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Morphofunctional basis of the cutaneous immune system

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This article provides a comprehensive review of the morphofunctional basis of the cutaneous immune system, detailing the cellular composition and integration within a complex neuro-immune-endocrine network. The main immune competent cells including keratinocytes, dendritic cells (Langerhans, myeloid), macrophages, mast cells, and lymphocytes are characterized in terms of their roles in maintaining skin homeostasis and defense against external and internal factors. The literature search was conducted using scientific databases such as *Scopus*, *PubMed*, and *Web of Science*. Particular attention is given to the concept of inducible skin-associated lymphoid tissue (iSALT) and its role in local immune regulation. The conclusions emphasize the complexity of cellular interactions in the skin and their contribution to systemic immune responses.

Key words: cutaneous immune system, keratinocytes, lymphocytes, dendritic cells, macrophages, mast cells, immunocompetent cells

Introduction

The skin is the largest and most complex organ of the human body. Its extensive surface area in contact with the external environment, along with the specific features of its tissue composition and blood supply, necessitates powerful defense mechanisms against adverse external factors as well as against internal factors in cases of homeostatic imbalance [13, 31, 43, 45]. For many years, skin was regarded primarily as an organ providing mechanical and chemical barriers. However, this concept has undergone a profound transformation in recent decades.

Modern research has demonstrated that the skin is an active immunocompetent organ with its own complex immune network, capable of systemic immune responses and interactions with the cutaneous microbiota. Investigations into the protective functions of the skin have led to a new understanding of it as an immunocompetent organ possessing a set of organ-specific defense mechanisms. The resistance of skin structures to damaging agents is determined by mechanisms of nonspecific defense and immunological reactivity [13, 45, 56, 75, 77]. The latter is mediated by cellular and humoral reactions aimed at the elimination of microbial and non-microbial elements. Various cell populations involved in immune surveillance of the skin constitute the local immune defense and are collectively referred to as the "skin immune system" [26, 40, 45, 71].

Occupying a barrier position, the skin is continuously exposed to external and internal adverse influences, which may lead to disturbances of varying severity in its protective complex. Understanding the mechanisms of interaction and regulation of all components of the skin immune system is of great importance for medicine, particularly in light of the increasing recognition of the role of the skin microbiome and its influence on immunity.

Materials and Methods

The aim of this review is to comprehensively summarize the current knowledge on the morphofunctional basis of the cutaneous immune system, highlighting the cellular components and their roles in maintaining skin homeostasis and systemic immune interactions. To achieve this, a systematic literature search was conducted using major scientific databases including *Scopus*, *Web of Science*, and *PubMed*. The search covered articles published between 2010 and 2025 and employed keywords related

to skin immunity, immune cells of the skin, neuroimmune interactions, and immune regulation in dermatology. Selected publications were screened for relevance, focusing on both original research and recent comprehensive reviews, to provide an up-to-date synthesis of the subject.

Cutaneous immune system

In recent decades, the cutaneous immune system has been increasingly recognized as an integral and functionally coordinated component of overall immunity, contributing to the maintenance of systemic homeostasis by providing protection against foreign biological agents [10, 13, 55, 79]. Due to its vast surface area in constant contact with the external environment, the skin is uniquely positioned as the first line of defense against a wide range of exogenous factors, including antigenic stimuli [66].

Pioneering work in the 1980s by J. W. Streilein introduced, by analogy with MALT (mucosa-associated lymphoid tissue), the concept of SALT (skin-associated lymphoid tissue). This term referred to populations of immune cells, including lymphocytes and antigen-presenting cells, residing in the epidermis and dermis. Building on this concept, J. D. Bos and colleagues later proposed the broader term skin immune system (SIS), encompassing SALT together with the epidermis, dermis, and regional lymph nodes [15, 21, 46, 64].

Current evidence supports a functional subdivision of skin defenses into nonspecific mechanisms — mechanical, biochemical, and cellular defenses — and specific immune responses, comprising both cellular and humoral components. The nonspecific arm of cutaneous defense is mediated primarily by epidermal elements such as keratinocytes and dendritic cells, as well as dermal populations including macrophages, mast cells, and granulocytes. In contrast, specific local immunity is ensured by lymphocytes, which orchestrate antigen-specific responses within the skin [45, 51].

