Immunology
The Journal of cells, molecules, systems and technologies

British Society for immunology

doi:10.1111/imm.13152

IMMUNOLOGY REVIEW ARTICLE

REVIEW SERIES: BARRIER IMMUNITY
Series Editors: James A. Harker and Laura J. Pallett

Skin barrier immunity and ageing

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doi:10.1111/imm.13152
Received 30 September 2019; revised 6 November 2019; accepted 7 November 2019.
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Summary

The skin is the outermost layer of the body with an extensive surface area of approximately 1·8 m^2, and is the first line of defence against a multitude of external pathogens and environmental insults. The skin also has important homeostatic functions such as reducing water loss and contributing to thermoregulation of the body. The structure of the skin and its cellular composition work in harmony to prevent infections and to deal with physical and chemical challenges from the outside world. In this review, we discuss how the structural cells such as keratinocytes, fibroblasts and adipocytes contribute to barrier immunity. We also discuss specialized immune cells that are resident in steady-state skin including mononuclear phagocytes, such as Langerhans cells, dermal macrophages and dermal dendritic cells in addition to the resident memory T cells. Ageing results in an increased incidence of cancer and skin infections. As we age, the skin structure changes with thinning of the epidermis and dermis, increased water loss, and fragmentation of collagen and elastin. In addition, the skin immune composition is altered with reduced Langerhans cells, decreased antigen-specific immunity and increased regulatory populations such as $Foxp3^+$ regulatory T cells. Together, these alterations result in decreased barrier immunity in the elderly, explaining in part their increased susceptiblity to cancer and infections.

Keywords: ageing; immunosenescence; skin; tissue resident.

Skin barrier

The skin is the outermost layer of the body with an extensive surface area of approximately 1·8 m^2, and is the first line of defence against a multitude of external pathogens. The skin consists of three layers: the top layer is the epidermis, a thin layer (approximately 0·1 mm thick) of stratified squamous epithelium, composed of four strata of keratinocytes in progressive stages of differentiation. The stratified epithelium provides a watertight barrier from the external environment and prevents excessive water loss from the body. The epidermis is mainly composed of keratinocytes; however, there are also melanocytes, which provide a barrier from ultraviolet (UV) radiation through expression of melanin. The epidermis does not have a blood supply of its own, but instead is nourished from blood vessels below. The second layer is the dermis, a thicker layer (up to 3–4 mm depending on body site), which has a relatively low cell volume compared with the epidermis. The dermis predominantly consists of the extracellular matrix, such as collagen, which is made by fibroblasts. In addition to the extracellular matrix, the dermis contains structures such as blood vessels, lymphatics, nerves, sweat glands and pilosebaceous units. The deepest layer of the skin is the subcutaneous layer, which consists of subcutaneous fat and connective tissue.[1]

Abbreviations: DC, dendritic cells; DETCs, dendritic epidermal γδ T cells; IL, interleukin; ILC, innate lymphoid cell; LCs, Langerhans cells; MMP, matrix metalloproteinases; TLR, Toll-like receptor; Treg cells, T regulatory cells; T_{rm} cells, T resident memory cells; UV, ultraviolet; VZV, varicella zoster virus

