



Cutaneous immune system: Age specificities

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Abstract: The review is dedicated to the modern concepts in understanding the age-related changes of skin protective functions, with an emphasis on the impairments in interaction between the immune cells of innate and acquired immunity, resulting in a decrease in antigen-specific T cell immune surveillance in the skin. We discuss the various defects of T cells and their environment as well as focus on the issue of possible correction of T-reg and other cells activity in the skin which would increase the level of immune surveillance in elderly persons and reduce the risk of malignant neoplasms or skin infections developing.

Keywords: skin; innate and adaptive immunity; aging

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Introduction

Substantial sensitivity increases to infections and malignant neoplasms observed in elderly persons designates skin protective properties decline during aging. This review focuses on the modern concepts in understanding the age-related changes of skin protective functions focusing on how the impairments in interaction between the immune cells of innate and acquired immunity result in a decrease in antigen-specific T-cell immune surveillance in the skin. A criterion for the inclusion of literature sources in this review was research in the field of skin immunology in a young and aging people, exclusion criteria were studies in the field of immunology and the pathogenesis of skin diseases.

Skin and immunity

Cutaneous integument forms the body interface with the environment and performs the main barrier function. Skin defends the body, making it impervious from a multitude of harmful exogenic substances, maintains homeostasis and prevents from moisture and heat loss. In addition, it is a highly specialized immune system, composed of resident, activated or migrated to a tissue leucocytes (**Table 1**). These cells are distributed in the epidermal and dermal

skin layers and participate in the mechanisms of innate and acquired immunity. They are responsible for a “self” and “non-self”, being fundamentally important, as skin every day contacts with exogenic substances. Close interrelation between these two ways of innate and acquired immunity realization plays an important role in activation and strengthening of cutaneous integument immune response.

Skin immune function decreases in elderly persons, resulting in the growth of bacterial (*Streptococcal* and *Staphylococcal cellulitis*) and fungal (mostly *Candida*) infection^[3], contributing to an increase in cases of malignant neoplasms of the skin^[4]. One of the key mechanism of skin aging is a reduction in a cell self-renewal. Progressive decrease of a cell proliferative activity causes the elevation in the old cells count and driving of adaptation, hypotrophy, and other processes^[5]. Aging skin is noted to involve mononuclear infiltration, Langerhans cells count decreasing as well as changes in production of immunocompetent cytokine cells responsible for proliferation and differentiation of skin cells^[6]. Cutaneous immune system, morphologically presented with skin-associated lymphoid tissues (SALT), from the one side, is a rather autonomic structure of the bodily immune system, from the other side, it is closely morphologically and regulatory interconnected with the bodily immune system. Disturbances of normal cutaneous immune reactions result in an onset of diverse

Table 1. Cells of innate and acquired skin immunity^[1,2]

	Resident	Activated	Migrated
Innate immunity	Keratinocytes	Monocytes	NK-cells
	Endothelial cells	Granulocytes	Dendritic cells
	– vascular	– basophils	
	– lymphatic	– eosinophils	
	Dendritic cells	– neutrophils	
	Mast cells	Mast cells	? Promonocyte
	Tissue macrophages	Epithelioid cells	
Acquired immunity	T-lymphocytes	T-lymphocytes	T-lymphocytes

? – Reflects the probability in this case

dermatological diseases and in the most of aesthetic problems, a premature skin aging being among them. With aging cells start to secrete a complex of cytokines and growth factors, modifying tissue microenvironment. This phenomenon is named senescence-associated secretory phenotype (SASP)^[7,8]. Gomez (2007) correlates advanced age with the hyperproduction of proinflammatory cytokines (determining this process as “Inflamm-aging”), such as IL-1 β , IL-6 and TNF α ^[9]. Bojarskih and coworkers^[7] have compared the transcriptional profiles of young and aged human fibroblasts of three cell lines by means of the replicative aging model. The authors concluded that fibroblast aging has been accompanied with the manifested elevation of gene expression, coding secreted proinflammatory cytokines IL-6 (in 3.7 times; $p = 0.05$), IL-8 (in 2.5 times; $p = 0.04$) and insufficient rise of gene expression IL-1 β (in 1.3 times; $p = 0.04$).