More recently, an important conceptual advance has been the recognition of the cutaneous neuroimmune endocrine (CINE) system, a complex network integrating neurons, immune cells, and endocrine cells. This system enables rapid and precise skin responses to stressors by modulating immune defenses and homeostatic processes through neurotransmitters, hormones, and cytokines. Importantly, the CINE system operates both locally within the skin and systemically, thereby influencing not only cutaneous but also organismal immunity. This perspective underscores the integration of the skin into broader neuro–immune–endocrine interactions and highlights the critical role of intercellular communication across the nervous, immune, and endocrine compartments [4, 61].

The extensive surface area of the skin in contact with the external environment, together with its specific tissue composition and vascularization, necessitates the presence of powerful defense mechanisms against adverse external factors, as well as internal factors arising from disruptions of homeostasis [33, 45]. In this context, the traditional view of the skin merely as a mechanical and chemical barrier has been substantially broadened: the skin is now regarded as an immunocompetent organ equipped with a complex network of local and systemic defense mechanisms. The resistance of cutaneous structures to damaging agents is mediated by both nonspecific and specific immune mechanisms, which include cellular and humoral responses directed at the elimination of microorganisms and altered host cells [31, 45].

Components of Innate Immunity

Keratinocytes

Keratinocytes represent the principal cellular component of the epidermis. Through differentiation and apoptosis, they give rise to corneocytes of the *stratum corneum*, which provide the physical barrier of the skin. Beyond this structural role, keratinocytes produce a wide range of regulatory factors, including growth factors and cytokines, and upon injury they secrete antimicrobial peptides such as defensins and cathelicidins.

Keratinocytes of the granular, spinous, and cornified layers express pattern-recognition receptors (PRRs), enabling them to sense microbial invasion and initiate immune responses. Recent studies have shown that PRR activation triggers the NF-κB signaling pathway, leading to the production of pro-inflammatory cytokines and chemokines that recruit immune cells to sites of injury or infection. Moreover, keratinocytes express Toll-like receptors (TLRs) upon activation, thereby acquiring functions resembling those of antigen-presenting cells. Strong activation of keratinocyte TLRs has been associated with polarization toward a Th1 immune response and the synthesis of pro-inflammatory interferons [18, 41, 52].

Keratinocytes also engage in contact-dependent interactions with Langerhans cells and intraepidermal lymphocytes through adhesion molecules such as E-cadherin and ICAM-1. Disruption of these adhesion pathways has been implicated in the pathogenesis of several skin disorders. In addition, activated keratinocytes release chemokines that attract T lymphocytes from the circulation to sites of tissue damage [12, 65].

Recent evidence highlights the regulatory role of keratinocyte apoptosis in maintaining Treg cell populations and skin tissue homeostasis. Coculture experiments further suggest that keratinocytes can suppress the proliferation of phytohemagglutinin (PHA)-activated lymphocytes *in vitro* [2, 19, 29, 50, 59].

Of particular interest is the interaction between keratinocytes and immature T lymphocytes. Several studies suggest that keratinocytes, which share lineage similarities with thymic reticuloepithelial cells, can produce factors influencing T-cell differentiation [73].

Dendritic Cells (DCs)

Dendritic cells (DCs) represent a heterogeneous population of professional antigen-presenting cells (APCs)

that play a pivotal role in both the initiation of adaptive immunity and the maintenance of immune tolerance. Multiple subsets of DCs are present in the skin, each with distinct phenotypic, functional, and molecular characteristics.

The major subsets include:

— Langerhans cells (LCs) in the epidermis, specialized in antigen presentation and epidermal immune homeostasis;

— dermal myeloid DCs, including $CD11b^+$ and $CD11b^-$ subsets, which contribute to T-cell activation, cytokine secretion, and migration to lymphoid tissues;

— plasmacytoid DCs (pDCs), potent producers of type I interferons during viral infections, with additional roles in immune tolerance [7, 60, 78].