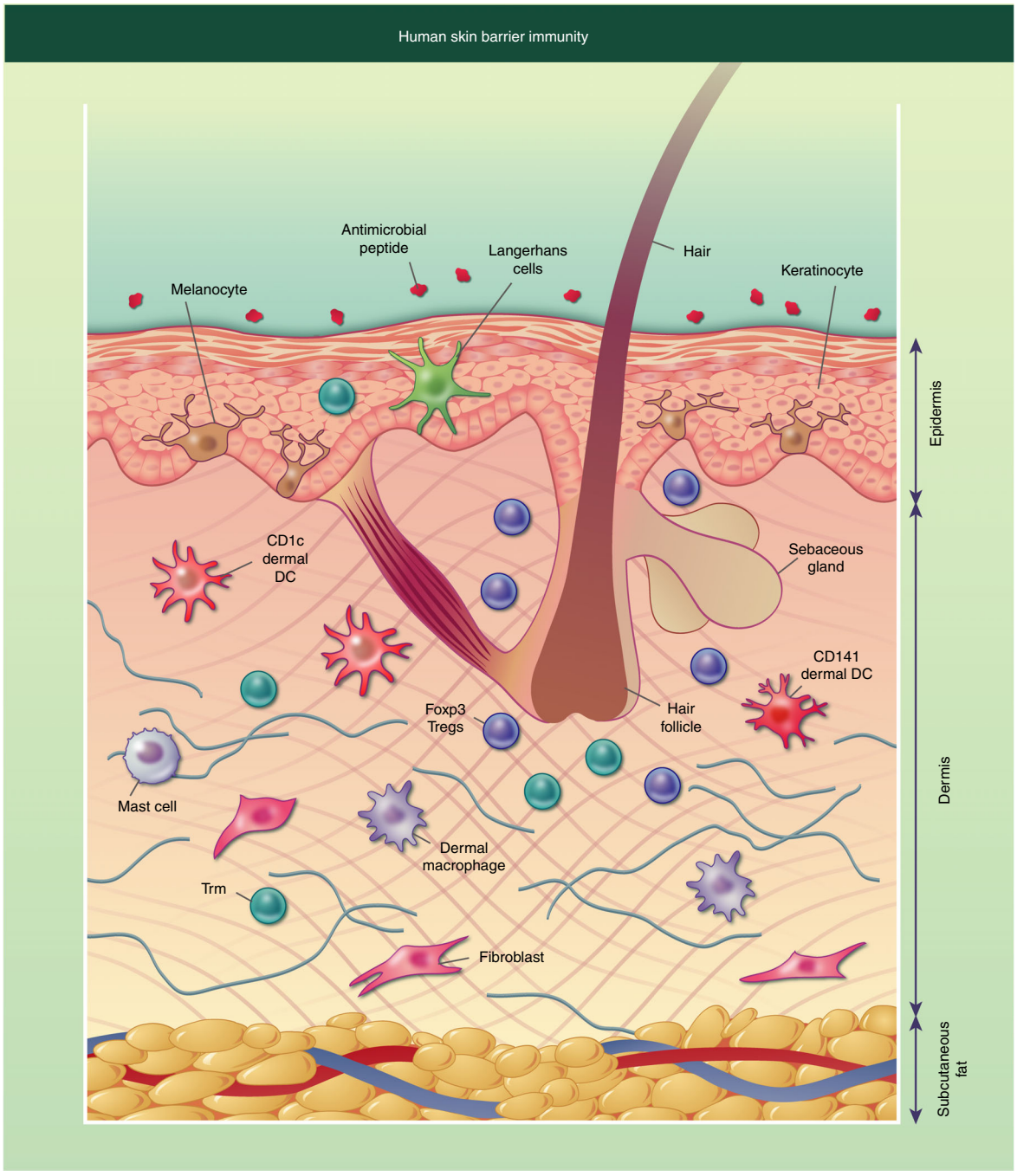

Figure 1. Diagrammatic representation of human skin barrier immunity. The surface of the skin is covered in antimicrobial peptides and lipids, some of which originate from the sebaceous gland located near the hair follicle. The epidermis consists of keratinocytes forming stratified corneum, with melanocytes interspersed. Langerhans cells and T resident memory cells (T_{rm}) can also be found in the epidermis. The dermis has a more diverse collection of cells including structural cells such as fibroblasts, and immune cells such as dermal dendritic cells (DCs) and macrophages, $CD4^+$ and $CD8^+$ T_{rm}, mast cells and $Foxp3^+$ T regulatory cells (Tregs), which are often located near the hair follicle. The final layer of the skin is the subcutaneous fat, which is primarily composed of adipocytes.

Skin barrier immunity

The skin is a complex organ that carries out numerous functions contributing to its barrier immunity function – the skin structure and stromal and immune cell composition can be seen in Fig. 1.

Antimicrobial peptides and lipids are secreted onto the cell surface to control bacterial growth. These include

dermcidin, which is secreted in human sweat and has broad antimicrobial activity against a range of pathogenic bacteria. Its antimicrobial activity is not affected by the low pH value and high salt concentrations of human sweat.[2] Sebum is made by sebaceous glands found independently of or near hair follicles. Within the sebum are antimicrobial lipids, such as lauric acid and sapienic acid, which play an important role in controlling pathogenic organisms.[3]

However, the skin is not a sterile site, and there is extensive research showing the role that the skin microbiota plays in immunity by restricting the growth of pathogenic bacteria.[4] Commensal bacteria have been shown to produce an antimicrobial peptide that synergizes with the human antimicrobial peptide LL37, which together kill the pathogenic bacterium *Staphylococcus aureus*.[5] However, insults and pathogens are mostly controlled and prevented entry due to structure and barrier immunity in the skin.

