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Review

Keratinocytes: Dynamic Gatekeepers and Immune Regulators of the Skin

Meilang Xue[1,*], Hui Wang[1], Siwen Han[1], Lyn March[1]

[1]Sutton Arthritis Research Laboratory, The Australian Arthritis and Autoimmune Biobank Collaborative (A3BC), Sydney Musculoskeletal Health, Kolling Institute, Faculty of Medicine and Health, The University of Sydney at Royal North Shore Hospital, St Leonards, NSW 2065, Australia
*Correspondence: meilang.xue@sydney.edu.au (Meilang Xue)

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Abstract

Keratinocytes (KCs) constitute more than 90% of epidermal cells and are increasingly recognized as key regulators of skin immunity. In addition to forming the stratum corneum barrier, KCs are essential for immune surveillance. They express various pattern recognition receptors, such as Toll-like and nucleotide-binding oligomerization domain (NOD)-like receptors, which enable the rapid detection of pathogen- and damage-associated molecular patterns. This detection then stimulates the release of cytokines and chemokines that regulate both innate and adaptive immune responses. In addition, KCs produce antimicrobial peptides and support barrier stability by synthesizing lipids and proteins. Abnormal signaling in KCs has been linked to inflammatory skin conditions, including psoriasis and atopic dermatitis. These findings highlight the dual role of KCs in regulating immune tolerance and inflammation. This review examines the molecular pathways by which KCs respond to environmental stressors and microbial signals while maintaining barrier integrity, highlighting their potential as therapeutic targets for skin diseases.

Keywords: keratinocytes; barrier; pattern recognition receptors; cytokines; inflammatory skin diseases; chemokines

1. Introduction

The skin, the body's largest organ, functions as a critical interface between the internal physiology and the external environment. As a physicochemical barrier, it safeguards the physical integrity by protecting against mechanical injury, dehydration, and environmental pathogens [1]. The epidermis, the outermost layer of the skin, is a stratified squamous epithelium predominantly composed of keratinocytes (KCs), which account for over 90% of the cellular population [1]. While KCs were traditionally viewed solely as structural progenitors of the stratum corneum (SC), the physical shield formed via terminal differentiation [2], their known role has expanded. These cells also actively establish a chemical barrier by enzymatically processing filaggrin into natural moisturizing factors (NMFs) and maintaining the acid mantle, an essential defence against opportunistic microbial colonization [2,3].

A significant paradigm shift has redefined KCs as active contributors to cutaneous immunity rather than merely passive barriers [4,5]. Positioned at the environmental interface, KCs act as sophisticated frontline sentinels through a sensitive detection system [4,6]. These cells express a myriad of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and nod-like receptors (NLRs). These receptors enable the immediate detection of both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) released during skin injury [4,5]. Upon activation, KCs rapidly release pro-inflammatory mediators that recruit and modulate local immune cells, thereby triggering the innate immune cascade [4].

This review focuses on KCs as key signaling hubs that process environmental, microbial, and internal cues [6]. We propose that the trajectory of the local immune response, whether it favours tolerance or shifts towards inflammation, depends significantly on KC activity. We describe the molecular mechanisms that influence both innate and adaptive immunity, and discuss how dysregulated signaling in KCs can lead to chronic conditions such as psoriasis and atopic dermatitis (AD) [7,8]. Sources for this review were selected from primary literature and key reviews published primarily between 2015 and 2025, identified via PubMed, to ensure a focus on recent mechanistic and translational advances.

2. Keratinocytes as the Foundation of the Skin Barrier

The skin barrier comprises multiple layers, with the epidermis providing the most effective protection. This protective ability is determined by the coordinated lifecycle and advanced biosynthetic processes of KCs [2].

2.1 Keratinocyte Differentiation and Epidermal Barrier Formation

The epidermis is a stratified squamous epithelium organized into four distinct layers (Fig. 1), each representing a progressive stage of KC differentiation, a tightly regulated process known as keratinization [1,2,9]. The process

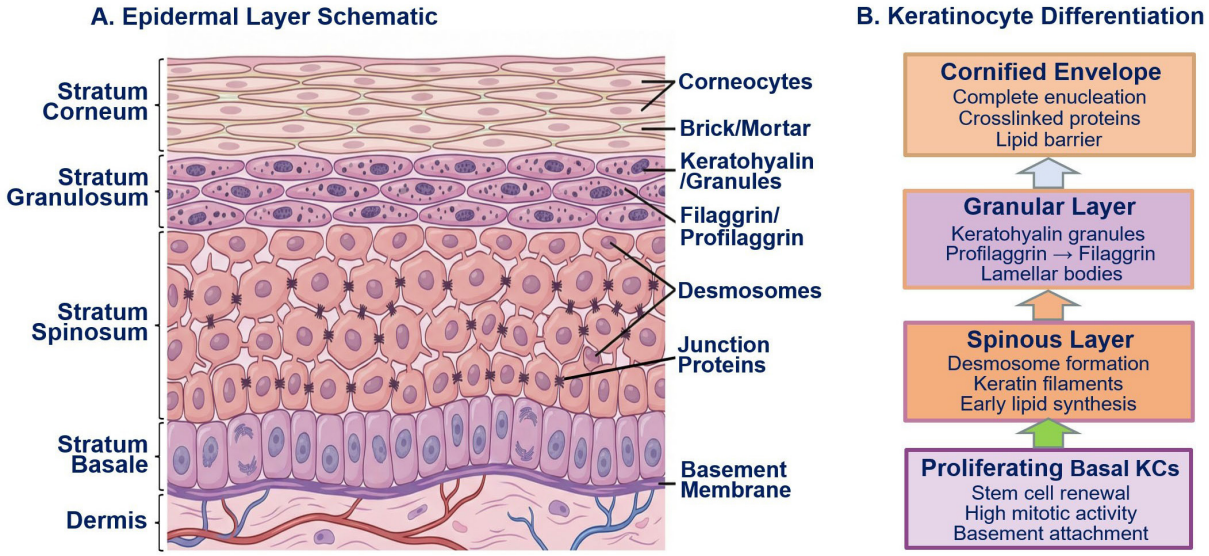

Fig. 1. Structural organization of the epidermis and keratinocyte differentiation. The epidermis is a dynamic, stratified squamous epithelium typically composed of four distinct layers (A). These layers represent the progressive stages of keratinocyte (KC) differentiation, a process known as keratinization (B). Part of Fig. 1A is created with BioRender.com.