Among proteins secreted by the aging cell, there are cytokines stimulating inflammatory response, some growth factors as well as secreted proteases and non-soluble components of the extracellular matrix. Therefore, aged cells exhibit capacity to alter their microenvironment and to regulate the characteristics of the adjusting cells by paracrine mechanisms^[7]. All this demonstrates that skin immunity defects are progressing with increasing age.

Antigen-presenting skin cells and aging

The basic components of the cutaneous innate immunity are Langerhans cells (LC), dendritic cells (DC), and resident macrophages (RM). These antigen-presenting cells produce inflammatory mediators in response to toll-like receptors (TLRs)-signals, antigen-presence and provide T-cell co-stimulation both in skin and in drain lymph nodes. This section summarizes the results of several investigations, underlining the unique role of the antigen-presenting skin cells.

Skin DC count and phenotype are comparable in the young and elderly persons but migration, phagocytosis, and capability to stimulate T-cells may decrease^[10,11]. Even if migration capability of aged DC being corrected, they are less effective in the antineoplastic immunity providing, correlating with the additional functional defect, associated with the selective dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) expression decreasing^[12]. DC comparison in the elderly

persons revealed the migration disturbances to MIP-1 β , notwithstanding the equivalent CCR7 expression^[12].

Plasmacytic dendritic cells (PDC) are the unique subpopulation of DC, though their count in the normal skin being a few. Nevertheless, they play an important role in the viral infections (for example, herpes zoster virus) and inflammatory skin diseases (psoriasis, systemic lupus erythematosus and lichen planus)^[13,14]. PDC are also observed in skin tumors (melanoma, basal-cell cancer and squamous cell carcinoma)^[13,14]. Skin lesions induce the immediate PDC activation and transient IFN type 1 secretion, enabling wound healing^[1,6]. In contrast to classical DC, cytokine secretion of PDC undoubtedly appear to deplete with aging^[6,13]. Jing *et al.*^[12] reported the number of circulating PDC and IFN α production to decrease in the elderly persons. It is an obvious example why persons of advance age have frequent herpes zoster virus activation, displaying PDC function disturbances in the skin: their migration, activation and cytokine secretion.

Multiple functions of the macrophages disturb with aging, including TLR decreasing (or reduced cytokine response to TLR-stimulation), phagocytes functional ability as well as chemokine and cytokine secretion decreasing^[13]. HRT-model demonstrates reduced macrophage ability in the antigen-activated elderly human skin to cytokine secretion, such as TNF α , accompanying the response to the antigen^[15]. TNF α strengthens the collagenolytic activity of matrix metalloproteinase (MMP)-1, presumably by MMP-3 activating, producing collagen type 1 gradual loss in human skin^[16,17–19]. Reactive oxygen species (ROS), resulting because of the cell oxidative metabolism, are of an extreme importance in the aging process. ROS induce transcription factor c-Jun by means of mitogen-activated protein kinase (MAPK), affecting the elevated MMP-1, MMP-3 and MMP-9 expression^[16]. Montecino-Rodriguez *et al.*^[20] do not exclude transforming growth factor (TGF) β role in the aging mechanisms of the immune system.

Langerhans cells (LC) are the myeloid DC derived, populated permanently epidermally, closely interconnected with the keratinocytes. Until now, LC were considered the main antigen-presented skin cells responsible for the development of the immune response to the invaded pathogen^[7]. The traditional concept considers LC to invade and proceed the antigen, then to migrate to the lymph node, presenting antigen to T-cells^[5,7]. Per the latest data, LC play the key role in the inducing IL-22 secretion by

the T-cells (Th22) which is an important element in the skin immune response. Other investigators suppose LC to play an important role in the suppressing of the immune response^[6,7]. Thus, LC take part in UV-induced suppression, implementing *via* regulatory T-cells (T-regs)^[6,7]. LC capacity to migrate into the drain nodes decreases in the elderly^[9]. Summarizing these data, it might be supposed that a wide range of disturbances can appear in the leucocyte skin population while aging, although it is not clear, how it contributes to a greater dependency on the skin infections or malignant tumors^[21].