Skin DCs display remarkable functional plasticity, adapting their properties to the tissue microenvironment, shifting from tolerance induction to strong immunogenic responses. Certain subpopulations also exhibit cross-presentation capabilities, crucial for $CD8^+$ T-cell activation and antitumor immunity. Modern classification based on molecular markers (CD1a, CD207, CD11c, CD1c, XCR1, CD14, among others) and transcriptomic profiling has refined the identification of functionally distinct dermal DC subsets. This is of particular relevance for the development of immunotherapeutic strategies in inflammatory and oncological skin diseases [6, 58].

Langerhans Cells (LCs)

Langerhans cells constitute the major specialized APCs of the epidermis, localized in the basal and spinous layers, accounting for 2–4 % of all epidermal cells. Most LCs are thought to originate from $CD34^+$ hematopoietic progenitors, although recent evidence suggests that resident $CD14^+$ dermal cells can differentiate into LC-like cells under the influence of TGF-β, underscoring the plasticity of LC development within the cytokine milieu of the skin [9, 20, 47, 80].

LCs, although tightly associated with keratinocytes, are highly dynamic, capable of migration and phenotype modulation. Their defining markers include MHC class II molecules, E-cadherin, langerin (CD207), and CD1a. A hallmark ultrastructural feature of LCs are Birbeck granules, rod- or racket-shaped organelle-like structures formed by the accumulation of langerin in endosomal compartments. Although their precise function remains incompletely understood, emerging evidence suggests they are involved in receptor-mediated endocytosis and antigen transport, significantly influencing the antigen-presenting capacity of LCs [39].

Upon inflammatory stimulation, LCs capture antigens in the epidermis, process them during migration, and travel via lymphatic vessels to regional lymph nodes, thereby forming a functional “skin–lymph node” axis [24, 68]. In lymph nodes, they present processed antigens to T cells, triggering downstream immune responses and antigen elimination [23, 47]. Human LCs preferentially drive Th2 cell differentiation and can prime both naïve and cross-present $CD8^+$ T cells [3, 38, 48].

LC activation is mediated by microbial molecules recognized via TLR and NOD-like receptors, as well as cytokines from the microenvironment. LCs are central to the initiation of cellular immunity, notably by stimulating natural killer cells and $CD8^+$ T lymphocytes. Importantly, they express distinct sets of Toll-like receptors, the activation of which promotes IL-15 secretion, a cytokine critical for $CD8^+$ T-cell proliferation [8, 63].

Dermal Myeloid Dendritic Cells (dDCs)

Dermal myeloid dendritic cells (dDCs) are functionally comparable to other interstitial DC populations identified within the stromal connective tissues of various organs. They are distributed throughout all layers of the dermis and characteristically express MHC class II and CD1c (BDCA1) molecules on their surface. Their principal functions include antigen presentation and the secretion of cytokines and chemokines. Upon activation, dDCs migrate to the paracortical regions of draining lymph nodes. Recent studies in models of allergic contact dermatitis have demonstrated that dDCs isolated from lymph nodes can induce robust T-cell proliferation [1, 37, 58].

Plasmacytoid Dendritic Cells (pDCs)

Plasmacytoid dendritic cells (pDCs) represent a distinct class of DCs that are much less frequent in the skin compared with dDCs. They are phenotypically defined by surface expression of CD123, CD45RA, and CD303 (BDCA2). Functionally, pDCs are potent producers of type I interferons, particularly IFN-α, during viral infections. Beyond their antiviral role, pDCs are also thought to modulate plasma cell activity and contribute to the induction of immune tolerance [14, 44].

Dermal Macrophages

Dermal macrophages are large amoeboid cells rich in lysosomes. They are also regarded as professional antigen-presenting cells; however, unlike dendritic cells, macrophages lack the capacity to initiate primary immune responses. Their contribution to nonspecific defense relies primarily on phagocytosis and the neutralization of infectious agents through the secretion of cytokines and chemokines. Skin macrophages originate from circulating monocytes, which in turn derive from bone marrow myeloid progenitors. Recent evidence suggests that macrophages in the skin retain proliferative capacity, highlighting their persistence and role in tissue homeostasis [34, 62, 74]. Macrophages express pattern recognition receptors (PRRs) on their surface, subdivided into membrane-bound and cytoplasmic receptors, which are crucial for the recognition of pathogen-associated elements. Once activated, macrophages migrate to sites of inflammation, where they produce interleukins and toxic mediators that suppress microbial activity [36].