begins in the stratum basale (SB), the deepest layer, where basal KCs proliferate before initiating upward migration. They transition into the stratum spinosum (SS), a layer characterized by abundant desmosomes that provide structural cohesion. Subsequently, in the stratum granulosum (SG), KCs enter a synthetic phase, consolidating intermediate filaments and producing structural proteins such as profilaggrin/filaggrin essential for barrier formation. Finally, the outermost SC consists of flattened, anucleated corneocytes embedded in a lipid-rich matrix, creating the "brick and mortar" architecture vital for maintaining barrier integrity [3].

2.2 Role of Keratinocytes in Physical and Chemical Barrier

The epidermis achieves mechanical strength and impermeability through specialized cell-to-cell junctions and the architecture of the SC. The SC is constituted by the overlapping arrangement of corneocytes, interconnected by unique adhesion complexes known as corneodesmosomes [10]. Within the SG, KCs establish a critical water permeability barrier through tight junctions (TJs) just before terminal differentiation. These TJs, formed by essential proteins such as claudins, occludin, and ZO-1, create a paracellular seal, preventing solute leakage [11]. Dysfunction in these TJs is associated with a number of skin inflammatory disorders [12,13].

The skin's chemical barrier is primarily supported by the KC secretome, a diverse collective of antimicrobial peptides (AMPs), lipids, enzymes, and small molecules (Table 1). These defense components act synergistically to acidify the skin surface, inhibit pathogen colonization [14,15], prevent transepidermal water loss [16,17], and modulate local inflammatory responses [18,19]. For instance, KCs produce a wide array of AMPs [20], including LL-37, human β-defensins (hBDs), and S100 proteins, which are critical for both immediate pathogen neutralization and immune modulation [21]. As detailed in Table 1, these molecules exert broad-spectrum activity against bacteria, fungi, and viruses while simultaneously acting as chemoattractants for leukocytes and maintaining barrier stability through microbiota management. Furthermore, AMPs such as LL-37 can form complexes with self-nucleic acids released during injury, acting as alarmins that break immune tolerance and drive pathogenic gene expression, a mechanism central to disorders like psoriasis [22,23,24].

3. Keratinocytes as Gatekeepers for Skin Immunity

Beyond their structural and chemical contributions, KCs act as responsive immune sentinels at the skin's environmental interface [4,22]. Equipped with versatile sensing mechanisms, these cells detect both microbial invaders and endogenous danger signals. By translating these cues into communication with resident immune cells, infiltrating leukocytes, and the commensal microbiota, KCs actively orchestrate cutaneous immune homeostasis [3].

3.1 KC Sensing Mechanisms

3.1.1 Pattern Recognition Receptors

Central to the immune competence of KCs is their diverse repertoire of PRRs, which include TLRs, NLRs, and retinoic acid-inducible gene-I-like receptors (RLRs) [22]. As the primary sensing mechanism, these receptors detect PAMPs and DAMPs, triggering rapid innate immunity and shaping subsequent adaptive responses [25].

Table 1. The key chemical defense components of the epidermis, their biological roles and clinical relevance.

Category	Components	Biological functions	Clinical relevance
AMPs	LL-37	• Broad-spectrum antimicrobial activity. • Chemotactic for immune cells. • Promotes wound healing and angiogenesis.	• Deficiency: Increased susceptibility to infections. • Overexpression/Dysregulation: Contributes to inflammation in psoriasis.
	hBDs	• hBD1: Constitutively expressed, broad-spectrum antimicrobial activity. • hBD2: Inducible, potent against Gram-negative bacteria. • hBD3: Inducible, broad-spectrum against antibiotic-resistant strains.	• Deficiency: Exacerbated infections in atopic dermatitis, impaired wound healing. • Dysregulation: Elevated in psoriasis, contributing to the inflammatory milieu.
	S100 Proteins	• S100A7: Potent against *E. coli*, specific against *S. aureus.* • S100A8/A9: Potent antimicrobial, pro-inflammatory DAMP, chemotactic for neutrophils.	• Deficiency/Imbalance: Increased susceptibility to *S. aureus*. • Overexpression: Driving inflammation and immune cell infiltration.
Lipids Fatty Acids	Free fatty acids	• Antimicrobial activity against bacteria, fungi, and viruses. • Acidification of the skin surface.	• Deficiency: Impaired barrier function, increased susceptibility to infection. • Dysregulation: Associated with dry skin and eczema.
	Ceramides	• Crucial for forming the lipid lamellae in the stratum corneum. • Water retention, prevention of transepidermal water loss. • Modulate immune response.	• Deficiency/Altered Ratio: Severely impaired skin barrier, leading to increased allergen penetration and inflammation. • Implicated in ichthyoses and other barrier disorders.
Enzymes Proteases	ASM	• Generates ceramides, critical for barrier formation and lipid lamellae. • Optimally active at acidic pH.	Dysfunction/Reduced Activity: Impaired ceramide production and barrier function, common in atopic dermatitis, ichthyosis vulgaris.
	Secretory leukocyte protease inhibitor	• Broad-spectrum protease inhibitor, protecting tissues from proteolytic damage. • Direct antimicrobial activity. • Immunomodulatory: can inhibit LPS-induced cytokine production.	• Deficiency: Increased proteolytic damage in inflammatory conditions, impaired resolution of inflammation. • Potential therapeutic target in atopic dermatitis.
	Other Proteases	• Involved in desquamation (stratum corneum turnover) and filaggrin processing. • Activity tightly regulated by endogenous inhibitors.	Dysregulation/Overactivity: Contributes to barrier dysfunction and inflammation in Netherton syndrome, atopic dermatitis.
Small Molecules Ions	NMFs	• Products of filaggrin breakdown. • Maintain hydration of the stratum corneum. • Contribute to the acidic pH of the skin surface.	• Deficiency: Major cause of dry skin. • Genetically linked to atopic dermatitis (filaggrin mutations). • Impaired barrier function and increased susceptibility to irritants/allergens.
	Acidic pH	• Optimizes activity of barrier-forming enzymes. • Inhibits growth of pathogenic bacteria while favouring commensals. • Crucial for lipid processing and desquamation.	Increased pH: Common in atopic dermatitis, ichthyosis, impaired barrier, increased *S. aureus* colonization, exacerbated inflammation, suboptimal enzyme activity.
	ROS, NO	• ROS: Low levels are involved in redox signaling; high levels contribute to oxidative damage, directly bactericidal. • NO: Direct antimicrobial, regulates blood flow and immune response.	• Chronic oxidative stress contributes to skin aging, inflammation, and carcinogenesis. • NO production can impact antimicrobial defense and wound healing.