One of the defense mechanisms of the skin is the development of antimicrobial peptides-defensins and cathelicidin that represent key molecular factors of immunity with a strong antimicrobial properties^[22]. Yamshikova *et al.*^[23] have shown that antimicrobial peptides inhibit bacterial-induced production of cytokines and stimulate angiogenesis and wound healing. Defensins are divided into two groups: α -defensins and β -defensins – which are chemotactic for monocytes, T cells and immature DC^[24,25]. Also defined θ -defensins – a macrocyclic peptides expressed by leukocytes and bone marrow of primates, but not yet finalized, neither for the human, nor to other higher classified primates^[26]. There are four different types of α -defensin (human neutrophil peptides 1-4-HNP-1-4)^[27]. β -defensins (human β -defensins (human β -defensins 1-3-HBD-1-3) produced mainly by epithelial cells of the mucous membranes of the gastrointestinal, urogenital and respiratory tract^[24,26]. HBD-1 is synthesized by epithelium, which is in constant contact with the medium or the microbial flora, as well as white blood cells, and it is all regulated by lipopolysaccharides and peptidoglycans. HBD-2, as well as HBD-1 can be found in the skin, pancreas, leukocytes, and bone marrow. HBD-3 was detected in the heart, liver and placenta, and HBD4 – in the testes, epididymis, lung tissue tumors and gastric epithelial cells^[27].

In human skin, during wound healing, antimicrobial peptides are synthesized, in particular HBD-3 is expressed by LL-37-amino acid sequence and participates in transactivation of the epidermal growth factor receptor. Furthermore, defensins in keratinocytes promote development FNO α , IFN γ , IL-1, IL-13 and IL-22. Cathelicidin and HBD-1-4 are also present in the skin at low concentrations, in healthy humans, but injury or infection dramatically increases their synthesis^[27]. Gibson *et al.*^[28] found a strong bactericidal effect of β -defensins in the skin in the treatment of burn wound colonized by *Staphylococcus aureus*. Clausen *et al.*^[29] found changes in the level of β -defensins in the skin in atopic dermatitis, and the researchers found correlation between level of β -defensins and severity of atopic dermatitis. Patients with psoriasis show significantly reduced defensins level in the skin layer, which explains the high susceptibility to infectious diseases of the skin. Wittersheim *et al.*^[30] reported that the level of antimicrobial peptides in human skin depends on the age, with β -defensins twice higher in the elderly people.

Ultrastructure of the basal cells witnesses their active part in keratin synthesis as well as in preparation to other

specific proteins synthesis. Basal layer is populated by stem cells of the G0-period. During mitosis, part of the cells transforms into transitional cells, the other part of the cell persists in the G0-period. Phenotype α 6 10G7 cells are shown to represent epidermal stem cells, composing the 8% of basal keratinocytes. Currently, the receptors to the vitamin D are detected on the stem cells. Nonetheless, all known nowadays markers fail to differentiate precisely the stem cells from the transitional ones. Keratinocytes synthesize membrane bound IL-1 α , facilitating their own participation in the antigen presentation. Besides, keratinocytes synthesize IL-1 β , IL-3, IL-8, IL-15 and IL-19^[31]. It is worth noting, that keratinocyte synthesized IL-1 enhances prostaglandin synthesis by the fibroblasts of the papillary layer. Prostaglandin, in its part, stimulates keratinocyte proliferation and differentiation. Keratinocyte recognition of pathogens by means of TLR 2 and TLR 4 results in proinflammatory cytokines production, among which precedence must be given to IL-8, responsible for the neutrophils, basophils, and leukocytes bringing to the epidermis.

All changes occurring with age, are characterized by the violation of the epithelial-stromal relations that underlie the formation of wrinkles. Type IV collagen is found in all basement membranes and plays an important role in adhesion, migration, differentiation and growth of cells. When photodamaging the skin occurs a reduction of thickness and level of border between derma and epidermis and particularly type IV collagen at the base of wrinkles. Byrne *et al.*^[32] investigated the ability of ternary complex peptide (TCP) IV to stimulate collagen production in fibroblasts of the skin and its effects on the skin photoaging. Their results showed that stimulation of individual peptides of TCP does not lead to destruction of collagen IV. The combination of individual peptides is necessary to synergistically stimulate the production of collagen IV. The researchers suggest that the TCP can play a role in strengthening the border between derma and epidermis through its ability to stimulate collagen production.

