in the epidermis by 9 weeks EGA[190]	Acquisition of MHCII and CD207 postnatally in mice while human epidermal LC precursors already express HLA-DR, CD1a, CD207, and Birbeck granules by week 11 of EGA[190,191]	Newborn and adult LCs express different surface markers Murine neonatal LCs mainly express CD14 and CD204 at birth, then start expressing MHCII (day 2 after birth), CD205 (day 7), CD207 (day 3), CD80, and CD11c[58] Murine adult LCs express CD207, CD205, CD11b, CD86, and MHCII[58] These differences in surface marker expression between murine neonatal and adult LCs may explain why antigen uptake has been reported to be lower in neonatal LCs compared with adults[4]	Reduced LC frequencies and numbers in germ-free mice[4] Limited responsiveness to extracellular bacteria[192]
Conventional Dendritic cells	Antigen presentation Migration to lymph nodes	Bone marrow-derived blood-borne precursors (pre-DCs)	Dermis	9 weeks of gestational age (human)	Gradual seeding between day 21 and adult age in mice while adult levels are reached by mid-gestation in humans	Antigen uptake and processing capacities are reduced in neonates compared with adults (mouse)[4]	Antigen uptake and processing function seem independent of microbiota (mouse)[4] Reduced frequencies and numbers in germ-free mice[4]
moDCs	Antigen presentation	Extravasated Ly6C^{hi} monocytes	Dermis	Dependent on cutaneous exposures	Murine dermal moDCs are phenotypically characterized as CD11b^{+}, CD24^{lo}, CCR2^{+}, Ly6c$^{+/lo}$, MHCII^{+}, and CD64$^{+/lo}$[193] Human dermal mo-DCs are CD11c^{+} CD14^{+}, CD1a^{-}, CD1c^{-}, CD141^{+}, and CD207^{-}[194]	Human neonatal moDCs have an altered cytokine response (reduced IL-12p70 production) and blunted expression of HLA-DR and CD86 after LPS stimulation *in vitro)* compared to adult moDCs. This altered phenotype might contribute to their T_H2-biased effector function and reduced capacity to elicit IFNγ production from naïve cord blood T cells[195]	Unknown
Macrophages	Tissue homeostasis and repair Antigen presentation phagocytosis	Bone marrow (early life) Extravasated circulating Ly6C^{hi} monocytes (early life and adulthood)	Perifollicular dermis	At birth In humans, macrophages were isolated as early as 17 weeks EGA[196]	Human dermal macrophages phenotypically characterized as CD209^{+}, LYVE1^{+}, F13A1^{+}, CD14^{+}, and autofluorescent-positive[193] Murine dermal macrophages are CD11b^{+}, CD24^{lo}, CD64^{+}, Ly6c^{-}, CCR2^{-}, and MHCII^{+} or MHCII^{-}[193] Murine monocyte-derived dermal macrophages are the homologs of monocyte-derived human dermal CD14^{+} cells[59]	In early life, high levels of IL-10 expression on dermal macrophages.	Reduced numbers in germ-free mice[4]. *S. aureus* elevates innate memory signature in mouse dermal macrophages[75]

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Table 2 (**continued**)