Footnote: ASM, Acid Sphingomyelinase; LPS, Lipopolysaccharide; NO, Nitric Oxide; ROS, Reactive Oxygen Species; hBDs, human β-defensins; DAMP, damage-associated molecular pattern; NMFs, natural moisturizing factors.

The first layer of detection is mediated by TLRs, which are strategically localized based on the threat they target [1,3,26]. Cell-surface TLRs (TLR2 and TLR4) recognize extracellular microbial signatures, such as lipopolysaccharides and lipoproteins, while intracellular endosomal TLRs (TLR3 and TLR9) sense nucleic acids derived from infection, including viral double-stranded RNA and unmethylated CpG DNA motifs [26,27]. Activation of either pathway engages Nuclear Factor (NF)-κB and Interferon Regulatory Factor 3, driving the expression of pro-inflammatory cytokines and type I interferons (IFNs) crucial for antiviral defense [1,3,26].

Complementing this is a second layer of intracellular surveillance provided by cytosolic NLRs [5]. While nucleotide-binding oligomerization domain (NOD) 1 and NOD2, two well-characterised PRRs, are responsible for detecting bacterial peptidoglycan fragments, the primary NLRs in skin immunity are the inflammasome-forming members, such as NLRP1 (nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing 1) and NLRP3. These inflammasomes promote the caspase-1-dependent cleavage of pro-IL-1β and pro-IL-18, releasing potent inflammatory cytokines essential for immune cell recruitment and tissue repair [8].

Additionally, RLRs, such as retinoic acid-inducible gene-I and melanoma differentiation-associated protein 5, serve as cytoplasmic sensors specifically designed to detect viral RNA [25]. Their activation triggers the rapid secretion of type I IFNs, effectively inhibiting viral replication and establishing an antiviral state in the local microenvironment [1].

3.1.2 Endogenous DAMPs

Beyond microbial detection, KCs possess the critical ability to recognize endogenous danger signals released during cellular damage. This capability allows the skin to initiate inflammatory responses even in the absence of overt infection, a process known as sterile inflammation [28]. Environmental stressors such as ultraviolet (UV) irradiation, mechanical trauma, and chemical irritants induce cellular injury, triggering the release of DAMPs or alarmins into the extracellular space [29].

KCs respond to these alarmins by activating pathways that, while intended for tissue repair, can also drive significant inflammation. For instance, high-mobility group box 1, a nuclear protein released during cell necrosis, acts as a potent alarmin by engaging TLRs and the Receptor for Advanced Glycation End-products [30,31]. Additionally, extracellular ATP released from damaged cells can trigger the assembly of the NLRP3 inflammasome via purinergic receptor signaling [32]. Furthermore, the interaction between self-nucleic acids and the AMP LL-37 forms complexes that break immune tolerance, driving the pathogenic gene expression characteristic of psoriasis [33].

3.2 The Keratinocyte Secretome

As immune gatekeepers, KCs utilize their secretome to orchestrate local and systemic responses [34,35]. In addition to the chemical defense components in Table 1, this includes a sophisticated repertoire of cytokines, chemokines, and growth factors summarized in Table 2. The following sections detail the molecular mechanisms governing their release and their influence on adaptive immunity.

3.2.1 Modulating Innate Immunity

Within the IL-1 family, release mechanisms differ fundamentally between members. While IL-1α is released passively during necrosis as a preformed cytokine, bioactive IL-1β requires proteolytic processing by caspase-1 following inflammasome activation [4]. In humans, the NLRP1 inflammasome is the predominant sensor for UV radiation, driving substantial IL-1β secretion [36,37]. Complementing this, the NLRP3 inflammasome responds to cytoplasmic danger signals, such as viral double-stranded RNA, triggering caspase-1-dependent cleavage and release of bioactive IL-1β and IL-18 [38]. Distinct from these inflammasome-dependent pathways, IL-33 is stored as a constitutively expressed nuclear alarmin and released passively upon mechanical stress or necrotic cell death [39].