Thus, it is possible that the decrease of immunity of the skin during aging may be related to impairment of innate immunity cells such as professional antigen-presenting cells, epithelial cells and fibroblasts.

T-cells of the skin in the process of aging

Normally, skin of a healthy person residents plenty of CD4+ and CD8+ T-cells. It has been estimated that approximately 20 billion of resident T-cells present in the skin of a healthy person, and about twice more are in the bloodstream^[7]. Intraepidermal lymphocytes present in the basal and suprabasal layers. They are thymus-dependent lymphocytes, subdividing into T-helpers (Th), T-killers and T-reg. T-helpers, in turn, subdivide into progenitor cells Th (Th0), effector lymphocytes, and memory lymphocytes. Th0 (expressing CD4) influenced by IL-2 and IL-12 differentiate into Th of the first type, not only secreting IL, IL-3, IFN γ and TNF, but also stimulating T-killers maturation and production of IgM, IgG and IgA by B-lymphocytes. Th of the second type produce IL-3, IL-

4, IL-6 and stimulate different immunoglobulins synthesis by plasma cells. T-reg, suppressing the immune response, express CD8, CD45PA^[31,33,34]. T-killers cause disturbance of allogenic cell permeability, resulting in their osmotic shock and subsequent necrocytosis^[31]. Elucidating the T-helpers' new functions (for example, Th17, Th22 and T-reg cells) leads to the reframing of T1/T2 paradigm, having been used for a long time for pathogenesis definition as well as cause of the infectious inflammatory and even tumor skin diseases^[34]. Hereby, all abovementioned specificities of epidermis structural organization advocate in favor of its active part in the skin protective function.

Toll-like receptors and aging

Endothelial activation and skin homeostasis transformation at the point of the antigen exposure, promoting leucocytes access from the bloodstream, are thought to be due to the secretion of proinflammatory cytokines by innate immunity cells, triggering the "alarm signals"^[1,2]. TLRs are one of the most common converters of the "alarm signals"^[6,34], being the result of antigen exposure to the traumatized skin. TLRs are expressed by the different cells of innate immunity, including monocytes, macrophages, DC, and LC as well as keratinocytes. TLR-expression or TLR-induced inflammatory mediators' production by innate immunity cells are supposed to decline with age^[35]. Moreover, the recent studies have demonstrated production decline of inflammatory cytokines, such as TNF α , IL-6 and IL-12, from the circulating DC in elderly persons stimulated by the different TLR-ligands^[36]. Consequently, skin immunity declines with aging is likely to be associated with the insufficiency of the innate immunity cells due to TLR-signals lesion.

Majority of human T-cells expresses CCR8 and acts as immunological surveillance cells, detecting epidermal APC, and triggering the safety program of the immune system, involving monocytes, granulocytes, inflammatory T-cells and antibodies^[6]. T-cells of immunological surveillance play a dual role in this scheme. Firstly, responding the antigen impact, they start the inflammatory cascade by secreting TNF α and IFN γ , resulting in other leucocytes engagement. Secondly, these cells migrate into drain lymph nodes where they can proliferate or stimulate activation of antigen-specific T and B-cell respond. Age skin immunity disturbances are likely to be also associated with the alterations of the resident T-cells. Intermittent long-life antigen stimulation might impair T-cells in two ways^[37]. Firstly, they become functionally depleted and lose their dominant functions significant for the immune defense^[7]. Functional depletion is a way to limitation of the effector T-cells' respond, commonly correlating with the elevating of expression of the surface receptors' inhibitors. Although, it may be a defense mechanism against autoimmune processes, but it jeopardies effectiveness of anti-inflammatory and antitumor immunity^[36,38]. Secondly, repetitive T-cell stimulation can cause loss of replicative capacity of some antigen-specific T-populations because of telomeres shortening and/or DNA damage (process known as a replicative aging)^[21,34]. It is interesting, that

escalating telomeres shortening is observed during immune skin response due to the inhibiting by IFN of the first type telomerase enzyme^[21].

