

Skin - a vast organ with immunological function (Review)

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Abstract. The skin is an organ with multiple functions, where important inflammatory and immunological processes take place. The integrity of the skin barrier is necessary for it to fulfill its roles. An intact skin barrier requires a physiological keratinization process, but also a normal cutaneous microbial flora. Any change in the proliferation and differentiation of keratinocytes entails the disruption of the skin barrier and the triggering of inflammatory and immunological processes at this level, in response to the aggression of external pathogens. Also, there are several specialised immune cells in the skin (Langerhans cells, T regulator cells, T helper cells), that maintain a balance between pro-inflammatory and anti-inflammatory processes at this level. Disturbing the immune homeostasis causes inflammation and allergic skin reaction. Psoriasis and atopic dermatitis are two inflammatory diseases of the skin, characterized by perturbation of the mechanisms of skin barrier formation. The immune system of the skin is also involved in the pathophysiology of vitiligo and pemphigus. The aim of this review is to offer a brief presentation of the inflammatory and immunological processes that occur in the skin.

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1. Introduction

The skin, which also participates in the hydro-electrolytic balance by limiting water loss, is the largest organ of the human body and it is a general protective barrier against external aggression, but this protection also includes important immunological functions. Thus, protection against external agents, as it is conferred by the tegument, also involves the active and integrated part of the immune system that is present here. The skin's immune system creates a permanent balance between the pro-inflammatory and the anti-inflammatory response. Structural and functional integrity of the skin are imperative conditions for it to be able to fulfill its many roles.

Epidermis, the most superficial layer of the skin, is the skin compartment that provides the barrier function. It consists of 4-5 cell layers (basal layer, cornified layers, granular layer, clear or translucent layer (present only in the skin of the palms and plantar part of the feet), and the spinous layer (1)). The epidermis acts as three lines of defense: physical barrier that limits mechanical aggression and penetration of pathogens; chemical barrier, including antimicrobial role; barrier against water and electrolyte loss (2).

Keratinocytes have an essential role in the formation and maintenance of the skin barrier function. These cells traverse all layers of the epidermis. Through a proliferation and differentiation process, in the cornified layer they turn into corneocytes, a process which is under the strict control of cytokines (3,4), produced by keratinocytes and by other resident cells of the skin. The perturbation of the physiological process of keratinocyte differentiation, caused by the disturbance of cytokine gene expression, modifications of the lipid composition of the keratinocyte membrane and corneocyte desquamation defects, lead to altered quality of the skin barrier. Thus, by increasing the permeability of this barrier, a number of substances/microorganisms penetrate the body, which promotes and perpetuates the inflammatory processes at this level and triggers immunological reactions. Defects in skin barrier formation have been observed in a number of inflammatory skin diseases, such as atopic dermatitis (5), psoriasis, ichthyosis and urticaria (6,7).

On the surface of the skin there is also a multitude of commensal bacteria, which form the cutaneous microbiota and which have a role in protection against invasion by pathogens. The skin has a powerful mechanism to repair its integrity

after traumas or aggression by ultraviolet radiation. This repair function also involves the immune cells present in the skin. Cutaneous homeostasis (8) is maintained by permanent coordination and communication between epithelial cells and immune cells in the skin. Any disruption of the skin microbiota and/or of the skin repair mechanism leads to inflammatory cutaneous processes, to an imbalance between proinflammatory and anti-inflammatory factors and to the occurrence of inflammatory and allergic dermatological diseases. In recent years there has been an increase in autoimmune skin diseases. Autoimmune skin disease affects the immune system and results in autoantibodies, i.e. antibodies against self-antigens. The concept of the immune system of the skin, can be seen like a complex relation between immune cells, epithelial cells, and the external environment.