Immune cell	Properties	Origin	Location in skin	Timing of skin appearance	Key differences between human and mouse skin	Differences in cell function between neonates and adults	Interactions with microbes
T lymphocytes (αβ and γδ T cells)	Skin homeostasis (*human + mouse αβ and γδ T cells)* Wound repair (*γδ T cells mouse, subset unidentified in human T-cell studies*) Skin immunity	Thymus	Dermal-epidermal junction	Fetal human skin T cells were isolated as early as 17 weeks EGA[196]	T cells develop *in utero* (human) Predominantly *αβ* T cells in human, whereas γδ-T cells are predominant in mouse skin Epidermal γδ T-cell population only present in mice	T cells from adult human skin mainly express CD45RO, whereas fetal skin T cells express CD45RA[196] Adult skin T cells also produce more T_H1 (IFNγ), T_H2 (IL-5, IL-13), T_H17 (IL-17A) in response to an IL-2/IL-15 *in vitro* stimulation compared to fetal skin T cells[196] Fetal human skin T regulatory cells express higher levels of FoxP3 compared with those in adult skin[78]	Skin commensals regulate the balance between regulatory and effector T cells specifically in the skin tissue[133]
ILCs	Host protective immunity Barrier regulation and microbial homeostasis Metabolism Tissue repair	Common lymphoid progenitors in fetal liver and bone marrow	Epidermis and dermis Epidermis predominantly contains ILC3 Dermis contains both ILC2 and ILC3	ILC2 peak during neonatal period and infancy Prenatal ILC2 precursors seed skin during fetal development and contribute to the adult pool ILC2s are found as early as embryonic day 17.5[85]	Human ILC2s are characterized by the expression of GATA-3, CD161, CRTH2, CD69 (variable), ICOS (variable), and $CD117^{hi}$ or $CD117^{lo}$ ILC2s represent the main ILC population in human skin[197] In mice, ILC2s express GATA-3, IL-$18R1^{hi}$, CD69, KLRG1, $ST2^{lo}$, and IL-$17RB^{lo}$[197]	Minority of tissue-resident ILC2 in adulthood replenished from hematopoietic cells	Skin ILCs can regulate commensal bacteria via mutual cross talk with hair follicles and sebaceous glands ILC2s do not depend on skin microbiome composition for IL-13 production at baseline (mouse)
Mucosal-associated invariant T (MAIT) cells	Antimicrobial immunity Tissue repair	Thymus	Interface of epidermis and dermis. Close proximity to basal layer	Accumulate in skin between 2-3 weeks postnatal (mouse) Development of skin MAIT in human not defined	MAIT cells are enriched in the skin, both in mice (20% of αβ T cells on average, and up to 40%) and in humans (2% of CD3+ lymphocytes on average compared to 1% in blood)[88] $CD4^-$ $CD8^-$ double negative (DN) skin MAIT in mice, CD8+ and $CD4^-$ $CD8^-$ DN skin MAIT in human	Unknown	Development dependent on microbial exposure Recognize specific bacterial riboflavin metabolites[89]

EGA = estimated gestational age; ILCs = innate lymphoid cells; LCs = Langerhans cells; MAIT = mucosal-associated invariant T cells; moDCs = monocyte-derived dendritic cells.

tion expressed higher levels of IL-1α and IL-1β in the skin than patients with AD without such mutation. In addition, NMF levels were inversely associated with these IL-1 cytokines and with skin pH values, resulting in higher skin pH in patients who are *FLG*-deficient[101]. The skin pH and compounds present in the NMF play an important part in host defense against skin pathogens, including *S. aureus*[51]. Although most of these studies have been performed in adults, it is likely that these, at least to some extent, can be extrapolated to the childhood setting. Hence, understanding how *FLG* mutations alter not only the structural barrier but also the immunological barrier in early life is pivotal and will aid in designing tailored therapeutic approaches for this vulnerable population.

Although *FLG* has been extensively studied, other genes involved in the formation and maintenance of the skin physical barrier [e.g. serine protease inhibitor Kazal-type 5 (*SPINK5*), *Claudin 1*, *ELOVL4*] have also been implicated in the etiology of AD and other skin diseases[96,102–104]. For instance, loss-of-function mutations in *SPINK5*, a gene coding for a protease involved in the regulation of the desquamation process of the skin, were shown to result in exaggerated exfoliation, ultimately leading to thinning of the SC. Patients carrying autosomal recessive *SPINK5* mutations develop the so-called Netherton syndrome, experiencing ichthyosis, erythroderma, hypernatremic dehydration, and severe atopic symptoms[105].

The abnormalities in genes directly involved in immunity can also cause diverse skin inflammatory processes and diseases. For instance, patients with dominant-negative mutations in *CARD11*, a gene coding for a caspase expressed in lymphoid cells and activated upon triggering of the T- and B-cell receptors, often present symptoms of severe AD[106]. Similarly, mutations in the gene coding for *CARD14*, a pro-inflammatory signaling molecule primarily expressed by epidermal KCs, have been associated with diverse skin disorders. Individuals carrying dominant-negative loss-of-function mutations of *CARD14* are predisposed to AD[107], whereas patients with gain-of-function *CARD14* mutations have a propensity to develop psoriatic Th-17-mediated skin inflammatory disorders[108,109]. Some of these findings could be observed in genetically-modified mice. Indeed, mice carrying a single *CARD14* gain-of-function mutation (*Card14*ΔE138) spontaneously develop an IL-17/IL-23-driven psoriatic skin inflammation[110]. Genetic alterations of other signaling molecules, notably those involved in the nuclear factor κ-light-chain-enhancer of activated B-cell pathway, have also been associated with skin inflammation. Reduction or genetic ablation of TNFα-induced protein 3 expression in epidermal KCs promotes AD and psoriasis both in humans and mice[111]. Furthermore, *RelB* and *Trim32* deficiency leads to AD or AD-like symptoms in mice but intriguingly, only after exposure to viruses[112] or engagement of the virus-specific TLR7[113]. The latter study also reported that lesional skin of patients with AD contained reduced levels of *TRIM32* compared with healthy or psoriatic skin, confirming the aforementioned murine findings.