Beyond cytokines, KCs orchestrate leukocyte trafficking through the secretion of specific chemokines [40], including CXCL8 (IL-8), whose transcription is rapidly induced by NF-κB activation downstream of TLR signalling and pro-inflammatory stimuli to promote neutrophil recruitment [41], CCL20, whose expression is induced by Th17 cytokines and TLR activation, and CCL27, upregulated by barrier disruption and inflammatory cytokines [42,43].

3.2.2 Shaping Adaptive Immunity

KC-derived signals extend far beyond simple innate alerts; they actively shape adaptive immune responses by bridging epithelial sensing with specific T cell differentiation pathways. In the Th17 axis, PRR activation, notably by TLR4 ligands, triggers NF-κB- and STAT3-dependent transcription of IL-1β, IL-6, and IL-23 in KCs [44], initiating a pathogenic feedback loop known as the IL-23/Th17 axis, which drives the epidermal hyperproliferation characteristic of psoriasis [45]. Conversely, barrier disruption triggers the release of a triad of type 2 alarmins, including TSLP, IL-25, and IL-33. Each functions through a mechanistically distinct pathway to drive type 2 immunity. TSLP is secreted constitutively via a classical ER-Golgi route and upregulated by protease-activated receptor signalling following allergen exposures [46], while IL-33 is a nuclear alarmin released upon mechanical stress or cell death, bypassing the secretory pathway entirely [47,48]. Additionally, IL-25 is secreted in response to epithelial stress and protease activity via the conventional secretory pathway, with clinical evidence showing a direct correlation between IL-25 levels and AD severity [49].

Table 2. Cytokines, chemokines, and growth factors secreted by keratinocytes and their respective biological functions.

Category	Components	Biological functions	Mechanisms	Clinical relevance
IL-1 Family	IL-1α	Early alarmin; activates local immune cells.	Cell stress, necrosis; TLR and DAMP signaling.	Acute inflammation, wound responses.
	IL-1β	Promotes neutrophil recruitment; amplifies inflammation.	Inflammasome activation.	Psoriasis, contact dermatitis.
	IL-33	Drives type 2 immunity; activates ILC2s, Th2 cells.	Cellular injury, nuclear alarmin release.	Atopic dermatitis, allergic inflammation.
Chemokines	CXCL8	Neutrophil recruitment.	NF-κB activation.	Bacterial infection, acute inflammation.
	CCL20	Attracts $CCR6^+$ T cells, dendritic cells, Th17 cells.	TLR activation; cytokine stimulation.	Psoriasis, microbial responses.
	CCL27	Recruits CLA^+ skin-homing memory T cells.	Barrier disruption; inflammatory cytokines.	Chronic dermatitis, eczema.
Cytokines	IL-23	Promotes Th17 expansion and maintenance.	PRR activation; cytokine amplification loops.	Psoriasis, chronic inflammation.
	TSLP	Conditions dendritic cells to drive Th2 priming.	Barrier damage; allergen exposure.	Atopic dermatitis, asthma.
	IL-25	Enhances Th2 cytokine production.	Epithelial stress, protease activity.	Atopic dermatitis, allergic disorders.
Growth factors	TGF-β	Immune suppression; extracellular matrix deposition; wound healing.	Tissue injury; repair processes.	Wound repair, fibrosis.
	Amphiregulin	Promotes re-epithelialization and keratinocyte growth.	Tissue stress, growth factor signaling.	Wound healing, barrier restoration.

Footnote: DAMP, Damage-Associated Molecular Patterns; IL, Interleukin; ILC, Innate lymphoid cells; TGF, Transforming Growth Factor; TLR, Toll-Like Receptor; TSLP, thymic stromal lymphopoietin.

3.2.3 Facilitating Resolution in Inflammation and Repair

To prevent excessive tissue damage, KCs orchestrate the resolution of inflammation and initiate tissue repair by releasing specific immunoregulatory and growth factors [50]. A central mechanism is the KC-mediated activation of latent TGF-β stored in the extracellular matrix, achieved through integrin αvβ6-dependent proteolytic cleavage of the latency-associated peptide. This activation step is critical for maintaining resident memory T cells in the epidermis, ensuring distinct long-term local immune surveillance [51,52]. Concurrently, KCs produce amphiregulin, a member of the EGF family, via metalloprotease-mediated ectodomain shedding from the cell surface, enabling both autocrine and paracrine EGFR activation to coordinate barrier restoration [53]. Collectively, these processes accelerate the restoration of the epidermal barrier, highlighting the intrinsic capacity of KCs to not only defend the skin but also actively return the tissue to homeostasis.

3.3 Crosstalk With Immune Cells

KCs function as pivotal mediators of cutaneous immunity, serving as an integrative signaling platform that directs the identity, mobilization, and functional outcomes of skin-resident and infiltrating immune cells [54,55]. This communication network, comprising a diverse array of cytokines, chemokines, and direct cell-to-cell interactions, is essential for shaping adaptive immune responses and maintaining immune tolerance [3,4].

3.3.1 Professional Antigen-Presenting Cells (APCs)

Langerhans cells (LCs) and dermal dendritic cells (DCs) act as the skin's primary APCs. Under homeostatic conditions, KCs help maintain LCs in a tolerogenic immature state. However, upon activation, KCs rapidly release pro-inflammatory cytokines such as TNF-α and IL-1β, which drive the maturation and migration of LCs [4]. Concurrently, KCs secrete specific chemokines, notably CCL20, to recruit $CCR6^+$ LCs and DCs to the epidermis. This recruitment is crucial for effective antigen capture and subsequent migration of these cells to draining lymph nodes for T cell priming [56]. The nature of this crosstalk dictates the immune outcome. During allergic inflammation, KCs release type 2 alarmins like TSLP and IL-33, activating LCs and DCs, to skew immunity toward a Th2 profile, as seen in conditions like AD [4]. Conversely, in psoriasis, KC-derived IL-23 acts on dermal DCs and ILCs, driving the characteristic Th17 inflammatory axis [57].