Epidemiological data show that psoriasis, a significant public health challenge, affects ~125 million people globally (9). Prevalence estimates within adult populations range from 0.91% in the USA to 8.5% in Norway (10). Another autoimmune skin disease, vitiligo affects ~1% of the general population (11), the risk of a patient's sibling developing the disease is 6%, and for an identical twin it is 23%, while pemphigus is estimated to affect ~0.5-30 cases per million globally (12).

2. Skin barrier formation

The process of keratinization. Cornification or keratinization is the complex process of normal formation of the stratum corneum, through which keratinocytes suffer important morphological and structural changes, eventually transforming into corneocytes. An intact cornified layer is essential for the skin to form an impenetrable barrier (13). Keratinocytes, cells that are permanently restored, undergo mitosis and proliferation in the basal layer. Differentiated and mature keratinocytes, pass through all layers of skin, lose their nuclei and cellular organelles, begin to secrete keratin, and turn into corneocytes in the cornified layer.

During the process, a membrane is formed that surrounds the keratinocytes at the periphery. The membrane is rich in proteins and lipids. The membrane formation process involves the binding of proteins, especially loricrine and involucrine, to keratinocyte filaments, when they transit from the granule layer to the *stratum corneum* (14). An important role in the stabilization of these proteins is the cross-linking of filagrin. The lipid barrier is located externally from the corneous membrane and is composed especially of ceramides, which bind covalently. The lipid layer limits hydro-electrolytic losses through the epidermis. The dead and flattened corneocytes, united by corneodesmosomes (modified desmosomal structures), form the stratum corneum, which confers resistance to mechanical stimuli.

Old corneocytes are removed from the surface of the epidermis by desquamation. Increasing the calcium concentration in the stratum corneum is the trigger factor of this process. A series of specific proteases that degrade cornodesmosomal proteins are activated, and thus the bonds of the cells of the stratum corneum become unstable and the cells are eliminated. The keratinization process involves a series of enzymatic reactions and is dependent on structural proteins, fatty acids and

lipids, whose gene expression and function are controlled by cytokines and intracellular signal molecules. Also, as they differentiate, keratinocytes secrete a series of fatty acids (15) and antimicrobial peptides (RNASE 7, psoriasin and calprotectin) that attach to the lipid membrane (16). Keratinocytes respond to inflammation caused by the pathogenesis of crackles of the skin barrier by catechidyl LL-37 secretion and defensins, two peptides with antimicrobial properties (17).

The keratohyaline granules. The keratohyaline granules are present in the granular layer of the epidermis and contain keratin filaments and proteins associated with these filaments: loricrine, filagrine and tricoxyaline (18,19). Depending on location, the keratohyaline granules are either present in the globular form (the oral mucosa epithelium) or in the stellate form (the normal epidermis) (20). These granules are insoluble in water and play an important role in the formation of corneocyte envelope. The keratohyaline granules contain ribosomes that are involved in initiating the formation of intermediate keratin filaments and in the proteins assembling process (20). The granules grow progressively as they move from the spinous layer to the stratum corneum (21) and participate in the homogenization of the keratin matrix (22). Profilagrin, the predominant content of keratohyaline granules, is the protein precursor of filagrin (23). Profilagrin, in the course of epidermal differentiation, turns into free monomers of filagrin, which interact with keratin filaments. The keratohyaline granules have been observed in the thymus medulla, in the cytoplasm of the Hassal corpuscles. They appear to be involved in the development of T lymphocytes because they produce IL-4 and IL-7 (24).

3. Immune cells of the skin

To summarize the overall picture of the skin as an immune organ, as described hereafter, a general scheme is presented in Fig. 1.