Several macrophage subsets have been identified in the skin and are generally classified into two main categories: resident and inflammatory. Resident macrophages are permanently present within the dermal con-

nective tissue and are essential for maintaining homeostasis. In contrast, inflammatory macrophages arise *de novo* at sites of infection or tissue injury. Classically activated macrophages exert pro-inflammatory functions and are characterized by the synthesis of IL-12 and IL-23 [17, 28, 34]. Alternatively activated macrophages, in contrast, secrete IL-10 while lacking IL-12 production, thereby suppressing T-cell proliferation and attenuating inflammation. Recent studies have shown that alternatively activated macrophages promote fibrogenesis, angiogenesis, and wound healing [11, 53]. Importantly, macrophages in wounds display a mixed and dynamic phenotype that combines features of both classical and alternative activation states.

Mast Cells and Dermal Granulocytes

Mast cells represent an integral component of nonspecific antibacterial and antiparasitic defense but are also key contributors to allergic and inflammatory reactions due to their production of cytokines, chemokines, lipid mediators, proteases, and biogenic amines. They have been implicated in the pathogenesis of stress-related effects on the skin. Under physiological conditions, mast cells participate in tissue homeostasis, regulation of interstitial fluid balance, and control of microvascular tone [27, 42, 72].

Neutrophils constitute another central element of nonspecific defense, capable of recognizing, phagocytosing, and destroying pathogens. Under normal conditions, their presence in the dermis is limited; however, during inflammation, they are rapidly recruited from the bloodstream. Recent research revealed a specialized population of neutrophils in the skin that synthesize collagen and other extracellular matrix (ECM) components, physically reinforcing the skin barrier beyond their traditional antimicrobial role. These “matrix-producing neutrophils” produce type III collagen (COL3A1) and other ECM molecules not only during injury but also in homeostasis, thus enhancing mechanical integrity and barrier function of the skin. After skin injury, these neutrophils form protective ECM “rings” around wounds (~1 mm diameter) that prevent bacterial and toxin penetration. This process is regulated by the TGF-β signaling pathway, with inhibition of this pathway impairing ring formation and increasing skin permeability. Additionally, their activity follows a circadian rhythm, showing increased migration and ECM formation during the night, correlating with enhanced skin mechanical strength at this time. In addition to their antimicrobial functions, neutrophils interact closely with other immune and stromal cells to regulate reparative processes [67].

Moreover, skin-resident dermal neutrophils differ from circulating blood neutrophils by their longer lifespan, immune-modulatory roles, and active interactions with skin cells such as fibroblasts and keratinocytes. They participate not only in classical defense mechanisms including phagocytosis, reactive oxygen species (ROS) production, and neutrophil extracellular trap (NET) formation but also engage in immunoregulation via cytokine secretion (*e.g.*, TNF-α, IL-1β, IL-17), affecting macrophages, dendritic cells, and T lymphocytes. Their coordinated “swarming” migration around infection foci helps isolate pathogens and modulate inflammation. These dermal neutrophils have been implicated in the pathogenesis of chronic skin diseases such as psoriasis, chronic wounds, and autoimmune dermatitis [67].

Innate Lymphoid Cells

The system of nonspecific defense also includes innate lymphoid cells (ILCs) — namely NK, NKT, and γδ T lymphocytes — which, according to most researchers, represent an evolutionarily more ancient layer of the lymphoid immune system. These cells not only perform classical protective functions but also contribute to histogenesis, tissue remodeling, and stem cell regeneration [25, 51, 70].

Natural Killer (NK) Cells

NK cells are capable of directly attacking virus-infected and tumor cells as well as producing cytokines. They are characterized by the phenotype $CD3^{-}CD16^{+}$, $CD3^{-}CD56^{+}$. However, many functions of NK cells under pathological conditions remain poorly understood, and recent studies have reconsidered their role. In particular, NK cells have been implicated in the pathogenesis of allergic and autoimmune diseases. In the skin, two distinct NK cell populations have been identified: one producing IL-22 alone, and another producing both IL-22 and IL-17. The latter are often referred to as lymphoid tissue inducer (LTI)-like cells, which participate in autoimmunity and inflammation, although current evidence about them remains limited [30].