Skin-resident stromal cells

Keratinocytes are the main component of the epidermis. They express Toll-like receptors (TLRs), which are crucial pathogen pattern recognition receptors that when triggered lead to the production of inflammatory cytokines and initiation of an immune response.[6] Keratinocytes have been shown to constitutively express TLR1, -2, -3, -5, -6 and -10.[7,8] They also have the ability to sense wound damage and produce inflammatory cytokines and chemokines such as interleukin-1β (IL-1β), IL-8 and CCL20 to recruit leucocytes to the site of damage.[9]

Keratinocytes express a raft of antimicrobial peptides that control bacterial growth, including adrenomedullin and β-defensins.[10,11] β-Defensin-1 is constitutively expressed by human keratinocytes and β-defensin-2 and -4 are up-regulated upon inflammatory challenge.[11–13] Keratinocytes can express the antimicrobial peptide Cathelicidin upon stimulation and can store Cathelicidin in cytoplasmic granules until needed.[14,15] Keratinocytes also constitutively express RNase 7, which is a very potent antimicrobial ribonuclease, and upon inflammatory or bacterial challenge there is further increased expression.[16]

More recently, it has been proposed that keratinocytes have the ability to process and present antigen to $CD4^+$ and $CD8^+$ T cells, initiating an adaptive immune response.[17] In addition, keratinocytes are the key site for the first step in the vitamin D metabolism pathway, when pro-vitamin D3 (7-dehydro-cholesterol) is metabolized into vitamin D3, catalysed by UVB. Vitamin D is an important component of a functioning immune system and its metabolism at the skin site contributes to barrier immunity.[18]

Dermal fibroblasts are the structural cells of the dermis; their primary function is to secrete extracellular matrix components such as pro-collagen. Fibroblasts express the full range of TLRs, at a higher level than keratinocytes, demonstrating their important role in the detection of pathogens.[19] *In vitro* studies have shown that dermal fibroblasts can have differing roles in immunity, indeed TLR4 signalling results in the production of inflammatory cytokines such as IL-6, IL-8 and the monocyte chemoattractant CCL2.[20] Conversely fibroblasts have been shown to suppress T-cell proliferation via indoleamine 2,3-dioxygenase production, and to skew the T cells to produce immunoregulatory cytokines such as IL-10.[21]

The subcutaneous layer of the skin is predominantly composed of adipocytes – their primary function is to be a repository of energy that responds to hypothermia by producing heat. More recent work has identified the important role of adipocytes in barrier immunity as a significant source of antimicrobial peptides. In response to infection, for example with *S. aureus*, dermal fibroblasts can differentiate into adipocytes and produce the antimicrobial peptide cathelicidin.[22]

Skin-resident immune cells

Mononuclear phagocytes

Within the epidermis there is a population of mononuclear phagocytes called Langerhans cells (LCs). These were believed to have been seeded at birth and maintained by local turnover to ensure a steady-state population.[23] However, a recent study demonstrated, in a murine model of immune injury, that repopulation of LCs from peripheral monocytes makes up for the slow repopulation from mature LCs.[24] Langerhans cells are located at the interface with the external environment and as such are multifunctional sentinels of the epidermis. They sample the environment by extension and retraction of their dendrites between the keratinocytes in an amoeba-like movement.[25] They present antigen to T cells within the epidermis to initiate a local immune response and also have the capacity to migrate to the lymph node and initiate immune responses.[26]

Within the dermis, there is a more diverse population of mononuclear phagocytes including dermal dendritic cells (DCs) and dermal macrophage populations. Dendritic cells are the sentinels of the immune system, they sample the microenvironment and either present antigen to the resident T cells or migrate through the lymphatics to the lymph node to initiate an immune response.[27] Historical assessment of dermal DCs identified that they are more activated then their blood counterparts; dermal DCs had increased expression of co-stimulatory receptors and were strong stimulators of T-cell proliferation relative to their peripheral blood counterparts.[28] Two main populations of dermal myeloid DCs have been identified; the $CD1c^+$ DCs and the $CD141^+$ DCs. $CD141^+$ DCs are the cells responsible for cross-presenting antigens to $CD8^+$ T cells and have homology to the mouse $CD103^+$ DCs.[29]

Very few plasmacytoid DCs are observed in steady-state skin.[30]

Macrophages are another type of antigen-presenting cell resident in the dermis and they sense pathogens and damage and initiate an appropriate immune response. In addition to the immune function, macrophages maintain tissue homeostasis through increasing appropriate anti-inflammatory mechanisms, contribute to wound healing, and heal nerves upon tissue injury.[31,32] Macrophages are thought to populate tissues early on but studies have also shown that they are replenished by circulating monocytes.[33] These data are supported by a study in humans showing that $CD14^+$ cells were a transient population of monocyte-derived macrophages.[34] CD163 has been proposed to be a good marker for dermal macrophages, as it specifically identifies skin-specific macrophages that are not recently migrated monocytes.[35]

Analysis of the location of these different mononuclear phagocyte populations in the dermis have shown that DCs can be found closer to the epidermis (around 0–20 μm beneath the dermo–epidermal junction) and macrophages are located deeper in the skin (around 40–60 μm beneath the dermo–epidermal junction).[36]

