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New aspects of the pathogenesis of psoriasis

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Psoriasis is a chronic multi-factorial immune-mediated inflammatory disease of skin and joints. The variety of clinical forms of dermatosis is consistent with various pathogenetic features of the disease progress which have been significantly supplemented and reviewed recently. Knowledge of these mechanisms will improve and personalize the prescribed therapy.
This study places the emphasis on modern ideas about the formation of T cell memory, the role of melanocytes and innate lymphoid cells. Development mechanisms of guttate and paradoxical psoriasis with important distinguishing characteristics are described separately.
Today, knowledge of the molecular basis of the disease progression has led to the creation and introduction of a number of highly effective targeted drugs into clinical practice. Further developments related to the inhibition of resident memory cells, innate lymphoid cells, as well as the study of guttate psoriasis perpetuation and the occurrence of paradoxical psoriasis will significantly increase the effectiveness of the therapy.

Keywords: **psoriasis, pathogenesis, T-cell memory, innate lymphoid cells, melanocytes, guttate psoriasis, paradoxical psoriasis.**

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Introduction

Psoriasis is a chronic multi-factorial immune-mediated inflammatory disease of the skin. According to the World Health Organization, about 125 million out of more than 7.7 billion of the world population suffer from psoriasis. The prevalence of psoriasis among the population varies widely: from 0.09% in Tanzania to 5.1% in the United States which is 1–3% of the world population on the average. Men and women suffer from psoriasis equally [1–3].

This report focuses on the issues of predisposition to disease development, the features of clinical findings and pathomorphology, the participation of T cell subpopulations in the inflammatory response, the formation of T cell memory, the role of dendritic cells, melanocytes and innate lymphoid cells. Distinctive characteristics of the pathogenesis of guttate and paradoxical psoriasis that affect the case management strategy are described separately.

Underlying risk for disease development

Major genetic studies have shown that the underlying risk for psoriasis is inherited poligenously and is associated with genes that manage adaptive and congenital immune responses and epidermal barrier functions [4, 5]. Moreover, the association between the Cw6 allele of the major histocompatibility complex (HLA-C) gene and underlying risk for plaque psoriasis, as well as the early disease onset remain the most reproducible in different ethnic groups [6–8]. The probability of the disease development in one of the monoovular twins, the second of which has fallen with psoriasis, is 60–75% [9].

The factors that provoke psoriasis development and worsen its clinical course include lymphoid periopharyngeal ring streptococcal infection, psychological stress, smoking, excessive alcohol consumption, use of certain medications (β-adrenergic blocking agents, α-interferon, aminoquinolines, etc.) [10–12].

Clinical, histopathological, and immunohistochemical states of psoriasis are heterogeneous, variable, and need to be studied and compared in detail to understand the disease development mechanisms.

Clinical features of psoriasis

The difficulties in studying psoriasis pathogenesis are considerably related to different clinical findings and disease progression. For example, plaque psoriasis is characterized by plane pink papules that have a propensity for the peripheral growth forming plaques, pustular psoriasis is characterized by amicrobic pustules, psoriatic erythroderma is characterized by “edematous spot” and exfoliative peeling, and psoriatic arthritis is characterized by inflammation of peripheral joints, fingers, entheses, vertebral column, and iliosacral pelvic joints. Psoriasis may be either a mild disease characterized by individual insignificant plaques during a long period of time or severe disease that affects a large area of the skin and characterized by arthritis mutilans development and the significant decrease in the patients' life quality.

Such heterogeneity of clinical implications can be explained by psoriasis polygenetic nature. Various combinations of different predisposing genes of a patient create individual psoriasis models in each patient; those models differ in phenotypic implications, the disease severity, and the therapy effectiveness. At the same time, identical twins with psoriasis often have similarities in clinical findings of the disease, the age of the disease onset, the nature of the disease progression, the presence or absence of joint damage [13–16].

Autoimmune inflammation

The autoimmune process in psoriasis is deemed one of the major mechanisms of disease development. It is expected that keratinocytes are trigger cells. In the event of a damage (trauma, infections, drugs, UV), they “supply” autoimmune antigens and activate antigen-presenting cells due to the secretion of a large set of congenital immunity factors (cytokines, chemokines, antimicrobial peptides) (Fig. 1) [17, 18].