Langerhans cutaneous cells. Langerhans cells are antigen-presenting dendritic cells (25,26) that play a role in long-term immunity. They were discovered in 1970 by Ralph Steinman and Zanvil Cohn and are involved in the generation of CD8⁺ lymphocytes and in the transformation of CD4⁺ lymphocytes into various cell subtypes (Th1, Th2, Th17) (21). Skin dendritic cells have a protective or suppressive role in skin disorders (27) and are found in the epidermis. These cells have myeloid origin and have characteristics close to monocytes (28). At the skin level, the dendritic cells are inserted between the keratinocytes and create tight junctions with them. When the epidermis is stimulated by mechanical stimuli, Langerhans cells increase the mobility of dendrites. The integrity of the barrier is monitored this way. Moreover, dendritic cells provide immunity without a real infection, against a series of antigens that have not penetrated the cutaneous barrier (29). The presence of important dendritic cells at the skin level makes the skin an important place for vaccination and creation of long-term immunity (30). In atopic dermatitis, skin dendritic cells play a role in the recruitment of eosinophils (31). The lichen may also involve autoimmune aspects (32,33), including an increased Th1/Th2 ratio.

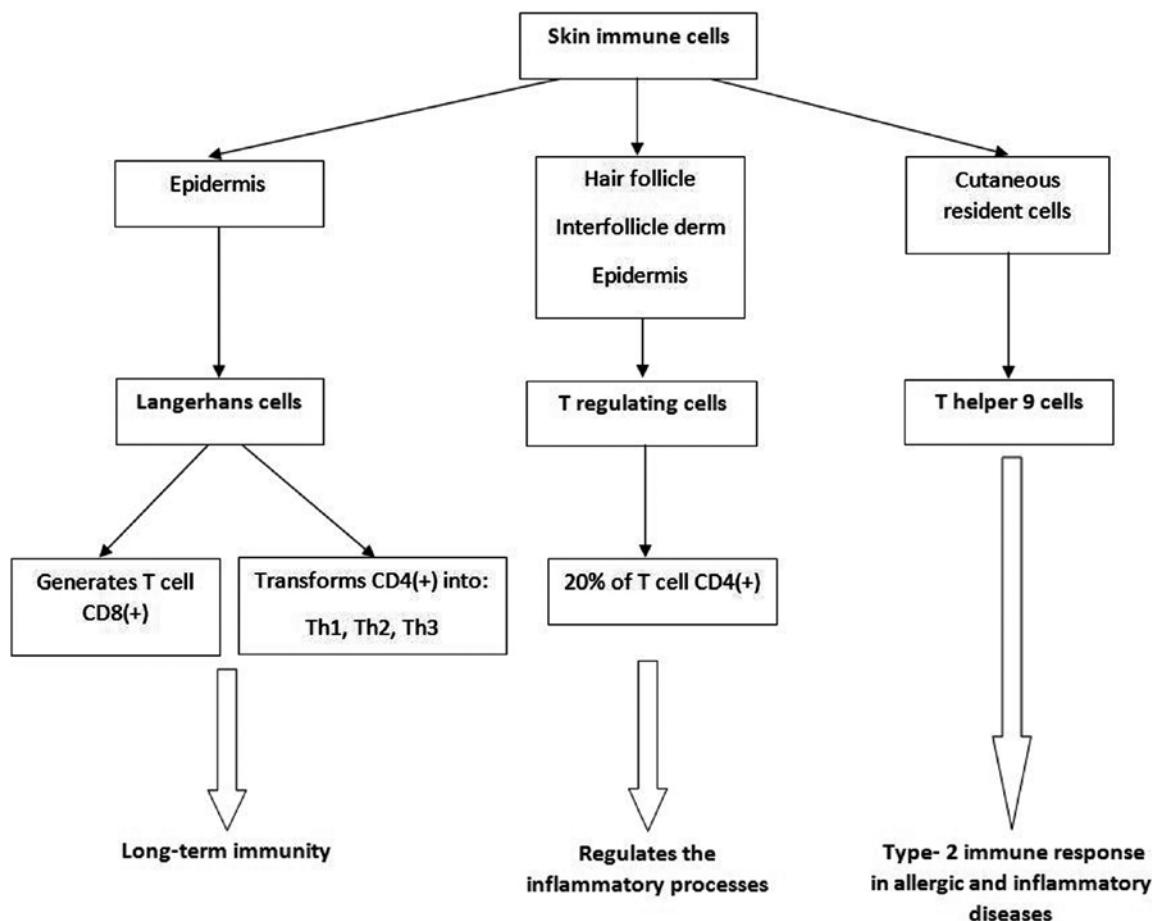


Figure 1. Skin immune cells.