Other innate populations

In rodent and cattle skin a population of $\gamma\delta$ T cells has been described called dendritic epidermal $\gamma\delta$ T cells (DETCs) – these cells are localized in the epidermis.[37] The DETCs express a limited T-cell receptor repertoire and recognize danger-associated molecular patterns induced on damaged or dysregulated keratinocytes. In addition, DETCs have been shown to play a role in maintaining keratinocyte homeostasis as in the absence of DETCs there was increased keratinocyte apoptosis.[37] However, DETCs have not been observed in human skin. Indeed, in human skin the predominant leucocyte population is $\alpha\beta$ T cells, $\gamma\delta$ T cells and natural killer cells were found in the skin but at very low frequencies (0·35% and 0·97%, respectively).[38] Neutrophils are not present in steady-state skin; however, upon sun exposure there is an infiltration of neutrophils that contribute to sunburn and photo-ageing.[39]

Innate lymphoid cells (ILCs) are a relatively recently described immune cell population and their function in the skin is still under investigation. In steady-state human skin, there are few ILCs, and those cells that are present tend to be ILC1 and ILC3. ILC populations are significantly increase in inflammatory conditions; there is an influx of ILC2s in atopic dermatitis, and in psoriatic plaques ILC1 and ILC3 populations have been observed.[40,41]

The dermis also contains mast cells, of which there are between 77 and 108 cells/mm^2.[42] Mast cells contain granules with pre-formed inflammatory mediators such as histamine that are released when receptors are crosslinked, contributing to local inflammatory responses. Mast cells also play an important role in allergic reactions and associated itching and rash.

T cells

Skin T resident memory (T_{rm}) cells are non-circulating T cells present in the skin that maintain immune surveillance and are crucial for initiating robust immune responses at times of infection.[43–45] In steady-state skin, there are around 1×10^6 T cells/cm^2 suggesting that in an average person, there are around 2×10^{10} T cells present in the whole skin.[46] The majority (80%–90%) of T cells found in the skin are T_{rm} and the remaining T cells are recirculating T cells.[47] Cutaneous T_{rm} cells are generated after exposure to antigen and provide memory at the site of initial exposure – T_{rm} cells are more potent effector cells compared with circulating T cells.[47] Of the $CD3^+$ T_{rm} cells present in the skin, the ratio of $CD4^+$ to $CD8^+$ T cells was found to be approximately 3 : 1 in human epidermis and 6 : 1 in dermis.[47]

The most commonly used markers to define T_{rm} cells are cell surface expression of CD69 and CD103.[48] T cells increase CD69 expression in response to antigen exposure or type I interferon signalling, and this blocks T-cell egress from the skin by inhibiting sphingosine-1-phosphate receptor function.[49,50] CD103 is an integrin that binds to E-cadherin, it has been associated with $CD8^+$ T_{rm} cells present in the epidermis.[47,48] CD103 expression is believed to be partly due to the expression of E-cadherin on the keratinocytes, which is important for retention of these cells in the epidermis.[51]

In addition to CD69 and CD103, CCR8 has been proposed to be a T_{rm} cell marker.[52,53] The sole ligand for CCR8 is CCL1, which is predominantly expressed by $CD1a^+$ LCs.[52] The epidermis and in particular keratinocytes have been shown to play a role in up-regulating CCR8 on naive T cells in the skin and generating T_{rm} cells, through production of Vitamin D3 and prostaglandin E_2.[53,54]

$CD4^+$ FoxP3 T regulatory (Treg) cells are an important regulatory cell type that plays an role in immune and tissue homeostasis.[55] $Foxp3^+$ Treg cells with a memory skin-resident phenotype have been observed in the dermis and in particular in steady-state conditions can be found located close to hair follicles.[56] The short-chain fatty acid sodium butyrate, which is a bacterial metabolite produced by skin commensals, can increase Foxp3 expression in non-Treg cells driving an increase $Foxp3^+$ Treg cells leading to increased immune tolerance to skin commensals.[57] In addition, UVB light has been shown to increase the number of $Foxp3^+$ Treg cells by facilitating the proliferation of thymically derived $Foxp3^+$ Treg cells.[58] This effect of UVB could be in part due to the production of Vitamin D3, which can drive $Foxp3^+$ Treg cell proliferation *in vitro*.[59] Indeed it is believed $Foxp3^+$ Treg cells accumulate around the hair follicle because of entry of

commensal bacteria to newly formed hair follicles during neonatal skin development.[60]

Ageing and skin structure

As we age our skin structure changes (Fig. 2), the epidermal layer is thinner due to keratinocyte atrophy.[61] This leads to increased trans-epidermal water loss in elderly individuals, resulting in increased skin dryness.[62] The extracellular matrix components collagen and elastin, which provide tensile strength and elasticity respectively, are substantially changed with age. The total amount of collagen has been shown to be reduced with age.[63] However, there is also increased collagen fragmentation, which is believed to be due to increased matrix metalloproteinase (MMP) expression in older skin.[64] Elastin is an inert protein that is formed during early development and is not replenished, therefore any changes to elastin that occur over a lifetime tend to be permanent.[65] MMPs, in particular MMP-1, -3 and -9, target elastin for fragmentation,[65] resulting in reduced skin elasticity and the classical sign of skin ageing, wrinkling.