Various compounds are considered probable autoimmune antigens: cathelicidin (LL-37) and β-defensins from the group of antimicrobial peptides; neolipid antigens produced by masT cell phospholipase; K16 and K17 keratins that are homologous to M protein of streptococcus, and the cellular antigen (ADAMTSL5 protein located in melanocytes) [19–23].

The key moment in the autoimmune inflammation initiation is the immune tolerance failure which is currently associated with the activity of cytosolic and extracellular DNA. Normally, a DNA molecule in the cell is only in the nucleus, small fragments are present in the mitochondria. DNA may be found in the cytoplasm at pathologically increased permeability of the nuclear membrane, mechanical or immune damage, and uptake of neighboring destroyed cells DNA by keratinocytes. In this case, when DNA enters the cytoplasm of keratinocytes, it stimulates the interleukine production (IL)-1β through interaction with various intracellular DNA sensors (protein AIM2 and others). In other cases, when forming stable complexes with antimicrobial peptides (cathelicidin LL37, beta-defensin (hBD) 2, hBD3 and lysozyme), extracellular nucleic acid fragments (DNA and RNA) acquire the ability to transport themselves through cell membranes to endosomal compartments with TLR7 and TLR9; it leads to the activation of plasmacytoid dendritic cells (pDCs) followed by secretion of I and II type interferons (INF) [24-28]. IL-1β and α-INF are important molecules that

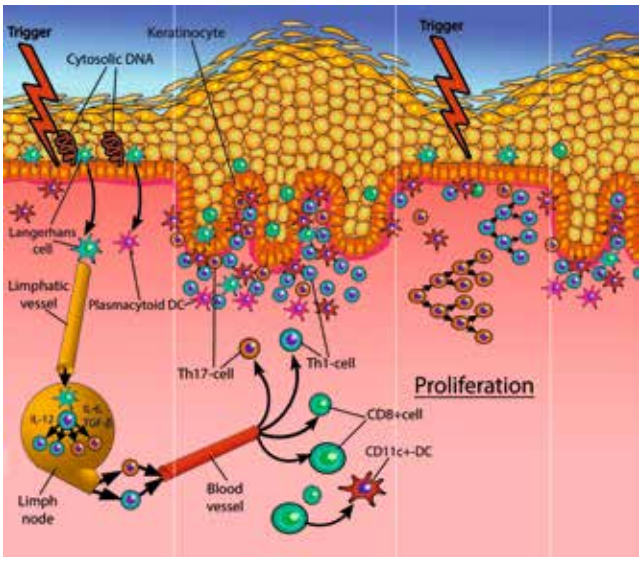

Fig. 1. Psoriasis immunopathogenesis

enhance the expression of HLA antigens, activation, and maturation of dendritic cells; therefore, they contribute to the immune tolerance loss.

Repeated location of the psoriatic eruption on the hairy part of the head, elbow, and knee joints may be connected with traumatization of these skin areas and damage of keratinocytes that leads to DNA yield into the cytosol. Isomorphic reaction development is explained in a similar way.

Role of T lymphocytes

The introduction of an immunohistochemical study of the affected skin of psoriasis patients allowed scientists to determine the phenotype of the main immune cells involved in the inflammatory process. One of the dominanT cell populations are T lymphocytes ($CD3^+$), the number of which in the eruption areas increases by 6–10 times compared with healthy skin. About 2/3 of T lymphocytes are represented by $CD4^+$-cells which are found exclusively in the dermis (they are located in groups (nests), and cytotoxic T lymphocytes ($CD8^+$) which are scattered: about 1/4 of them are found in the epidermis, and 3/4 are found in dermal papillae. CD4+-lymphocytes consist of subpopulations of 1 and 17 type T helpers (Th1 и Th17), and T regulatory cells (T reg). T regulatory lymphocytes make up about 20–25% of all T cells and are found mainly in dermal papillae as part of infiltrates. More than 90% of all T lymphocytes have a CD45RO molecule on their surface, which indicates the maturity of these cells and their transportation in the lymphoid organs of an antigen-specific differentiation.