Skin microbiome

Skin microbiome and immune development

Directly after birth, the skin is exposed to many environmental factors including microbes, chemicals, and allergens. These extrinsic factors can (in)directly influence development and maintenance of skin barrier function and skin immunity[114].

In utero, the skin develops in an environment that is considered sterile. Skin microbiota seeding starts during birth and continues to develop over the first weeks and month of life[115,116]. Microbes in the skin are located in the epidermal layers and the hair follicles, with the latter being the preferred colonization site for commensals[117,118]. Immaturity of skin structure and appendages, as observed in preterm infants, may influence skin microbiota composition and seeding in early life[119]. The skin microbiota composition is also greatly influenced by the mode of delivery (vaginal vs. cesarean section)[120–122], at least in the short term. The skin of babies born vaginally is predominantly colonized by *Lactobacillus*, whereas skin of those born through cesarean section harbors a microbiota dominated by *Streptococcus* and *Cutibacterium* genera[115]. After 6 weeks, the vaginal signature disappears and the infant skin exhibits a microbiota enriched in *Staphylococcus*, *Corynebacterium*, and *Cutibacterium* genera resembling that of adult skin[115]. However, how these initial differences in skin microbiota composition influence development of skin immunity remains under-investigated. Human skin site-specific microbiota profiles start to form after 4 to 6 weeks of life, and although the number and type of genera on a specific site do not significantly change during the first year, relative abundance and thus microbial diversification increases with age into adulthood (Table 1)[123]. However, unlike the gut microbiome, the skin microbiota is characterized by relatively low diversity but shows resilient stability over time (apart for puberty[124] where hormones and lipid-rich sebum alter the skin microbiome profile). Attaining this stability very early in life is paramount considering the central role played by the skin microbiota in the establishment of a robust skin barrier. Indeed, the skin microbiome (i) constitutes a barrier against the environment on its own (the so-called microbial barrier)[125], (ii) aids in strengthening both the physical and chemical barriers of the skin, and (iii) has a strong influence on host immune responses and maintenance of homeostatic immunity[125].

One of the first and probably most important events instigated by the skin microbiota is the induction of neonatal tolerance. Employing both murine and human models, this process was shown to be achieved by (i) the induction of a wave of T regulatory cells into the skin after early life skin colonization by commensals[79], an event that required the coordination between bacterial colonization, hair follicle development, and CCL20 production[126], and (ii) the interaction of commensal bacteria with neonatal CD301b$^+$ type 2 conventional DCs and subsequent production of retinoic acid by the latter population[127]. Establishing cutaneous immune tolerance is a key step in newborns, but so is instructing adequate innate and adaptive immune responses to establish homeostatic immunity, an event that heavily relies on the skin microbiota. Using an experimental mouse model, our group recently demonstrated that age-related microbial colonization of the skin can drive early life skin immune cell seeding and maturation (specifically, chemokine and alarmin production and seeding of the skin by antigen-presenting cells)[4]. Interestingly, *in vitro* studies revealed that skin commensals activate distinct signaling pathways compared to skin pathogens (*S. aureus*) in primary human KCs, promoting the expression of different antimicrobial peptides and amplifying the innate response to skin pathogens[128]. Mycolic acid, from the commensals *Corynebacterium*, elicits the expansion of IL-17A-producing γδT cells in adult mouse skin in an IL-23-dependent mechanism, without overt inflammation[129]. Lipoteichoic acid (LTA) from gram-positive commensals (e.g. *S. epidermis*) drives mast cell expansion in a TLR2-dependent manner by stimulating stem cell factor production in both adult murine