Nowadays, it is doubtful whether resident or activated during immune response to antigen skin T-cells could deplete or age in the elderly persons, insight into this phenomenon is very essential. At present, elevation of the memory T-cells count is a well-known aging sign^[6]. These cells generated after the first contact with the antigen are sustainable for a long time after the initial task, providing a source of effectors responding quickly to the antigen re-exposure. Over the time, exposure to the range of pathogens results in a diversity of the immune repertoire including the increased pool of the defensive memory cells. However, chronic stimulation with the viral infections, for example cytomegaloviruses, may deplete naïve cell pool and cause proliferation of the oligoclonal memory cells. This phenomenon is an important factor contributing to the CD8⁺ memory cells accumulating in the elderly persons^[8], but also CD8⁺ T-cells antigen independent proliferation may be evidenced^[21,31].

Regulatory T-cells (T-reg) are accumulated in the skin with aging

T-reg play a key role in a force of the immune response development. 5%–10% of the resident T-cells in the human skin in norm expresses Foxp3 and demonstrates other characteristics of the regulatory T-cells^[15]. These regulatory cells also proliferate during the response of delayed-type hypersensitivity (DHS) type. The investigations showed that T-reg circulate between the skin and lymph nodes and *vice versa* both at rest and in the immune response^[16]. These T-reg directly inhibit both T-cells and antigen-presenting cells, such as DC and macrophages. With the T-reg depletion, neutrophil infiltration rises significantly as the secondary response to the concentration rise of neutrophil chemoattractants (CXCL1 and CXCL2)^[14].

Elderly human and mice demonstrate the elevating of the ratio T-reg in the skin in norm^[34]. T-reg can prevent effective primary proliferation/functioning of the resident antigen-specific T-cells or inhibit activation of the innate immunity respond, resulting in immunity decline. Negative effect of T-reg accumulation in the effective immune response is clearly described in the oncological diseases. T-reg count rising is reported to be noticed in primary melanoma, in metastatic melanoma, and in basal cellular carcinoma^[39]. Moreover, in squama-cellular skin carcinoma 50% of the T-cells presents Foxp3⁺^[34]. Imiquimod topical treatment has shown to be effective in such patients, depleting T-reg percentage and decreasing their suppressive function^[39].

Causes and mechanisms of the T-reg accumulation in the skin and the other tissues in the elderly human and mice are not thoroughly obvious^[15]. T-reg are known to be induced in the skin by the UV-rays and then such T-reg influence DC *via* IL-10, activating more T-reg through this "tolerant" DC^[40]. Moreover, circulating T-reg may be directed preferentially into the skin, as their majority expresses the cutaneous lymphocyte-associated antigen

(CLA). Summarizing all these data, it could be concluded that T-reg accumulation in the skin with aging may contribute into the insufficiency of the immune response by the inhibiting of both T-cells, and the cells of the innate immune system.

Antigen-specific response declining of the human skin in the process of aging is the reason of immune surveillance reduction

The studies have shown that the elderly people have a reduced capability to maintain DHS – responds after antigen exposure^[35]. This is manifested by the reduction of the erythema intensity and induration at the point of the antigen exposure as well as T-cells count depletion in the infiltrate proved by the immune-histologic methods. Since activation and skin strengthening immunity have been known to be an integrated step-by-step process, the experimental models *in vivo* proved to be more informative. Relatively useful is the experimental model of the DHS with the intradermal antigen exposure^[35,40]. The extend of the DHS response is determined by the diameter of the skin area infiltrate and erythema proliferation at the antigen injection site in 48 hours of its injection in human and edema severity of the auricles or feet in 24 hours in mice^[40]. There are some differentiations in the kinetics and the nature of the disease in human and in mice, probably because of the different sites of the antigen injection but cell infiltrates are similar in both species^[40].