Th_1 lymphocytes produce a variety of proinflammatory cytokines in the skin of psoriasis patients; γ-interferon (γ-IFN) is the key one. The role of Th_1 cells at the earliest inflammation stages is to strengthen and expand the boundaries of this process, involving other participating cells in it. By synthesizing γ-IFN which controls the transcription of a group of interferon-stimulated genes, Th1 induces enhanced synthesis of neutrophil-activating factors, adhesion molecules, pro-inflammatory cytokines, and other biologically active substances by surrounding cells (keratinocytes, fibroblasts, endotheliocytes, etc.). Due to neutrophil-activating factors (CCR5, CXCL9, CXCL10, IL-8), a significant number of immune cells are concentrated in the area of the forming psoriatic papule which is represented mainly by various subpopulations of T lymphocytes, DCs, monocytes, and neutrophilic leukocytes. The secreted Th_1 cytokines TNF-α and IL-6 which have diverse effects are the most important mediators of the acute inflammation phase [29, 30].

$CD8^+$-lymphocytes of psoriasis patients interact with antigen-presenting DCs in lymphoid organs and skin and stimulate their production of IL-12 (IL-12p70 subunits). The secretion of this cytokine causes the differentiation of naive T cells in Th_1, significantly increases their number, and suppresses Th_2 formation. Another important function of $CD8^+$ cells in forming psoriatic plaques is their participation in the rapid differentiation of monocytes which migrate into the affected skin from peripheral blood, into $CD11c^+$ DCs [31, 32].

Role of T helpers of 17 types

Th_{17}-lymphocytes are practically not found in healthy skin. The participation of these cells in the inflammatory process is associated with the autoimmune response development [33]. Th_{17} are major figures in psoriasis pathogenesis, their participation in the inflammatory process gives it a specific character and leads to the development of clinical implications specifically attributed to psoriasis. Global genetic studies have revealed an association between psoriasis development and the polymorphism of IL23R and TRAF3IP2 genes which regulate the number and activity of Th_{17} subpopulation [34, 35]. The experience in the application of antibodies that block the common IL12/IL23 subunit, IL17 cytokine, or its IL17R receptor has demonstrated its high efficiency in psoriasis therapy [36–38]. Th17 express RORC transcription factor, receptor to IL23, CCR6 chemokine receptor, and receptor to lectin CD161. The differentiation in Th_{17} comes from precursors — $CD4^+CD161^+$-cells in the presence of IL-1β and IL-23. Mature Th17 produce anti-inflammatory cytokine; IL-17 and IL-22 interleukins are important. IL-17 that consists of IL-17A and IL-17F monomers can connect with IL-17 receptor which expresses itself on keratinocytes, endotheliocytes, T lymphocytes, monocytes, fibroblasts. Such interaction results in the production of IL-6 and IL-8 cytokines. The secretion of IL-8 which is a chemoattractive agent for neutrophilic leukocytes causes the accumulation of such cells in the area of psoriatic eruption and forms Munro's microabscesses [39–44]. IL-17 and IL-22 cause hyperproliferation and keratinocyte differentiation impairment which leads to the development of epidermal hyperplasia, agranulosis, and hyperparakeratosis [45, 46]. IL-17 also causes the expression of a variety of chemokines that involve T lymphocytes, monocytes, and DCs into the inflammation site. CXCL13 and CCL19 chemokines appear on fibroblasts under the influence of IL-17. These chemokines lead to migration of lymphocytes to the dermis and can induce the formation of ectopic lymphoid tissue, where new autologous-reactive T lymphocytes are formed [47, 48].

Formation of T cell memory at psoriasis

T lymphocytes that have passed special differentiation pass from lymphoid organs into the skin and joints (at patients with psoriatic arthritis) due to the trafficking of these cells provided by chemokines. As soon as the inflammation is ended and psoriatic eruption disappears, a part of these lymphocytes stays in the skin and forms immune memory. Such cells which store information about a certain antigen (resident memory T cells, TRM) are an integral part of the adaptive immunity.

The biological sense of forming the anamnesis lies in the development of a more rapid immune response to repeated contact of a memory cell with a known antigen. Activation of memory cells requires lower doses of antigen than for differentiation of naive T lymphocytes [49, 50]. Memory T cells are present in all peripheral tissues of a healthy person, including skin where their share is 95% of all lymphocytes. There are 2 times more memory T cells in the skin than in peripheral blood. These cells move at the border with the external environment and constantly screen pathogens. In the case of anti-infectious and anti-tumor defense, TRM undoubtedly play a positive role. However, the formation of TRM in response to allergens or autoimmune antigens becomes a serious problem for the body [51–53].