Dermal fibroblasts contribute to age-associated dermal thinning as they are reduced in size.[66] In addition, dermal fibroblasts from elderly individuals make less pro-collagen and have increased expression of MMP-1, contributing to increased collagen fragmentation.[66–68] Other changes in the skin that are observed with age are reduced sweat and sebum production.[69] Finally, there is a thinning of the adipose tissue observed with age due to a reduction in white adipose tissue – subsequent antimicrobial protection (by the dermal fat) in response to infection is significantly decreased. This reduction in adipocytes is believed to be due in part to the inability of fibroblasts to convert to adipose tissue.[70]

Changes in skin structure with age are dependent upon lifestyle choices and environment challenges, including UVB exposure and the use of sunscreen, smoking and environmental pollution.[71,72] Collectively these changes render older people more susceptible to mechanical injury, alter the skin microbiome and have important implications for skin barrier immunity.

Immunological changes in the skin with age

The decrease in cutaneous immune function has been well documented in older humans. A variety of bacterial infections are more common in the elderly, including cellulitis (in particular of the lower legs), erysipelas, necrotizing fasciitis, folliculitis, impetigo, folliculitis and furunculosis.[73] *Staphylococcus aureus* and β-Haemolytic streptococci are the most common skin pathogens in the elderly, although other bacterial infections caused by *Pseudomonas* spp. and *Klebsiella* spp. are also elevated in older individuals.[74] The prevalence of skin colonization by *Proteus mirabilis* and *Pseudomonas aeruginosa* in people over 65 years old is increased by about 25% compared with younger individuals.[74] Fungal infections (such as *Candida*) and viral infections such as shingles, herpes simplex virus-1 and human papillomavirus are also more common in the elderly.[74,75]

Non-melanoma skin cancer, including basal cell and squamous cell carcinomas, is more commonly diagnosed in persons older than 70 years. The highest incidence of malignant melanoma and melanoma is in individuals aged 65 years and older.[75–78]

Together these observations provide strong evidence for age-dependent changes in the skin barrier immunity. Although changes in peripheral immune cell populations have been well described (as reviewed previously[79–81]), we have focused on skin-specific immunological differences with age (Fig. 3).

Mononuclear phagocytes

Langerhans cells are reduced in number in the elderly. In addition, LCs from older donors have reduced capacity to migrate to the lymph node.[82] Using an *ex vivo* epidermal model, Pilkington *et al.*[83] have shown that lower levels of IL-1β observed in elderly skin result in reduced migration of the LCs to the cytokine gradient – demonstrating that the skin microenvironment plays a detrimental role. The specific source of IL-1β in the skin remains controversial, and both keratinocytes and LCs themselves have been proposed as the primary source. In addition, LCs from aged skin express less human β-defensin-3, an important antimicrobial peptide for response to infection.[84]

The number and phenotype of dermal DCs is comparable between young and old skin.[81] However, dermal DCs from aged skin appear to be functionally impaired in terms of migration, phagocytosis and ability to stimulate T cells in a mouse B16 melanoma model.[85] The effect of age on macrophage function is still contentious – some studies demonstrate reduced TLR expression and TLR-induced cytokine production.[86] In contrast other studies have shown that there is increased inflammatory cytokine production after TLR ligation.[87] However, there are limited data on the effect of age on dermal macrophage populations. We have shown that $CD163^+$ macrophages produce less tumour necrosis factor-α in antigen-challenged old skin, but upon removal of the macrophages from the skin environment they produce similar amounts of pro-inflammatory cytokine in response to TLR ligands.[82] This suggests that it is the skin environment itself that is altered with age rather than intrinsic dysfunction of macrophages.