T regulating cells of the skin (Treg). An intact skin barrier also requires the integrity of its attachments: hair follicle, sebaceous glands and sweat glands. Treg cells (34) represent a subset of CD4⁺ lymphocytes, which are predominantly found in the hair follicle, especially in regions with high follicular density. They have also been identified, but in small amounts, in the interfollicular dermis and epidermis (35). These represent 20% of CD4⁺ T cells in the skin. Treg lymphocytes play a role in maintaining immunological homeostasis of the skin (36) by regulating inflammatory processes at this level. These cells come from either the thymus, after mature T-lymphocytes (they become capable of recognizing their own antigens), or formed from the naive CD4⁺ T lymphocytes with peripheral antigens (37). Treg cells offer protection against skin cancer (38) because they secrete IL-10 and TGF- β , cytokines that suppress immune response and inflammation (39). Treg cells actively maintain the skin microparticle homeostasis (40), which provides protection against bacterial and parasitic agents, hair follicle regeneration and skin stimulation of cell differentiation processes and mucosal cell regeneration. IL-7 is essential for the normal function of Treg and IL-2 is important for their normal development in the thymus (41).

T helper 9 (Th9). A subset of IL-9 secreting CD4⁺ cells, Th9 lymphocytes are cutaneous resident cells. These, by regulating the synthesis of pro-inflammatory cytokines (42), are involved in triggering the type 2 immune response from allergic

and inflammatory diseases (43). *In vitro*, IL-9 increases the synthesis of IL-8 and vascular endothelial growth factor (VEGF) (44-46).

4. Inflammatory skin diseases

Psoriasis - an immune-mediated inflammatory disease. World Health Organization (WHO) has recently stated that psoriasis is a serious, chronic, disfiguring, disabling, noncommunicable disease (47). The WHO report highlights the need for data collection documenting prevalence and incidence of psoriasis in order to estimate accurately the social and economic burden of the disease (48). The etiology of the disease is unclear but genetic and environmental factors (49) are thought to be the reason behind the abnormal immune response in psoriasis patients. Epidemiological studies in psoriasis have reported a significantly increased risk of inflammatory comorbid conditions (50), including psoriatic arthritis, depression, obesity, diabetes, liver disease, metabolic syndrome and cardiovascular disease (CVD).

Psoriasis is a T cell mediated autoimmune disease, characterized by keratinocyte proliferation, while psoriasin (S100A7) and koebnerisin (S100A15) are proinflammatory proteins that are upregulated in psoriasis and act as chemoattractants for the immune cells. A protein group called antimicrobial peptides (AMP) has been well studied concerning the immune mechanism of psoriasis. They are highly expressed, especially

cathelicidin, β -defensins and S100 proteins (51). Psoriasis is a T cell mediated autoimmune disease and it is hypothesized that the effector T cells accumulate in lymph nodes and finally they migrate into the skin via the blood. Moreover, psoriatic skin is shown to be another source for inflammatory T cells (52). In psoriatic patients various proinflammatory cytokines are in higher plasma concentration, such as IL-6, IL-2, IL-10, IFN- γ , IL-17 (53), IL-21, IL-22, IL-23, IL-9, while low concentrations were found for IL-4 and IL-27 (54-56).