Psoriasis is a chronic immune-related dermatosis, and the formation of a T cell immune response that develops autoimmune inflammation plays the main role in its pathogenesis. The preservation of memory T cells after psoriasis onset is the formation of the disease's immunological memory; they explain its incurability and relapsing course.

Memory T cells are presented by long-lived populations of central (TCM) and resident T lymphocytes. TRM are mostly located in the skin, they do not move to the systemic blood and have the phenotype $CD45RO^+CCR7^-CD69^+CD103^+$ [54–58]. The further study of TRM's subpopulation pattern in psoriatic eruptions has detected the predominance of Th22 cells ($CD4^+$-cells that produce IL-22) and Tc17 ($CD8^+$-cells that produce IL-22) which form the memory about the disease and can provoke the disease recrudescence in case of their stimulation [59–61].

The appearance of eruptions at psoriasis recrudescence can occur only with the participation of dermal TRM s without involving lymphocytes from lymphoid organs. This fact may be proved by studies on the application of E-selectin inhibitors at research animals. E-selectin antibodies hinder the migration of T cells from blood to the skin. Clinical studies at immunocompromised mice have shown that after the introduction of E-selectin inhibitors and transplantation of clinically unchanged skin of psoriasis patients, psoriatic eruptions have developed spontaneously or in case of stimulation with TNFα [62, 63].

With the development of psoriasis recrudescence, T cell proliferation is observed in the dermis (in the psoriatic papule). Immunohistological analysis of the skin of psoriasis patients during the disease progression using the double staining method for CD3ε and Ki67 has allowed to find out that about 30% of all T lymphocytes in dermal infiltrates have been positive for both markers at the same time, i.e. they have been in the stage of mitosis. Therefore, the formation of inflammatory infiltrates in the foundations of psoriatic papules may be caused by an intradermal proliferation of T cells [64].

Studies of the 1st phase of the drug which inhibit resident memory T cells in psoriasis patients have already been completed and the first positive results have been obtained [65].

Role of innate lymphoid cells

The last scientific findings also point to the important role of innate lymphoid cells (ILCs) in psoriasis pathogenesis [66, 67]. ILCs are characterized by the expression of a molecule of leukocyte common antigen (CD45), α-chains of IL-7 receptor (CD127) and the absence of specific markers of DCs, T, and B-lymphocytes including the engineered receptor for recognizing the antigen [68, 69].

ILCs family may be divided into three groups according to their need in activation with cytokines, expression of transcription factors, and production of effector cytokines. ILCs of the 1st group include NK-cells and ILC1 which are activated by IL-12, depend on T bet, and produce IFN-γ. The 2nd group includes ILC2 which are activated by L-25, IL-33, and TSLP, express GATA-3 and produce IL-4, IL-5, and IL-13. ILCs of the 3rd group include LTis (lymphoid tissue inducer cells) and ILC3. They are activated by IL-1 and IL-23, depend on RORγt and produce IL-17A and/or IL-22. ILC3 is further subdivided based on the expression of natural cytotoxicity receptors (NCR). Interestingly, all activating cytokines may be produced by keratinocytes, Langerhans cells, and DCs of the skin [68, 70].

All three subsets of ILCs are present in the healthy skin and may functionally (according to the production of cytokines) match with adaptive response phenotypes mediated by T lymphocyte helpers (ILC1 (Th_1), ILC2 (Th_2) and ILC3 (Th_{17}). It is acknowledged that ILCs are important regulators of tissue homeostasis and inflammation [69, 71, 72].

The first report on the possible role of ILC3 in psoriasis development has been made by Pantelyushin S. et al. in 2012. They have shown that RORγt+ILC3 and $\gamma\delta$T cells have been the main cells producing IL-17 and IL-22 in the experimental psoriasis model in mice [73]. Subsequently, several studies have confirmed the primary outcome. For example, Brüggen M.C. et al. have performed a comparative analysis of ILCs subsets in the skin of patients with psoriasis, atopic dermatitis, and skin of healthy people and have revealed the predominance of ILC3 and ILC1 in psoriatic foci, while the main population is ILC2 at atopic dermatitis. Moreover, topographic mapping of ILCs using in situ IF staining has shown the predominant location of ILCs near the epidermis and in close proximity to T lymphocytes, which suggests a direct interaction between these cell types [71]. The other study by Dyring-Andersen B. et al. has shown the increase in the number of $ROR\gamma t^+CD56^+$ILC3 producing IL-22 in both affected and unaffected skin of psoriasis patients in comparison with the skin of healthy persons and patients with nickel contact allergy [74].