KCs and primary human KCs[130]. LTA can also elicit anti-inflammatory effects in adult mouse KCs through an LTA-TLR2-mediated suppression of TLR3-driven inflammation after skin injury[131]. Developing immune responses in the skin of the newborn is pivotal, but this process is delicate and must be well regulated to avoid excessive inflammatory signals. One example of this fine line is the transitory skin rash nearly 50% of all newborns develop after birth called erythema toxicum neonatorum. This rash is thought to be caused by commensals that colonize the skin and hair follicles of the neonate, activating local macrophages to produce IL-6[132]. Attaining homeostatic immunity is thus paramount for the developing newborn skin, so that ongoing colonization by the skin commensals is tolerated, cutaneous immunity matures, and excessive inflammation is avoided. Using murine models (germ-free *vs.* colonized mice), Naik *et al.* demonstrated that, similar to what occurs in the gut, skin commensals regulate the balance between regulatory and effector T cells, specifically in the skin tissue (with no effect in the skin-draining lymph nodes)[133]. Moreover, *S. epidermis* was shown to regulate skin effector T-cell function (IL-17A and IFNγ production) by promoting IL-1 signaling and consequently protective immunity against the skin pathogen *Leishmania major*[133]. In another study performed in mice, humans, and non-human primates, Naik and colleagues demonstrated that commensals, particularly *S. epidermis*, are critical for inducing seeding of the skin with IL-17A-producing $CD8^+$ T cells without causing inflammation[134]. Furthermore, IL-17A-producing $CD8^+$ T cells helped enhance innate barrier immunity by stimulating the antimicrobial response of interfollicular KCs to the fungal pathogen *Candida albicans*. This effect was dependent on the coordinated response of local commensal-sensing $CD103^+$ DCs and IL-1-producing $CD11b^+$ DCs. The same team demonstrated that this skin commensal-driven homeostatic immunity is governed by non-classical MHC class I presentation of commensal-derived antigens to $CD8^+$ T cells in adult murine skin[135].

Skin microbiota is also key to tissue repair. This is exemplified by the seeding of the neonatal skin by MAIT cells, a subset of specialized T cells capable of sensing metabolites, particularly microbial-derived riboflavin (vitamin B2) derivatives. Absent in germ-free mice, their expansion necessitates early life microbial colonization by riboflavin-synthesizing commensals[88]. The authors showed that MAIT cell stimulation by *S. epidermis*-derived riboflavin induces an IL-17A-dependent intrinsic tissue repair program[88]. Conversely, members of the skin microbiota can drive dysbalanced cutaneous immune responses. For instance, excessive *S. aureus* colonization was observed in both children (colonization rate: 57%–100%) and adults (colonization rate: 54%–100%) with AD[136], as well as in the lesional skin of patients with psoriasis[137]. Of note, the influence of the microbiome in early life on skin immune and structural development was outlined in the recent review from Zhang and colleagues[138].

Alterations in the skin microbiome and its impact on skin immunity

Throughout life, skin microbiota composition can be influenced by antibiotics usage, hygiene (excessive usage of topical cleaners), diet, and living environment, among others. These factors can consequently influence local immune responses potentially leading to the development of skin disorders, such as AD, psoriasis, rosacea, or acne[139]. Oral antibiotic administration (vancomycin) in mice led to skin dysbiosis, an event that reduced the cutaneous expression of RegIIIγ, a C-type lectin promoting proliferation and differentiation of KCs, thereby impeding wound healing responses[140]. Conversely, using an antibiotic treatment targeting *S. aureus* and *Corynebacterium bovis* helped restore the skin bacterial diversity and prevented eczematous inflammation in adult mice[141]. In infants, particularly premature babies receiving broad-spectrum antibiotics, *Candida albicans*, a normal skin resident, can cause cutaneous candidiasis, a condition that can lead to invasive fungal infection in the most vulnerable patients[142].

Breastfed infants tend to have a reduced likelihood of developing atopic disorders. This is primarily due to the presence of human milk oligosaccharides in breast milk that alter the gut microbiota of breastfed infants, promoting the growth of probiotics, particularly *Bifidobacteria*[143,144]. The impact of breastfeeding on the skin microbiota is, however, less understood. Golebiewski and colleagues demonstrated that breastfeeding rendered the dysbiotic gut and cutaneous microbiomes of allergic children more similar to the ones found in healthy children as compared with allergic children that received infant formula[145].