3.3.2 T Cells

KC-derived chemokines, specifically CXCL9, CXCL10, and CXCL11, establish critical chemotactic gradients that recruit activated $CXCR3^+$ T cells into the epidermis [58]. Furthermore, KCs are essential for the retention of tissue-resident memory T cells, primarily through the secretion of TGF-β [22,59,60], thereby ensuring sustained local immunological surveillance. Interestingly, in response to IFN-γ stimulation, KCs are capable of expressing MHC Class II and intercellular adhesion molecule 1, facilitating direct interactions with T cells, although the capacity of KCs to function as *de novo* APCs remains a subject of debate [61].

3.3.3 Neutrophils and Macrophages

KCs also orchestrate the infiltration and function of innate effector cells during injury or infection. In the acute phase, KCs are a primary source of CXCL8 (IL-8), promoting a rapid influx of neutrophils essential for pathogen clearance [62,63]. Moreover, KCs significantly influence the macrophage polarization. Initial inflammatory signals promote the activation of pro-inflammatory M1 macrophages. In contrast, during the resolution phase, KC-derived signals such as amphiregulin facilitate the transition toward an anti-inflammatory M2 phenotype, which supports tissue repair [64]. Additionally, KC signals can guide efferocytosis, the engulfment of apoptotic cells by macrophages, reprogramming macrophages into a pro-resolving state to accelerate healing [65].

3.4 Interactions With Environment and Microbiota

As primary sentinels at the immunological interface, KC continuously monitor physical, chemical, and microbial stressors to maintain skin homeostasis [4]. Their function relies on the ability to translate these diverse external signals into precise physiological responses. Acting as a bridge between the environment and the host, KCs determine the outcome of these interactions: they trigger protective tolerance pathways under steady-state conditions or, when equilibrium is disrupted, initiate inflammatory cascades that can lead to pathology [3].

3.4.1 Environmental Factors

The skin is perpetually exposed to environmental stressors, most notably UV radiation, pollutants, and allergens. Among these, UV light serves as a primary disruptor of cellular integrity. It induces direct DNA damage, which triggers internal repair mechanisms or, in cases of severe insult, apoptosis [66,67]. Beyond structural damage, UVB radiation is a significant inducer of sterile inflammation. Specifically, it activates the NLRP1 inflammasome within human KCs, resulting in robust IL-1β release and subsequent recruitment of immune cells [37]. This inflammatory cascade not only manifests clinically as sunburn but also serves as a critical link between photodamage and systemic pathology, potentially fuelling autoimmune flare-ups in conditions like cutaneous lupus erythematosus (CLE) [68,69].

In parallel, atmospheric pollutants, such as particulate matter and ozone, and chemical irritants challenge skin integrity by disrupting the lipid barrier and generating ROS. Central to the KC response against these xenobiotics is the

aryl hydrocarbon receptor (AhR) signaling pathway [70]. While physiological AhR activation is crucial for barrier maintenance, chronic stimulation by pollutants can dysregulate KC differentiation and drive persistent inflammation [70,71]. A similar inflammatory shift occurs during exposure to allergens and chemical haptens, which trigger the release of DAMPs and alarmins to initiate the sensitization phase of allergic contact dermatitis (ACD) [72].

3.4.2 Microbiota

KCs maintain a dynamic, symbiotic relationship with the skin's commensal microbiota, a partnership that is foundational to both innate immunity and immune tolerance [73]. Under homeostatic conditions, KCs exercise "immune vigilance" through tightly regulated PRR signaling, most notably via TLR2 [12], which allows them to manage microbial populations without triggering overt inflammation [74]. This controlled interaction fosters a stable coexistence with commensals such as *Staphylococcus epidermidis* and *Cutibacterium acnes*, while stimulating a basal level of AMP production that reinforces the skin barrier.

However, barrier disruption or infection can rapidly destabilise this equilibrium. Pathogenic colonization, particularly by *Staphylococcus aureus*, drives excessive PRR activation and KC hyperresponsiveness. In the context of AD, this results in a massive release of type 2 alarmins that fuel persistent inflammation [4,75]. Such signaling often initiates a self-perpetuating cycle: inflammation further impairs barrier integrity and amplifies microbial dysbiosis, which in turn reinforces disease progression [4,22]. Ultimately, the convergence of barrier dysfunction, microbial imbalance, and aberrant KC signaling sustains the chronic inflammatory states seen in various dermatoses [73].

3.4.3 Epigenetic Plasticity

The epidermis functions as a molecular archive, recording the lasting impact of environmental and microbial stress through the epigenetic flexibility of KCs, a phenomenon increasingly known as epithelial-trained immunity or inflammatory memory [76]. While acute stress triggers transient inflammatory gene expression via the NF-κB and janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, chronic or repetitive exposure induces enduring epigenetic remodeling. Mechanisms such as DNA methylation shifts and the retention of active histone acetylation "poise" specific genomic regions, locking them into a constitutively accessible state [77,78,79].

Recent evidence suggests this "locking" mechanism involves the persistent accumulation of active histone marks and the depletion of repressive marks at key promoters and enhancers. For example, the loss of H3K9 dimethylation at the *IL-23A* promoter in KCs is directly linked to the sustained overexpression of IL-23, a primary driver of chronic psoriatic inflammation [80]. Such alterations culminate in "transcriptional scarring", a permanent reshaping of the chromatin accessibility landscape that traps KCs in a pro-inflammatory phenotype. Consequently, even after the original stimulus is removed, these "scarred" KCs remain hypersensitive, mounting exaggerated inflammatory responses to even minor secondary insults.