T cells

Repeated antigen stimulation throughout life can have significant effects on human antigen-specific T cells, including

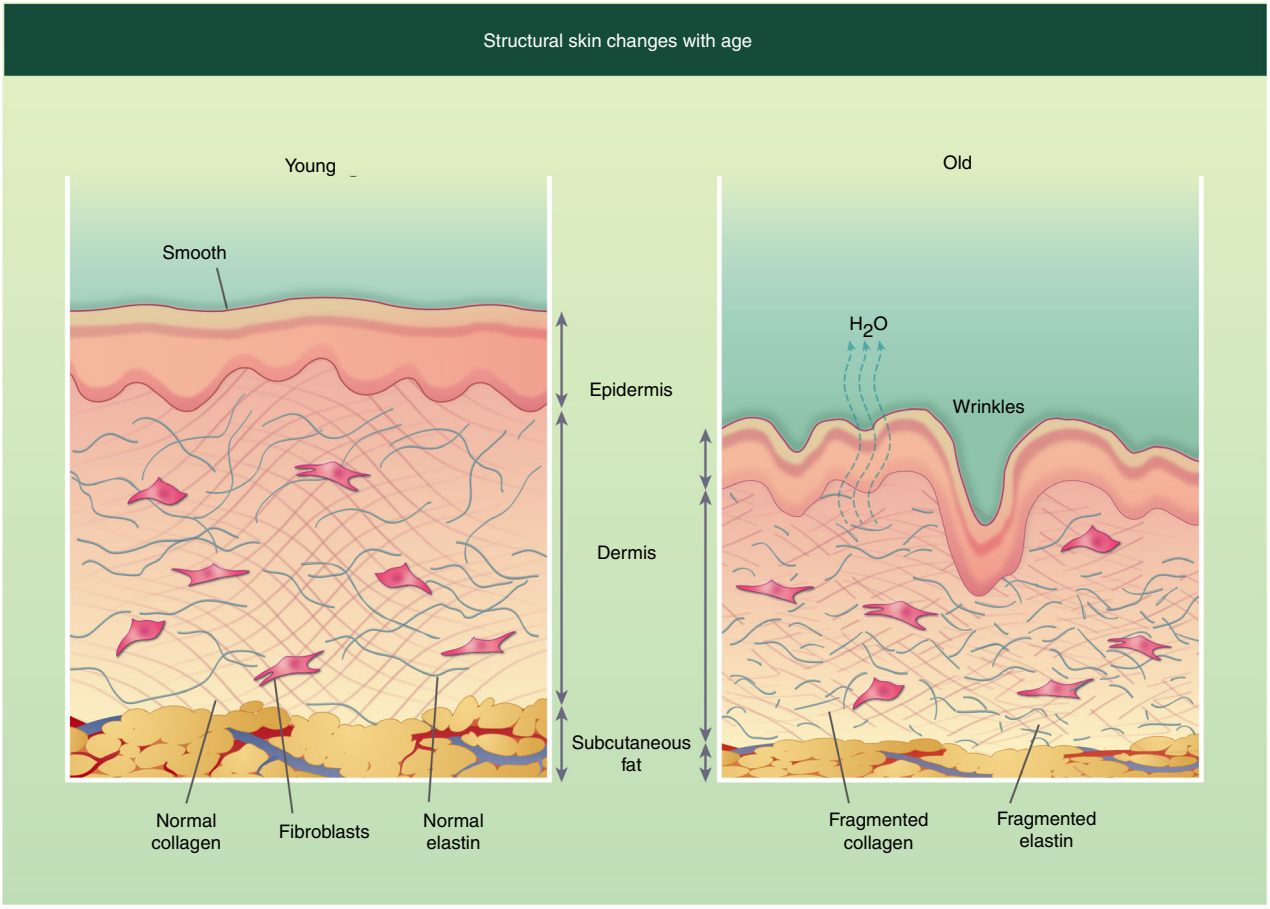

Figure 2. Structural changes in human skin with age. Young skin structure (left) and compared with older skin structure (right). Older skin has fragmented elastin and collagen, increasing water loss, which leads to skin dryness and increased wrinkles. In addition, the skin is thinner with all three layers being less thick then the younger counterpart.

the induction of exhaustion and senescence. Functional exhaustion of T cells is characterized by loss of functional activity, increase in inhibitory receptor expression [such as programmed cell death protein 1 (PD-1)]. It is a mechanism necessary for limiting the magnitude of the effector T-cell response but it also contributes to the functional decline in adaptive immunity with age. Senescence, a loss of replicative capacity, is often induced by repeated stimulation, and is primarily induced through the process of telomere erosion. Although the age-related changes in the circulating T-cell pool have been well characterized and extensively reviewed,[79] the age-related changes in the skin-resident T-cell population have not been extensively studied. The differences in the regulation of senescence and the importance of telomere shortening between mouse and human T cells should also be taken into account when extrapolating from mouse models.[88]