From the histological point of view, antigen exposure and skin integument injury induce nonspecific warning signals to the attraction and activation of the innate immunity cells, and on the earliest stages (4–6 hours) most of such cells are neutrophils^[17,20]. Cell infiltration depends on the proinflammatory cytokines production, such as IFN γ and TNF α , stimulating adhesion molecule expression on the endothelium and increasing vascular permeability on the local level^[1,2]. E-selectin is expressed on the capillary endothelium not later than 1–2 hours after antigen injection, and within 12 hours adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are activated too. These molecules interact with lymphocyte function-associated antigen 1 (LFA-1) and very late antigen-4 (VLA-4) on the monocytes and lymphocytes, helping to ensure the concentration of these cells in the skin^[15]. Simultaneously with the endothelium activation and transformation at the site of the antigen exposure, antigen-presenting cells transport antigen from the skin to the lymph node, presenting it to the activated T-cells migrating after that *via* blood vessels to the inflammatory lesion^[2]. T-cells infiltration in DHS is a biphasic process, including early proliferation by these cells, emerging around dermic blood vessels approximately within 12 hours after antigen exposure^[2] and the subsequent accumulation peak of the antigen-specific T-cells which might be associated with these cell proliferation in the skin^[1,2]. Maximum macrophages count is revealed within 24 hours, but in 48 hours the prevailing cells in the infiltrate

are T-cells^[2,39].

The current scientific studies of the skin HSV-1 infection have proved that HSV-specific cells migrated to the site of antigen injection, staying resident in the skin till the antigen elimination^[1,6]. These long-living resident cells promote rapid response in the skin to the subsequent exposure of the same pathogen, presented by the tissue dendritic cells, and drive processes of the inflammatory cascade^[2]. The immune response in the DHS type in the elderly human and mice has shown to have disturbances, these processes can reflect insufficient development of the immune memory to the antigen with aging.

The published data prove that DHS reaction to the bacteria, fungi, and viral antigens decreases with aging, despite the same capability of the T-cells to respond the same antigens *in vitro*^[15]. It is noteworthy to suppose that the skin reactivity decrease is a local, not a systemic immunity defect, and it emphasizes the opportunity to highlight the disturbances of migration of the specific T-cells to the skin after the antigen exposure.

It has been unproved that decrease of T-cells capability to migrate after DHS is associated with the insufficiency of the expression of the chemokine receptors or integrin by the circulating T-cells^[15]. Moreover, T-cells in the elderly persons also retained their migrative properties while passing through a monolayer of endothelial cells *in vitro*^[15]. It is conceivable that instead of the DHS-response insufficiency, there is a decrease of the endothelium activation. Endothelium activation is driven by E-selectin, VCAM and ICAM adhesion molecules are the key chains in the T-cells transmigration to the cell. TNF α and IFN γ are the basic inductors of the endothelium activation and DHS-response in young persons, these cytokines are predominantly secreted by the macrophages^[21]. In the elderly persons, their secretion was significantly decreased at the site of antigen injection after its exposure, despite the macrophages count stayed at the normal level^[21]. Macrophages isolated from the skin, remained fully capable to secrete these cytokines and stimulated TLR-ligands *in vitro*, supposing their inhibition *in vivo*. Relevance of TNF α for the effective skin immune response has been proved by the isolated cases of the observation of the sensitivity increase in rheumatoid patients to the cutaneous infections and tumor masses while being treated by the anti-TNF-medications^[13].

An explanation to the proinflammatory cytokines' secretion decrease in response to antigen exposure in the elderly persons might be T-reg ratio elevation, inhibiting macrophage activation, and cytokine secretion. T-reg have demonstrated to inhibit TNF α secretion, transmitting macrophages and creating the anti-inflammatory profile^[10].

Conclusion

Immunological skin aging is a multifactorial process and it is evident that different cells become defect with aging. DHS reaction and memory T-cells respond are impaired in the elderly persons. Defects might not be inherited in the T-cells, but are rather in their environment, in the site of antigen exposure, thus resulting in the insufficient

endothelium activation and failure of the adequate migration of the circulating T-cells to the place of destination. Skin immune respond reducing to the antigen may be related both to the adaptive and to the innate immunity, T-reg count elevating, revealed in a wider range of the elderly persons. Thus, all the mechanisms of immune system weakening, including the older age, are not completely known. Ample evidence poses the number of questions as to whether the T-reg and others cells activity correction in the skin could increase the immunological surveillance in the elderly persons, improve its quality and reduce risk of malignant tumor or cutaneous infection development.

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