Additionally, when this epigenetic imprinting occurs within epidermal stem cells, the memory becomes heritable, propagating the inflammatory phenotype to all subsequent differentiated progeny [81], thus disrupting terminal differentiation pathways. As these stem cells give rise to KCs that retain inflammation-associated signatures, often characterized by sustained H3K4me3 marks and Activator Protein-1 binding at pro-proliferative gene loci, the result is a continuous cycle of hyperproliferation and incomplete differentiation [82,83]. This "trained immunity" of the epithelium not only impairs the barrier function of the stratum corneum but also creates a permissive environment for genomic instability, ultimately predisposing the epidermis to malignancies such as squamous cell carcinoma (SCC) [84,85,86,87,88]. The progression from actinic keratosis to invasive SCC follows a defined epigenetic trajectory in which loss of H3K9me2 at *p16INK4a* and *p14ARF* loci silences the RB1/p53 checkpoint, while elevated p300 cooperates with ΔNp63α to enforce chromatin accessibility at proliferation gene clusters [89]. Constitutively active STAT3, a hallmark of transcriptionally scarred KCs, completes the oncogenic loop by upregulating PRECSIT, a lncRNA that sustains STAT3 activity and induces matrix metalloproteinase-dependent invasion [90]. Multiomic profiling confirms that TP53 and NOTCH1 mutations act as gatekeepers that break epigenetic buffering, permitting the mutation-burden escalation characteristic of invasive SCC [91].

At the same time, photoaging, another environmental stressor, adds a layer of complexity to epigenetic plasticity in the skin. UV radiation induces rapid DNA methyltransferase dysregulation and histone acetylation shifts, notably H3K9ac and H3K27ac, that mirror those found in chronic inflammatory states [92,93]. These changes alter the expression of genes affiliated with keratinocyte proliferation and apoptosis [78]. This dual impact of chronic inflammation and photoaging on genomic accessibility further exacerbates the risk of malignant transformation, establishing a feedback loop where inflammatory memory not only contributes to skin disorders but also primes the epidermis for cancer development.

In summary, the interplay between inflammatory memory, transcriptional scarring, and epigenetic alterations resonates through various skin pathologies, including hyperproliferative states and malignancies. Understanding these mechanisms offers crucial insights into the prevention and therapeutic strategies against skin cancer and other dermatological disorders linked with chronic inflammation and environmental stress exposure.

4. Keratinocytes in Inflammatory Skin Diseases

The transition from skin health to chronic disease is largely governed by a shift in KC behaviour. In these pathological contexts, KCs lose their homeostatic "gatekeeper" status and instead function as primary drivers of inflammatory progression [4].

4.1 Psoriasis

Psoriasis is a chronic, immune-mediated skin disorder characterized by the formation of hyperproliferative epidermal plaques [8]. The disease process often begins with KC injury [22,94], a phenomenon known as the Koebner effect. Injured KCs release DNA-LL37 complexes [94] that activate plasmacytoid DCs, stimulating a robust production of type I IFNs [22]. In response to this inflammatory milieu, KCs secrete IL-23 and IL-1β, fuelling the expansion of Th17 and Th22 cells [95,96]. These T cell subsets produce IL-17A and IL-22, which act directly on KCs to amplify their proliferation and stimulate the release of pro-inflammatory chemokines such as CXCL8 and CCL20 [8]. This reciprocal relationship establishes a self-amplifying feedback loop, transforming a localized injury into a sustained, chronic psoriatic plaque [8,22,24,95,96].

4.2 Atopic Dermatitis

AD is characterized by recurring eczematous lesions caused by significant dysfunction of the epidermal barrier, with KCs being the primary site of this functional defect [97]. Mutations in the filaggrin gene are strongly associated with AD [98]. This mutation directly impairs the formation of NMFs and increases the penetration of allergens and pathogens [99], which stimulates the KCs to release high levels of TSLP, IL-33, and IL-25 [3]. These alarmins interact with LCs and other DCs to drive Th2 polarization, which promotes an allergic response characterized by the production of IL-4, IL-5, and IL-13 [100]. These Th2 cytokines directly inhibit KC differentiation, decrease lipid synthesis, and reduce TJ proteins [4]. This creates a destructive feed-forward cycle where inflammation further destabilizes the barrier, which in turn invites further allergen penetration and immune activation, locking the skin into a chronic state of AD [100].

4.3 Other Inflammatory and Autoimmune Conditions

Beyond psoriasis and AD, KCs contribute to contact hypersensitivity and autoimmune disorders through distinct mechanisms, such as the formation of hapten-induced neoantigens and impaired clearance of apoptotic debris. ACD and CLE represent prime examples of these KC-driven pathologies.

In ACD, KCs serve as the primary site for sensitization. Low-molecular-weight haptens penetrate the SC and covalently modify self-proteins on the KC surface, creating "neoantigens". KCs recognize these modifications as danger signals, triggering the release of DAMPs and pro-inflammatory cytokines that prime local APCs to initiate the sensitization phase [101]. Following this initial stage, KCs sustain the effector phase by secreting chemokines such as CCL20 and CXCL8, which orchestrate the recruitment and precise positioning of effector T cells within the epidermis, ultimately driving the eczematous reaction [101].