Two more studies have revealed the significant increase in NCR+ILC3 at psoriasis patients not only in the skin but also in the peripheral blood. After in vitro stimulation of IL-1 and IL-23, NCR^+ILC3 derived from psoriatic foci have mainly produced IL-22 and IL-17 (fewer). Significant differences have been obtained in comparing the amount of NCR^+ILC3 in the unaffected skin of psoriasis patients and healthy persons. This fact points to the amended allocation of ILCs in the skin of psoriasis patients which may be a predisposing or initiating factor for dermatosis development [69, 75].

The study using the humanized mouse model of psoriasis has proved that ILC3 cells not only increase quantitatively in the foci of the affected skin but can also lead to the development of a psoriatic phenotype even in the absence of Th17 cells [76].

Thus, ILC3 can make a significant contribution to psoriasis pathogenesis by producing key anti-inflammatory IL-17 and IL-22 cytokines. Therefore, ILCs modulation is a new therapeutic approach to psoriasis patient management in the future.

Role of dendritic cells

Dendritic cells (DCs) are presented in the skin of psoriasis patients by single plasmacytoid DCs (pDCs) which express CD123+ and a large population of myeloid DCs. The latter include several varieties of DCs. These are Langerhans cells (young DCs, Langerin+, CD1a+) which are located in the lower epidermis layers at healthy persons and psoriasis patients during the remission; they form a chain by connecting with their processes. A significant number of them can be found in the dermal papillae during the progressing period of the disease. $CD11c^+$-cells (TNF-α/iNOS-producing DCs) are localized mostly in dermal infiltrates, their number is equal to all T lymphocytes. About 10% of myeloid DCs are mature $CD83^+$-cells located in the dermis (near epidermal and dermal linkage) and the epidermis.

Langerhans cells play a key role in the formation of the immune response; they uptake foreign antigens/autoimmune antigens, process them along with II class MHC molecules, and if an activation signal has been obtained from keratinocyte, they move to the dermis where they involve pDCs into the inflammation. pDCs are found in the skin of psoriasis patients mainly in the initial stages of the inflammatory process. These cells secrete

significant numbers of α- и β-IFN which make the migration of T lymphocytes to the forming psoriatic papule [77].

The activation of Langerhans cells after moving to the dermis is accompanied by their differentiation into dermal myeloid DCs, a change in the immunophenotype (a loss of the specific marker CD207⁺/Langerin⁺is observed), and a loss of phagocytizing properties. Due to the expression of the CCR7 chemokine receptor, such DCs migrate to the regional lymphoid organ (lymphoid ring, lymph nodes) where they participate in the antigen-presenting differentiation of naive T lymphocytes as antigen-presenting cell and ensure the development of the adaptive immune response [78].

CD11c⁺-DCs represent one of the most numerous populations found in the skin of psoriasis patients. Most monocytes migrate to the dermis, are accumulated in the foundation of the psoriatic papule, and are differentiated in CD11c⁺-DCs. The increase in the number of CD11c⁺-cells at psoriasis patients is observed only in the skin, not peripheral blood; this shows their intradermal differentiation. These cells are the main source of the inflammatory key cytokine synthesis (TNF-α) and inducible nitrogen oxide synthase (iNOS). That is why they are called TNF-α/iNOS-producing DCs (Tip-DCs). INOS ferment causes pronounced vasodilation of the dermal vessels in psoriatic eruptions by forming nitrogen oxide [79–81]. CD11 molecule is the integrin that performs the cellular interaction at B- and T cell proliferation. When treating psoriasis patients with efalizumab (CD11a-antibodies, Raptiva), a significant decrease in CD11c⁺-DCS has been noted in the skin. Moreover, the decrease in CD11c⁺-cells has been preceded by a decrease in T lymphocytes' amount in the infiltrate and the keratinocyte proliferative rate normalization. The population dynamics of CD11c⁺-cells has had the best correlation with the clinical response to anti-cytokine therapy [82].