Gut-skin axis

The gut microbiota composition has been associated with skin diseases and can indirectly influence skin immune responses. This cross talk between the gut microbiota and the skin is called the gut-skin axis[146]. In early life, seeding of the gut microbiota is strongly influenced by vertical transmission from the pregnant individual. Over the past years, many studies have reported that changes in the gut microbiota can alter bacterial metabolite production such as the short-chain fatty acids (SCFAs) butyrate, propionate, and acetate. Consumption of a diet high in fermentable fiber can enhance SCFA levels and consequently modulate immune responses both locally (gut) and distally (lung and skin)[147–150]. High-fiber diet consumption or oral SCFA administration in weanling mice enhanced skin barrier function by promoting epidermal KC differentiation[150]. This effect led to diminished AD-like skin inflammation after epicutaneous allergen sensitization. Of note, children and infants with AD have a dysbiotic gut microbiota characterized by a blunted capacity to produce SCFAs, particularly butyrate[151,152]. Moreover, in the Childhood Allergy nutrition and Environment study cohort, it was observed that children with AD were more likely to have low levels of fecal butyrate at 360 days of life than those without AD[153], suggesting that fecal SCFA levels, and specifically butyrate, may have a protective effect in allergic skin disease development or progression. However, the reinforcement of skin barrier by oral SCFA administration observed in experimental animal studies should be confirmed in clinical studies, and if successful, this nutritional intervention could represent a promising new treatment regimen for children with AD. Probiotics have also been studied extensively in the context of AD. Several randomized clinical trials demonstrated the beneficial effects of probiotics using both preventative[154,155] and therapeutic[156,157] measures. Nevertheless, probiotic supplementation failed to treat AD in more recent clinical trials and further investigation using standardized probiotic strains, doses, and applications is necessary[158]. Skin microbiota-derived tryptophan metabolites can also alter cutaneous immune responses. Indeed, indole-3-aldehyde was shown to protect adult mice against MC903-induced AD, whereas indole-3-aldehyde levels are reduced in the skin of patients with AD [159].

Other environmental exposures

Other major environmental factors affecting the skin include sun, chemicals, and allergens[114]. The adoption of a westernized lifestyle has led to the daily use of many chemicals, such as sodium dodecyl sulfate and sodium dodecylbenzene sulphonate, which are present in liquid soaps and laundry detergents. It was shown that trace concentrations of laundry detergent, specifically anionic surfactants, can disrupt epithelial barrier function by damaging the tight junction structure as shown in air-liquid interface cultures of human adult KCs[160]. Notably, experimental animal studies indicate that microbial proteases present in laundry detergent, such as alcalase and savinase, can induce more severe damage to the skin in neonates than in adults[161], suggesting that either the neonatal skin is more susceptible to those proteases or that these proteases arrest adequate skin barrier function development in early life. These barrier disruptions contribute to enhanced skin permeability[160,161] and thus, greater susceptibility to skin inflammation and allergic disease development. Sun exposure influences the skin immune balance. Vitamin D3, a vitamin mostly synthesized in the skin epidermis through a chemical reaction requiring ultraviolet light (ultraviolet B) exposure has been shown to have immunomodulatory properties. In a randomized, double-blind, placebo-controlled trial, Camargo and colleagues showed that a 1-month vitamin D3 oral supplementation could significantly ameliorate winter-related AD in children[162].

SKIN DISEASE DEVELOPMENT IN EARLY LIFE

Genetic factors, lifestyle factors, or environmental exposures can render the skin susceptible to disease development. So far, we have discussed how the impairment of the physical barrier has consequences for skin immunity and health. Here, we briefly discuss the early life onset of skin diseases and alterations in skin composition throughout life, which can render the skin more susceptible to disease.

IV is a genetic disease characterized by homozygous loss-of-function mutations in FLG, leading to impaired skin barrier function[97]. The skin is "normal" at birth but scaling and roughness start developing during the first years of life. Genetic mutations altering skin barrier function generally lead to disease onset in early life and may thus predispose to other conditions, such as allergic diseases and skin infections, among others. Indeed, given the influence of FLG mutation on skin barrier function, IV is strongly associated with allergic diseases, such as AD.

AD often develops in early life and commonly presents by 5 years of age, yet it can occur at any age. AD is characterized by skin barrier dysfunction. Enhanced skin permeability in the first years of life can lead to enhanced allergen penetration at an age when infants explore their surroundings and are exposed to many allergens and microbes. Importantly, such skin barrier impairment during infancy can precede sensitization to food allergens[93] or aeroallergens[163] later in life, a phenomenon called "the atopic march." This concept underlines the important interplay between early life skin barrier function and immune homeostasis. As discussed previously, genetic predisposition (e.g. FLG mutation, parental atopy) plays an important role in AD pathogenesis. AD manifests differently in children and in adults. Skin biopsies from infants with AD contain elevated expression of T_H17-T_H22-T_H2-related immune genes, whereas those of adult AD is characterized by a T_H1-T_H2 immune signature[164].