In contrast, CLE represents a condition where KCs are both the initiators and the primary targets of autoimmune damage. In genetically predisposed individuals, UV irradiation induces extensive KC apoptosis. In CLE, however, the defective clearance of this apoptotic debris leads to secondary necrosis and the release of nuclear autoantigens into the extracellular space [68,69]. These autoantigens function as DAMPs, activating plasmacytoid DCs via endosomal TLRs and driving a robust production of type I IFNs. The resulting "IFN signature" amplifies local inflammation and establishes a cytotoxic feedback loop, wherein IFN-stimulated genes further sensitize KCs to apoptosis, perpetuating the autoimmune cycle [102].

Collectively, these studies indicate that KC dysfunction, whether originating from barrier failure or aberrant immune activation, is a cornerstone of diverse skin pathology [4]. Understanding how KCs transition from regulatory barriers to hyperactive immune sentinels is essential for developing targeted interventions to disrupt these chronic inflammatory pathways.

5. Conclusion

Recent advances have fundamentally redefined KCs, establishing them as active immunological regulators rather than passive structural components of the epidermis (summarized in Fig. 2). Upon activation, KCs undergo a profound functional shift, transitioning from barrier-forming cells into potent immune effectors that secrete a sophisticated repertoire of cytokines, chemokines, and antimicrobial peptides. These molecular outputs do more than initiate local inflammation; they serve as a critical bridge between innate and adaptive immunity, orchestrating the recruitment, differentiation, and polarization of diverse immune cell subsets. However, this immunological plasticity is inherently double-edged. In chronic inflammatory conditions such as AD and CLE, dysregulated KC signaling triggers self-amplifying inflammatory loops. These loops drive persistent tissue remodeling and exacerbate barrier dysfunction, locking the skin into a state of chronic pathology.

6. Therapeutic Implications and Future Directions

6.1 Translational Implications

Recognizing KCs as dynamic "immune hubs" necessitates therapeutic strategies that directly target KC-specific signaling nodes. The mechanisms reviewed here map onto five clinical or emerging axes.

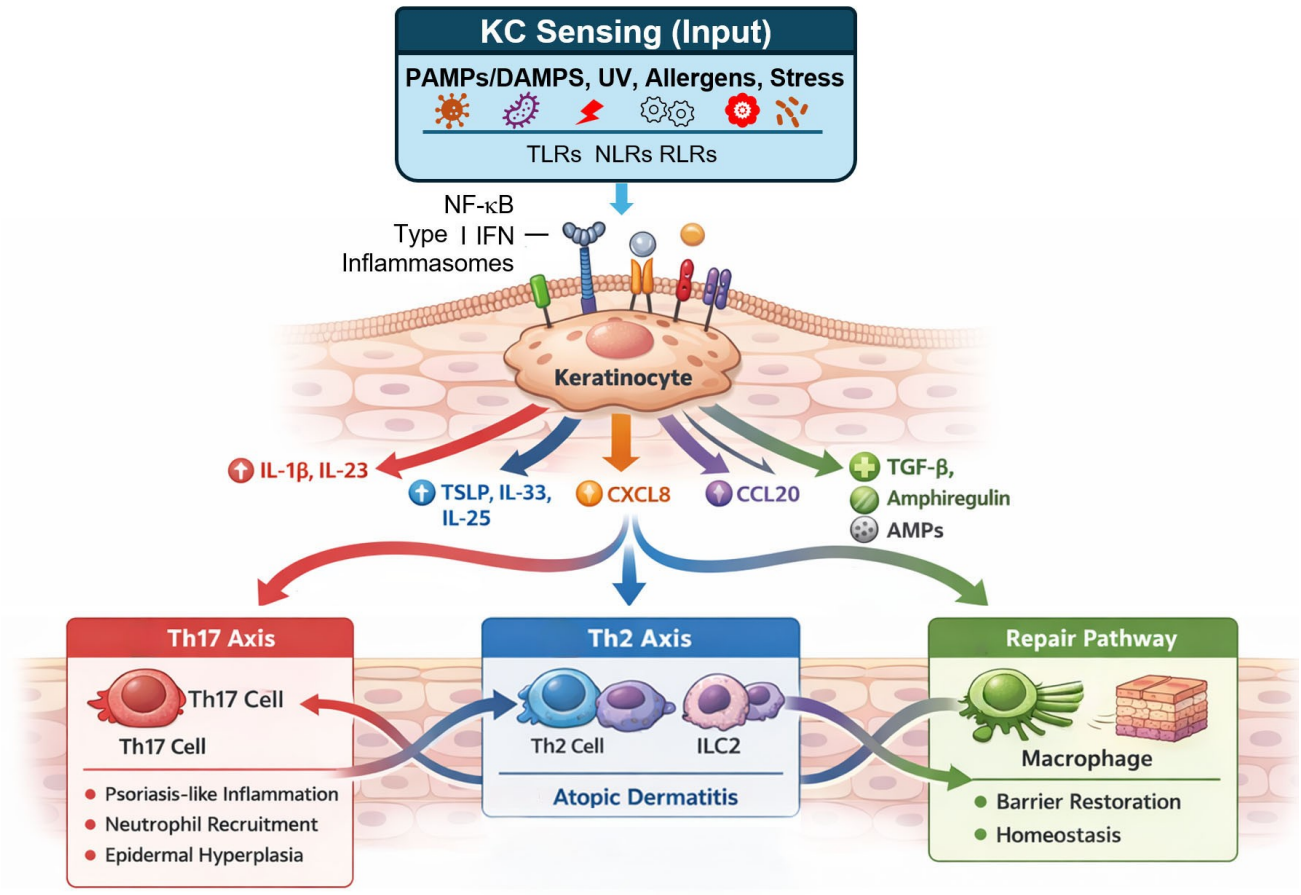

Fig. 2. Keratinocyte sensing and signalling pathways linking environmental cues to immune outcomes. Keratinocytes (KCs) detect pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), environmental stressors, and microbial signals through pattern recognition receptors, including Toll-like receptors (TLRs), Nod-like receptors (NLRs), and RIG-I-like receptors (RLRs). This induces cytokine and chemokine release that drives three axes: the Th17 axis (IL-1β, IL-23 → IL-17/IL-22) promoting psoriasis-like inflammation; the atopic dermatitis axis (TSLP, IL-33, IL-25) driving type 2 responses; and the repair pathway (TGF-β, amphiregulin, antimicrobial peptides (AMPs)) supporting barrier restoration and homeostasis.