Vitiligo - immunologic mechanisms. Vitiligo is a common, disfiguring autoimmune disorder that negatively influences patients self-esteem and quality of life. The characteristic of this disease is that epidermal melanocytes are targeted and destroyed in various ways and the consequence is the appearance of irregular depigmentation of the skin. Numerous studies show that melanocytes from vitiligo patients have intrinsic defects that reduce their capacity to manage cellular stress (57). The pathogenic factors of vitiligo include CD8 $^{+}$ T lymphocyte/T helper 1 infiltrates in lesional skin (58,59), with increased expression of IFN- γ (60) and tumor necrosis factor- α (61-64), decreased transforming growth factor- β , and circulating autoantibodies against tyrosine hydroxylase (65). Additionally, several studies have found a high prevalence of antecedent psychological stressors in vitiligo patients, suggesting that specific stressors may trigger or exacerbate vitiligo (66-69). Studies reveal that CXCL16 expression increased and showed a positive correlation with oxidative stress levels in serum and lesions of patients with vitiligo. CXCL16 produced by stressed keratinocytes induced migration of CXCR6 $^{+}$ CD8 $^{+}$ T cells derived from patients with vitiligo. CXCR6 $^{+}$ CD8 $^{+}$ T cell infiltration is accompanied by melanocyte loss in lesions of patients with vitiligo (70). It is assumed that infiltration of the cytotoxic CD8 T cells might be responsible for the melanocyte destruction in vitiligo.

Pemphigus - immunologic network base. Pemphigus and bullous pemphigoid are autoantibody-mediated blistering skin diseases, in which IgG autoantibodies are produced mainly against autoantigens Desmoglein-1 (DSG1) and Desmoglein-3 (DSG3). In pemphigus the keratinocytes in epidermis and mucous membranes lose cell-cell adhesion, while in pemphigoid the basal keratinocytes lose adhesion to the basement membrane (71,72). Also, in pemphigus patients, activated B cells act as pathogenic regulators by secreting anti-DSG3 autoantibodies. B regulatory cells (B reg) are able to down regulate immune responses in mice and humans by secreting IL-10, TGF- β and expressing FOXP3 (73,74). An early cytokine of Th1 type, osteopontin (OPN), augments production of IFN- γ , IL-12 and decreases IL-10 production (75). In pemphigus, as in other autoimmune disorders, OPN production is elevated, which indicates a Th1 response (76).

Atopic dermatitis – immune disorder in correlation with microbiota. Atopic dermatitis (AD) is a chronic Th2 type inflammatory skin disease associated with cutaneous hyper-reactivity to environmental triggers (74). A chronic relapsing skin disease, AD has a characteristic phenotype, with typically distributed skin lesions, that often render its diagnosis very simple and clear-cut (75). *Staphylococcus aureus* is found

in >90% of the patients with chronic AD skin lesions (76). Acute exudative skin lesions can contain over 10 million of these organisms per square centimeter, and increased numbers have been found even in normal skin and the nasal vestibula or intertriginous areas of patients with AD. Scratching is an important factor, enhancing the binding of bacteria, by disturbing the skin barrier and exposing extracellular matrix molecules known to act as adhesins for *S. aureus* (fibronectin, collagens, fibrinogen, elastin, laminin) (77). In addition, bacterial binding seems to be higher at skin sites with Th2-mediated inflammation and the respective cytokine medium, due to induction of an enhanced production of these adhesins and downregulation of antimicrobial peptides needed to control the replication of *S. aureus* (78,79). IgE autoreactivity is an immune pathogenic factor in AD. In addition, molecular analysis of allergens has revealed striking similarities between environmental allergens and human proteins, leading to the hypothesis that autoimmune reactions also might play a role (80,81).

5. Conclusion

The skin is important both as barrier and as connection between the environment and the body. It is well known that the skin provides a receptor function, translating to the organism substantial information from the environment, in many different ways. The skin immunological function could be regarded as an extremely multifaceted and intricate interplay between signal processing and the defense reactions. This is further complicated by many autoimmune aspects. The continuous huge progress in immunology clearly impacts our understanding of the immunological function of the skin, with multiple insights to various etiopathogenic entities. This review is an invitation to the wide area of roles and mechanisms involved in the immunology of the healthy and diseased skin.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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