Tissue-resident $CD8^+$ T cells have recently been shown to promote a long-lasting state of equilibrium between melanoma and the immune system.[89] Depletion of these T_{rm} cells demonstrated that they actively suppress tumour progression.[89] How anti-tumour surveillance and control by skin-resident T_{rm} cells is affected by age and age-related changes within the CD8 population has not been studied. It is known that skin-resident T_{rm} cells are vital to clear skin infections,[90–92] so defects in T_{rm} cells may explain the increased incidence of infection seen in the elderly. We and others have shown that there are decreased delayed-type hypersensitivity responses to recall antigens such as *Candida* or varicella zoster virus (VZV)[75–78] in older adults due to a reduced infiltration of T cells at the site of antigen challenge. Our group has shown that the function of skin-derived $CD4^+$ T cells was not impaired with age in response to both mitogen- and antigen-specific stimulation *ex vivo*,[93] although the skin residency markers were not used for cell isolation. Interestingly old skin actually had a higher proportion of VZV-specific T cells compared with young – possibly suggesting accumulation over a lifetime of subclinical reactivation.[94] There was, however, an increase in PD-1 expression on both CD4 and CD8 T cells in old individuals compared with young skin, suggesting that older T

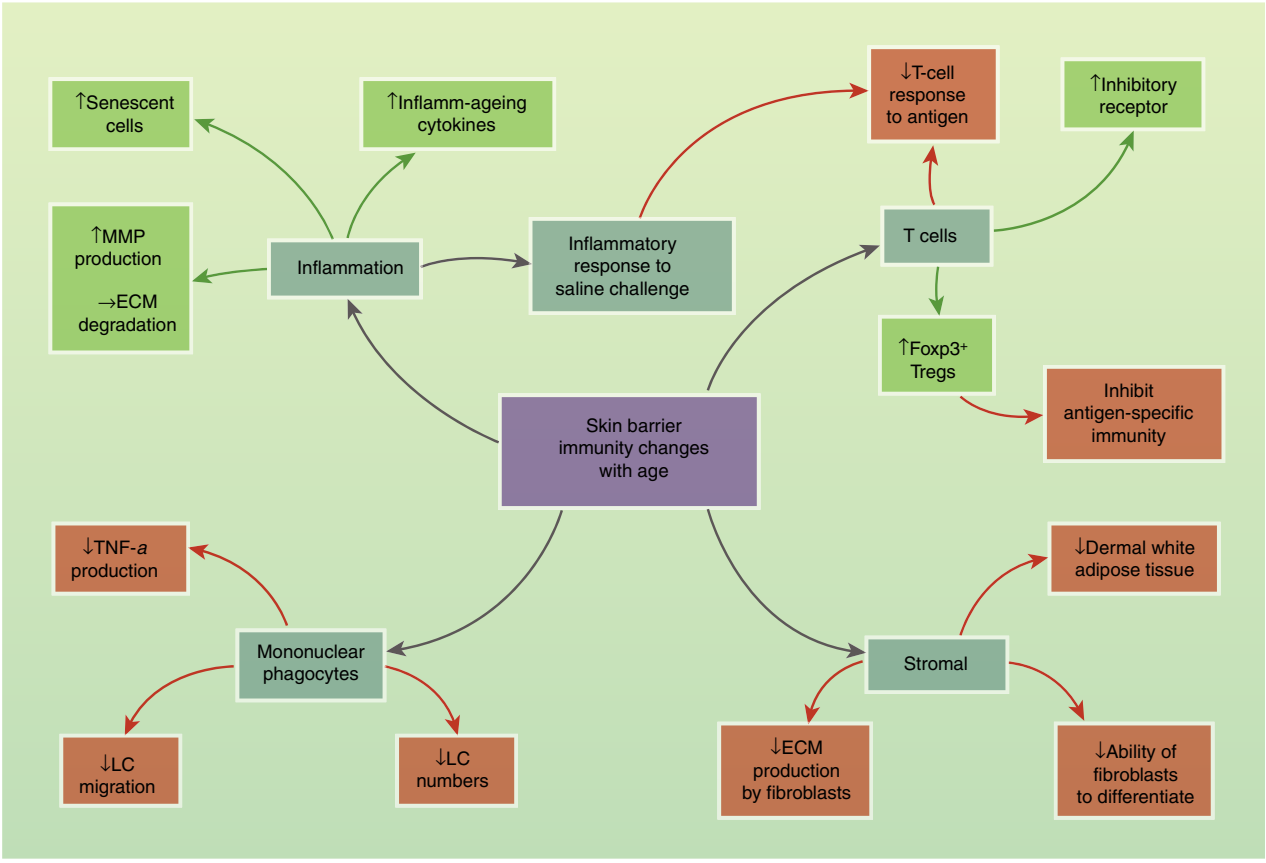

Figure 3. Skin barrier immunity changes with age. Schematic showing the effect of age on skin-resident populations. Negative/inhibitory effects are shown in red and positive/enhancing effects are shown in green. ECM, extracellular matrix; LC, Langerhans cell; MMP, matrix metalloproteinases; Treg, T regulatory cells.