Natural Killer T (NKT) Cells

NKT cells, or natural killer T lymphocytes, co-express CD16, CD56, CD57, CD94, and CD161. Unlike conventional T lymphocytes, they recognize glycolipid antigens presented by CD1d molecules. NKT cells rapidly secrete cytokines and exhibit cytotoxic activity through the expression of perforin, granzymes, and granulysin. They mediate both protective and regulatory immune functions [69, 81].

γδ T Cells

γδ T cells are abundantly present in the epidermis and are considered part of the first line of defense against pathogens, as well as key players in maintaining epidermal homeostasis. They are capable of recognizing non-peptide antigens, including autoantigens expressed by damaged keratinocytes. Close interactions between γδ T cells and dendritic cells (DCs) have been established: DCs activate γδ T cells, which in turn accelerate the maturation of immature DCs. Skin-resident γδ T cells expressing NKG2D play a pivotal role in cutaneous malignancies. In addition, human γδ T cells produce growth factors essential for wound healing, including CTGF, FGF9 (GAF), KGF, and IGF1 [5, 22, 76].

Adaptive Immunity

T Lymphocytes

Adaptive immunity in the skin is primarily mediated by effector T lymphocytes, which constitute more than 90 % of all cutaneous lymphocytes. $CD4^+$ and $CD8^+$ T-cell subsets are present in the dermis in approximately equal proportions, with most of them belonging to the memory cell pool. In the epidermis, $CD8^+$ T cells predominate. Studies of inflammatory processes have identified the main types of $CD4^+$ T cells: Th1, Th2, Th17, and regulatory T cells (Tregs). Th1 cells are activated during intracellular infections; Th2 cells participate in allergic responses; Th17 cells provide protection against fungal and bacterial pathogens; and Tregs regulate (limit) immune responses. Most $CD4^+$ T lymphocytes express memory T-cell markers ($CD45RO^+$) and activation markers ($HLA\text{-}DR^+$, $CD25^+$). Resident T lymphocytes also express cutaneous homing receptors, which ensure tissue-specific migration and differentiation. More recently, a subpopulation of Th22 cells producing IL-22 has been identified in skin cell cultures derived from patients with atopic dermatitis [49, 54, 71].

B Lymphocytes

B lymphocytes are present in small numbers in the deeper layers of the dermis, where they contribute to immunoglobulin production and immune regulation. However, some studies have reported the absence of B lymphocytes in normal skin. Particular attention has been given to recently described “regulatory B cells” (Bregs), which have been identified in the skin under conditions of transplantation and malignancy. Bregs suppress inflammation, tumor progression, and autoimmune responses, and they contribute to the establishment of immune tolerance [16, 32, 35].

In conclusion, this review synthesizes current understanding of the morphofunctional basis of the cutaneous immune system, emphasizing its complex cellular composition and dynamic interactions. The findings highlight the skin’s role as an active immunocompetent organ, capable of orchestrating both local and systemic immune responses. Recognizing the intricate network of immune cells and their functions is essential for advancing therapeutic strategies in dermatology and immunology, as well as for understanding skin pathology and microbiome interactions. Future research should focus on elucidating the mechanisms of cell communication within the skin and exploring novel approaches to modulate immune responses for clinical benefit.

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Морфофункціональні основи імунної системи шкіри

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Стаття надає систематичний огляд сучасних уявлень про морфофункціональні основи імунної системи шкіри, її клітинний склад та інтеграцію в складний мережевий нейро-імунно-ендокринний механізм. Наведено характеристику основних типів імунокомпетентних клітин: кератиноцитів, дендритних клітин (Лангерганса, мієлоїдних, плазматичних), макрофагів, мастоцитів, лімфоцитів та їх ролі у підтримці гомеостазу та захисті шкіри від зовнішніх і внутрішніх чинників. наукові бази. Для пошуку літератури використані сучасні бази (*Scopus*, *PubMed*, *Web of Science*). Окремо висвітлено концепцію периферійної лімфоїдної тканини шкіри (iSALT) та її значення в регуляції місцевого імунітету. Висновки підкреслюють складність взаємодій між клітинними компонентами шкіри і системними імунними реакціями.

Ключові слова: імунна система шкіри, кератиноцити, лімфоцити, дендритні клітини, макрофаги, мастоцити, імунокомпетентні клітини

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