Acne vulgaris (acne) can occur in all ages from infancy to adulthood; however, it most commonly occurs in puberty. Acne is associated with enhanced sebum levels, which are greatly influenced by androgens. Indeed, appearance of disease in the first 4 weeks of life (neonatal acne) has been linked to neonatal and maternal androgen-mediated increases in sebum production. In addition, starting in adolescence and puberty, the sebaceous glands increase in size resulting in enhanced skin sebum production[165], with most sebum secreted between 15 and 35 years of age. Enhanced sebum production can induce the proliferation of *Cutibacterium acnes, Staphylococcus epidermidis,* and *Corynebacterium*[166–168]. Although *C. acnes* abundance has been reported to be similar in subjects with acne and those without, and the pathogenicity and virulence of the strains can differ, leading to different responses[169,170]. In addition to enhanced sebum secretion, hormonal changes, and alterations in the microbial composition, local inflammatory events (largely IL-1-mediated) are also implicated in disease pathogenesis[171–173]. These complex interactions have been predominantly studied in adolescence/puberty and much is to be learned on the effects of altered sebum levels on cutaneous immunity in early life.

CONCLUSION AND FUTURE DIRECTIONS

The development of cutaneous immunity is initiated *in utero* and develops over time. However, the exact timing of skin immune cell seeding and maturation and their localization remains under-investigated because preclinical studies using neonatal and infant skin samples or using neonatal animal models are scarce. Most current knowledge comes from either association studies in infants or from extrapolation of findings from studies in the adult setting to the childhood setting to gain an enhanced understanding of early life skin barrier and immune development.

Although skin biopsies are difficult to obtain in childhood, non-invasive sampling, such as the use of skin swabs for microbiome analysis, has contributed to the substantial progress that has been made in understanding the influence of specific microbes or microbial communities on skin health and disease. This has led to the identification of particular environmental stimuli associated with changes in the skin microbiome. An important avenue for future research is to enhance our understanding of the interactions between host genetics, microbial composition, and environmental stimuli and how these complex interactions impact upon neonatal immune development. Moreover, it is imperative to investigate whether timing (during infancy, adolescence, or adulthood) of such interactions may differentially impact skin immunity and barrier function.

Human and murine skin vastly differ at both the structural and immunological level, which impacts upon the translation of mechanistic findings from experimental rodent models to humans. Therefore, it is important to improve such extrapolations from mechanistic studies. In addition to using human *in vitro* and *ex vivo* models, advances have been made in using humanized immunodeficient rodent models with full-thickness human (fetal) skin grafts and co-engraftment with autologous lymphoid tissues and immune cells, which resemble the microanatomical structure of adult skin[174]. Future investigations have to focus on identifying whether such models can be used to study neonatal skin development and immune maturation.

Skin pathologies are often linked to disease manifestations in mucosal tissues, including the gut and the lung; hence, it is suggested that close cross talk between the cutaneous and mucosal barriers exists. In allergic diseases, such bidirectional relationships have been linked to local acute allergic reactions, which

consequently influenced remote mucosal tissue seeding. Specifically, cutaneous allergen challenge did not only induce a local allergic inflammatory response but was found to also initiate allergic inflammation in distant non–allergen-exposed mucosal tissues (gut and lung)[175]. However, the exact mechanisms underlying these changes in remote tissue homeostasis remain unknown, and future studies should focus on understanding kinetics of and mechanisms governing immune cell trafficking in such conditions. Moreover, changes in skin or gut microbiota composition and for example bacterial metabolites, can directly and indirectly influence local and remote immune responses. Much is to be learned about the differential responses to such changes during early life tissue immune seeding and maturation.

The advances in the field of skin barrier immunology in the adult setting have led to identification and enhanced understanding of the different barrier components and their interconnectivity, which are required for the maintenance of skin barrier function. Adequate development of skin immunity and the barrier in early life are imperative for long-term skin health. Learnings from other mucosal barrier tissues, such as the gut and the lung, show that early life development of the local immune system and barrier can be impacted by host and environmental factors and set the immunological tone. The focus of future studies should be directed toward gaining insights into the development of immune cell populations in healthy skin during the early stages of life and take the possibility of inter-organ cross talk with mucosal tissues into consideration. Moreover, it is imperative to develop experimental models and design clinical studies in which such cross talk can be studied.

AUTHOR CONTRIBUTIONS

A. T. and N. D. U. drafted and edited the manuscript. Both authors approved the final manuscript.

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