Participation of melanocytes in psoriasis development

When studying the skin of psoriasis patients, Arakawa A. et al. (2015) have found that a major part (37%) of cytotoxic lymphocytes (CD8⁺) directly contact with epidermal melanocytes [19]. It is also established that psoriatic plaques have an increased number of melanocytes [83]. Assuming that melanocytes are the target of autoimmune inflammation at psoriasis, Arakawa A. et al. have studied the antigens presented in these cells and have found a possible autoimmune antigen. They have found ADAMTSL5 melanocytic protein which has formed an auto-aggressive clone of CD8⁺-cells (together with HLA-C*0602 antigen) and has stimulated them to produce IL17 (the so-called Tc_{17}-cells) initiating psoriatic inflammation in the skin. The researchers have noted that the HLA-C*0602 allele is involved in the development of the autoimmune response against melanocytes, so the carriers of this antigen have a huge risk of psoriasis development [19].

The results of our studies have also confirmed that the absolute number of melanocytes in the affected skin of psoriasis patients has been significantly higher than in the unaffected skin and skin of healthy persons, while the ratio between melanocytes and basal keratinocytes is the same (Fig. 2). It is important to note that no melanocytes in the proliferating stage have been found in all groups except for 1–2 cases (Fig. 3). Thus, we have reached the conclusion that the increased number of melanocytes is not connected with mitosis in the epidermis but probably occurs in the hair follicle bulge where the germ-line cells are located. Fig. 4 shows multiple contacts of MelanA⁺ and CD8⁺ cells in the affected skin of psoriasis patients which may be indicative of the immune interaction between these cells (Fig. 4).

However, it is not understood how psoriatic eruptions appear on the depigmented skin areas of patients with acquired leukoderma which do not have melanocytes. Also, pre-melanocytes (which are the predecessors of melanocytes) located in the hair follicle (bulb area) which may take part in the formation of eruptions in depigmented areas have not been studied to date.

We should describe more specifically two forms of psoriasis: guttate psoriasis and paradoxical psoriasis. It is related to the anormogenesis and importance of their study for understanding the disease as a whole. Guttate psoriasis is often the first stage of the disease, and the detection of a mechanism of its transformation into the chronic plaque form has an important prognostic significance. Paradoxical

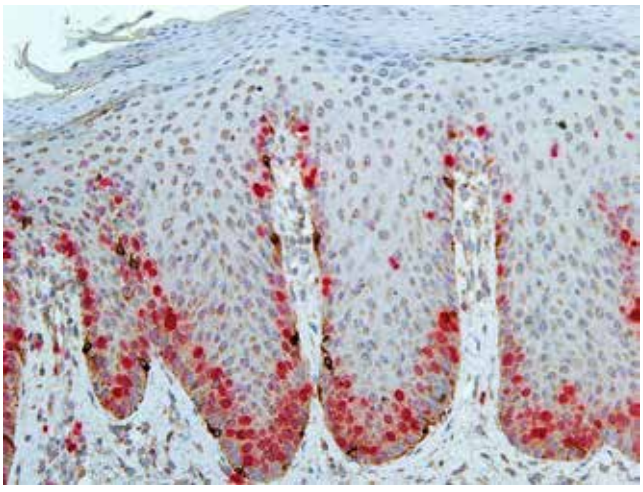

Fig. 2. Immunohistochemical study (dual detection system): neutral red staining — marker Ki-67, Bismarck brown staining — marker MelanA); magn: ×200, 696 × 507 μm

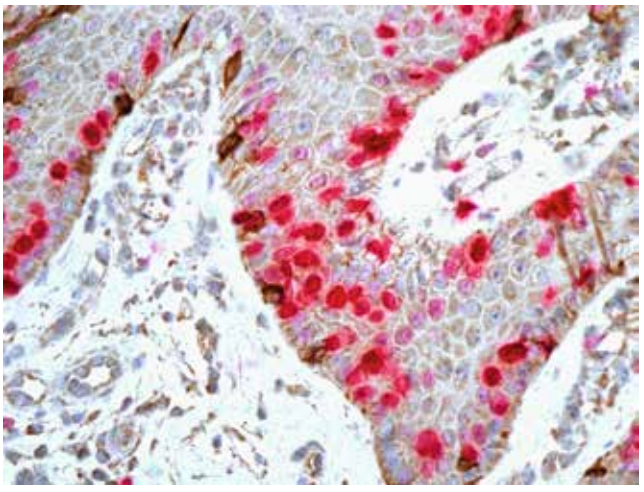

Fig. 3. Immunohistochemical study (dual detection system). Sporadic proliferating melanocyte (MelanA⁺-Ki67⁺-cell) in the epidermis of psoriasis patients (marked by an arrow); magn. ×400, 348 × 253 μm