Targeting the IL-23/IL-17 axis in psoriasis. PRR activation in KCs drives NF-κB- and STAT3-dependent IL-23 transcription, sustaining Th17 expansion and the epidermal hyperproliferation of plaque psoriasis. Biologics targeting the IL-23 p19 subunit, guselkumab, risankizumab, and tildrakizumab, interrupt this axis at source, yielding durable clearance in phase 3 trials [103,104]. KC inflammasome-driven IL-1β, a co-inducer of Th17 differentiation, further identifies NLRP3 inhibitors as candidate adjuncts in inflammasome-driven flares.

TSLP and type 2 alarmin blockade in AD. Barrier disruption triggers PAR-dependent TSLP secretion, nuclear IL-33 release, and protease-induced IL-25 production, synergistically amplifying ILC2 and Th2 responses. Dupilumab, targeting the shared IL-4Rα subunit, remains the cornerstone of moderate-to-severe AD management. Tralokinumab, specifically a neutralizing IL-13 antibody, demonstrated superiority over placebo at 16 weeks with sustained tolerability to 52 weeks [4]. Despite a compelling mechanistic rationale, upstream alarmin blockade has proven clinically challenging: tezepelumab (anti-TSLP) failed to meet its phase IIa primary endpoint in AD [2], underscoring that KC-derived alarmins may be more critical for disease initiation than chronic maintenance.

AhR modulation. AhR, highly expressed in KCs, suppresses NF-κB-driven cytokine production while promoting barrier gene expression. Tapinarof, a topical AhR agonist, demonstrated significant efficacy in psoriasis (PSOARING 1–3) [105,106,107] and AD (ADORING 1–2) [108], validating KC transcriptional reprogramming as a therapeutic strategy distinct from single-cytokine neutralization.

Epigenetic and JAK/STAT targeting. Durable KC epigenetic reprogramming, including NF-κB locus hypomethylation and BRD4-driven super-enhancer activity, sustains pathological secretome output in chronic disease [109,110]. Concurrently, JAK1 inhibitors (abrocitinib, upadacitinib) in AD [111,112] and the TYK2 inhibitor deu-

cravacitinib in psoriasis [113] intercept shared intracellular nodes downstream of multiple KC-relevant cytokines.

Restoring barrier integrity. Since PAR activation, mechanical stress, and DAMP sensing all depend on barrier breach, upstream barrier restoration can suppress the entire KC inflammatory cascade before initiation. Crisaborole (PDE4 inhibition) [114] and ceramide-based formulations directly reduce the threshold for KC immune activation, representing a prevention-oriented complement to cytokine-targeted therapies.

6.2 Future Directions

Despite this progress, significant mechanistic gaps remain. Future research must leverage multi-omics platforms and single-cell technologies to map the spatial and temporal complexity of the KC–immune cell interactome with resolution sufficient to reveal how disease-specific KC subpopulations differ in their secretome composition, PRR repertoire, and epigenetic state. Spatial transcriptomics applied to lesional versus non-lesional skin has already revealed that KC inflammatory activation is regionally heterogeneous, implying that bulk-tissue approaches have systematically underestimated the diversity of KC immune states. Integrating these datasets with proteomics of the KC secretome and phosphoproteomics of activated signaling nodes will be essential for identifying precise molecular targets capable of restoring epidermal homeostasis. Critically, therapeutic candidates emerging from these platforms must be evaluated in systems that preserve the KC–immune cell crosstalk described in this review, including organotypic skin equivalents, patient-derived explants, and humanized mouse models, to ensure that mechanism-based efficacy translates into clinical benefit. Breaking the self-perpetuating cycle of chronic inflammation will ultimately require not only identifying new targets but understanding the order, timing, and cellular context in which each node of the KC secretome contributes to disease initiation, perpetuation, and resolution.

Abbreviations

ACD, allergic contact dermatitis; AD, atopic dermatitis; AhR, aryl hydrocarbon receptor; AMP, antimicrobial peptide; APC, antigen-presenting cell; ASM, acid sphingomyelinase; DAMP, damage-associated molecular pattern; CLE, cutaneous lupus erythematosus; DC, dendritic cell; hBD, human β-defensin; IFN, interferon; ILC, innate lymphoid cell; JAK/STAT, janus kinase/signal transducer and activator of transcription; KC, Keratinocyte; LC, Langerhans cell; LPS, lipopolysaccharide; NMF, natural moisturizing factors; NF, nuclear factor; NLR, Nod-like receptor; NLRP, nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing; NO, nitric oxide; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptors; RLR, Retinoic acid-inducible gene-I-like receptors; ROS, reactive oxygen species; SB, Stratum basale; SC, stratum corneum; SCC, squamous cell carcinoma; SG, stratum granulosum; SS, stratum spinosum; TGF, transforming growth factor; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin; UV, ultraviolet.

Author Contributions

MX developed the concept and design of this review; MX wrote the original draft, LM, HW and SH assisted with literature collection and manuscript drafting. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Grammarly to check spelling and grammar. After utilizing this tool, the authors reviewed and edited the content as necessary and take full responsibility for the publication's content.

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