cells are more susceptible to inhibition via programmed death ligand 1/PD-1 signalling.[93]

Foxp3$^+$ Treg cells

The proportion of regulatory cells in normal skin is increased in older mice and humans.[95,96] People who had the highest proportion of Foxp3$^+$ Treg cells had the worst delayed-type hypersensitivity response to VZV recall antigen – showing that Foxp3$^+$ Treg cells in the skin can interfere with antigen-specific immunity.[97] Indeed, in a mouse model of melanoma, Treg cells can suppress very early stages of the inflammatory response to antigen challenge.[98] It is known that there is an increase in Foxp3$^+$ Treg cell numbers in cancers such as melanoma and basal cell carcinoma.[99–101] In human squamous cell carcinoma, 50% of cells have a Foxp3$^+$ Treg phenotype, reduction of Foxp3$^+$ Treg cell percentage in these patients and their function led to clinical improvement.[102] The reasons why Foxp3$^+$ Treg cell numbers are increased in older skin are not clear. It has been shown that UVB irradiation can lead to the induction of Foxp3$^+$ Treg cells and that these Foxp3$^+$ Treg cells suppress other immune cells through the production of IL-10.[58,103] It is also tempting to postulate that Foxp3$^+$ Treg cells could be induced or accumulate as an attempt to the immune system to control unwanted low-grade inflammation, which accompanies ageing.

Inflamm-ageing and senescence in the skin

Chronic low-grade inflammation, termed inflamm-ageing, is characterized by high serum C-reactive protein.[104] Inflamm-ageing is known to negatively impact on immunity because older people with elevated IL-1β had increased risk of morbidity and mortality.[105] It has been postulated that innate immune cells such as macrophages are a contributor to the inflamm-ageing phenotype, because due to changes in tissue structure – such as skin thinning – they are exposed to more bacteria, which leads to chronic activation and subsequent inflammatory cytokine production, such as is seen with increased gut permeability in an aged mouse model.[106]

Another contributor to inflamm-ageing, especially in the skin, is UV damage. Repeated exposure to UVB, as

would be the case in old skin, leads to the accumulation of macrophages and increase in reactive oxygen species and MMP, and subsequent damage to the extracellular matrix. Inappropriate complement activation may also be caused by the increase in oxidative stress and accumulation of damaged cells, in line with observations in atherosclerosis.[107] Another contributor to increased inflammation in the old is the accumulation of senescent cells; senescence is defined as irreversible growth arrest. It is known that there is an accumulation of senescent dermal fibroblasts, as classically defined by p16 expression in the skin of old mice and humans.[108–110] Senescent fibroblasts secrete a raft of inflammatory mediators such as IL-8, IL-6, tumour necrosis factor-α and CCL2.[110] This production of inflammatory mediators from senescent cells is termed senescence-associated secretory phenotype, which contributes to the low-grade inflammation observed in older individuals.[111] A recent paper has shown that senescent dermal fibroblasts persist in the skin by evading recognition and killing by natural killer cells and $CD8^+$ T cells, through increased expression of HLA-E.[110] Other skin-resident cell populations that have been shown to be senescent include endothelial cells and melanocytes.[112,113] Although increased frequency and number of senescent T cells have been observed in the periphery,[80] their contribution to the skin environment is unknown and warrants further investigation.

How this inflammation directly negatively affects cutaneous immune responses is not clear. Our studies have shown that skin from older individuals has a propensity to mount an inappropriate response to saline injection, which negatively correlates with antigen-specific cutaneous immunity.[94] Furthermore, blocking inflammation using a p38-mitogen-activated protein kinase inhibitor, Losmapimod, reduced this non-specific inflammation while improving the ability of old individuals to respond to recall antigen challenge.[94]

Concluding remarks

Skin barrier immunity is comprised of stromal cells such as keratinocytes and adipocytes and immune cells such as Langerhans and T_{rm} cells working in concert to prevent pathogen entry and to deal with continuous physical and chemical challenges. With increasing lifespan, it is important to understand how skin changes with age and the impact that these changes have on barrier immunity. Clearly, the skin environment is detrimental to a successful immune response of older people as removal of individual cells from the skin microenvironment results in restoration of immune function. Specifically which cells alter the ageing skin environment is unknown, certainly senescent cells such as fibroblasts will contribute greatly. However, there more research is required to understand fully which cells are responsible for the ageing skin microenvironment and which cell types, such as keratinocytes, endothelium and adipocytes, warrant further investigation. Better understanding of the inhibitory and inflammatory mechanisms that operate in older skin is crucial for the development of new strategies to combat infections and cancer.

Disclosures

The authors declare that they have no competing interests related to this work.

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