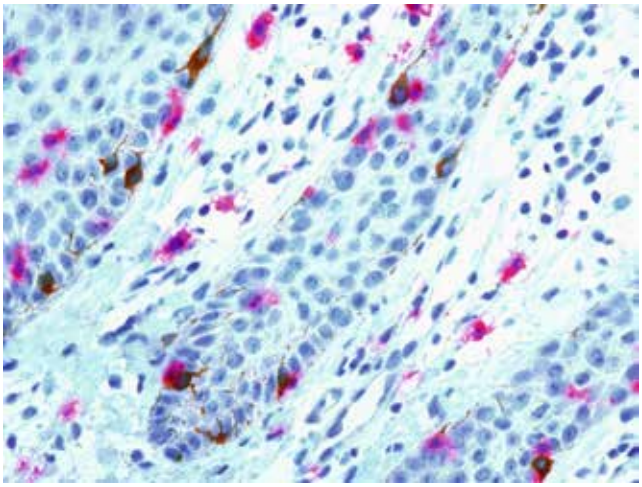

Fig. 4. Immunohistochemical study (dual detection system). The contacts of MelanA+ cells (Bismarck brown staining) and CD8+ cells (neutral red staining) in the epidermis (marked by arrows); magn. ×400, 348 × 253 μm

psoriasis occurs at treatment with genetically engineered biologic drugs, and the explanation of this phenomenon can help to revise views towards key effect points at psoriasis treatment.

Guttate psoriasis development mechanism

This form is generally associated with the presence of focal infection in the form of chronic tonsillitis (CT). According to our information, 85.0% of GP patients have associated dermatosis development or recrudescence with CT recrudescences, while a similar relationship was observed only in 22.4% of cases with plaque psoriasis. Today, *Streptococcus pyogenes* is the key factor of guttate psoriasis pathogenesis; the infection's main reservoir is located in palatine tonsils.

The interaction of several factors that lead to the development of a specific clinical pattern of GP (tiny disseminated mildly-infiltrated papules which do not have a propensity to peripheral growth) is supposed. Firstly, the expression of a cutaneous lymphocyte antigen (CLA) molecule is induced under the influence of streptococcus superantigens on the surface of lymphocytes' $CD4^+$ and $CD8^+$ tonsils formed in T areas, which means that they are able to penetrate the skin [84]. Secondly, the antigen mimicry mechanism is triggered. In this case, T cells can interact not only with peptides of M6 streptococcal protein but also with homologous keratine sequences in the skin [85, 86]. Thirdly, blood monocytes uptake the destroyed sacculus components coming out of the inflammation focus (M-proteins, peptidoglycan), migrate to the skin, differentiate to immature DCs, and activate lymphocytes which infiltrate dermis (CLA^+CD4^+) and epidermis (CLA^+CD8^+) [87–89]. $CD8^+$T-cells trigger the keratinocyte proliferation, and $CD4^+$T-cells support immune inflammation [1]. It is important to recognize that over time, as a result of the cross-presentation of the released autoimmune antigens, it is possible to switch the immune response from the tonsil axis→skin, to the skin axis↔regional lymph nodes which will result in a decrease in the eruption relapse dependence from CT recrudescence and the transition of the process into a plaque form of dermatosis.

This hypothesis is based on the following scientific findings. Psoriasis patients have an increased number of $CD4^+$ and $CD8^+$ T-lymphocytes in palatine tonsils and peripheral blood which express the CLA targeted molecule on their surfaces. Moreover, a high level of receptor expression to interleukine-23 (IL) which plays a key role in their differentiation in Th_{17} is found at psoriasis patients on CLA-positive T lymphocytes of tonsils [84]. These data clearly demonstrate the fact that pharyngeal lymphoid tissue ring (secondary lymphoid organ) is a source of effector T lymphocytes that migrate to the skin (resident dermal T lymphocytes) at psoriasis. The inflammatory process in the pharynx lymphoid tissue often caused by *Streptococcus pyogenes* only stimulates the intensive proliferation and differentiation of T cells, their release into the systemic circulation. The hematogenous spread of these lymphocytes can be inferred by the disseminated nature of eruptions with this psoriasis form.

Paradoxical psoriasis development mechanism

Psoriasis development mechanism during treatment with genetically engineered biologic drugs (GEBD) is not fully understood. Initially, some authors have considered psoriasiform eruptions as a delayed-type hypersensitivity reaction on the skin, but histological studies have demonstrated the identity of pathomorphological changes in patients with paradoxical and ordinary psoriasis [90].

The most possible is the hypothesis of the development of a disbalance between TNF-α and INF-α cytokines in patients who take genetically engineered biologic drugs. TNF-α inhibits activity and maturation of pDCs which are the main sources of INF-α. These cells appear in the dermis at the early stages of psoriatic papule formation, and it appears that they take part in the immune inflammation initiation. The secreted pDCs of INF-α lead to the increase of CXCR3 expression which causes the migration of Th_2 auto responsive cells. The transfer of the inflammatory process in the skin is accompanied by an increase of TNF-α concentration in psoriatic papules and INF-α synthesis depression. The application of TNF-α inhibitors may lead to activation of pDCs and excessive production of INF-α which triggers the psoriatic inflammation in the skin [91, 92].

The participation of TNF-α in the regulation of the interaction between T effector and T regulatory cells in the inflammatory process has been reviewed in experimental studies by Chen X. et al. (2007). They have demonstrated on cell cultures consisting of $CD4^+CD25^-$ T lymphocytes and T regulatory cells that the short term (<48 hours) exposure of TNFα leads to depression of T regulatory cells' suppressor effect upon the proliferation of T effectors. A longer-term presence of TNFα has been accompanied by the suppressor activity restoration in T regulatory cells, cytokine secretion suppression, and $CD4^+CD25^-$ T lymphocyte proliferation. The authors have assumed that the physiological implication of this phenomenon is in the suppression of immunosuppressive action of T regulatory cells in order to initiate the inflammatory process by T effectors with the subsequent immune response inhibition [93]. The TNFα has a direct effect on T cells through the TNFRII receptor expressed on their surfaces. The application of anti-TNFRII monoclonal antibodies leads to a decrease in the population of T regulatory cells in psoriatic eruptions [94]. From this point of view, we can try to explain the paradox when psoriasis has manifested in patients or psoriatic arthritis patients who have had psoriatic eruptions on the skin

during the treatment of rheumatoid arthritis with monoclonal antibodies to TNFα [95]. In these cases, the neutralization of the TNFα stimulatory effect must have been accompanied by the suppression of T regulatory cells that have led to the psoriatic inflammation initiation in the skin.

Conclusion

Since the last century, our visions of psoriasis pathogenesis have changed a lot. The concept of the immune system malfunctions has replaced the prevailing theory of the key role of a primary abnormality of keratinocyte differentiation. It is assumed that the balance change towards the increased synthesis of pro-inflammatory cytokines by immune-competen T cells leads to the development of psoriatic manifestations in the skin.

This review presents the main components of psoriasis pathogenesis based on the disease development immune theory. The immune system cells which participate in the formation of a psoriatic phenotype are described. Recent studies on the role of melanocytes, congenital lymphoid cells, and T cell memory in the disease development are highlighted. The emphasis is on the fact that the autoimmune inflammation is the guide link explaining the pathogenesis of this dermatosis. At the same time, no autoreactive antibodies have been detected up to the present, and the autoimmune antigens proposed to researchers are either underexplored or are localized in other organs and tissues where the inflammation does not develop.

The necessity for a detailed study of a focal infection during guttate and plaque psoriasis is of special interest. Despite the fact that there is no large-scale study that proves the significance of the chronic infection foci in plaque psoriasis formation risk up to the present, most researchers have experimentally established a positive effect of indolent inflammatory disease sanation in regression and a more favorable dermatosis course. However, it is not understood why the disease course becomes chronic in only a third of patients with guttate psoriasis and what factors contribute to it.

Today, the study of the molecular basis of the disease progression has led to the creation and introduction of a number of highly effective targeted drugs into clinical practice. Further developments related to the inhibition of resident memory cells, innate lymphoid cells, as well as the study of guttate psoriasis perpetuation will significantly increase the effectiveness of the therapy.

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