

The role of regulatory T cells and anti-inflammatory cytokines in psoriasis

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Abstract

Psoriasis is a chronic inflammatory disease with a genetic predisposition that can be triggered by environmental factors. Pathogenesis is characterized by activation of the Th1/Th2 axis and abnormalities of the Th17/Treg balance as well as deficiency of anti-inflammatory cytokines (IL-10, TGF- β). Regulatory lymphocytes (Treg), which are involved in homeostasis mechanisms, maintain tolerance and prevent autoimmune disorders. Only a few studies have investigated the presence of Treg marker expression and levels of anti-inflammatory cytokines in psoriatic skin and sera of patients with psoriasis. The results of studies are controversial. This article reviews and analyzes what is known about the role of Treg cells and anti-inflammatory cytokines in psoriasis.

Keywords: psoriasis, immune tolerance, Treg, IL-10, TGF- β

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Introduction

Psoriasis is a chronic inflammatory disease with a genetic predisposition that can be triggered by environmental factors. Pathogenesis is characterized by activation of the Th1/Th2 axis and abnormalities of the Th17/Treg balance (1). The current state of knowledge suggests that the IL-23/Th17/IL-17 axis plays a key role in the initiation of inflammatory psoriasis, known as “autoinflammation”. The predominance of Th1/IFN- γ and proinflammatory cytokines develops in the chronic phase (2–4). An essential factor of pathogenesis is the dysfunction of regulatory lymphocytes (Treg), which are involved in homeostasis mechanisms to maintain tolerance and prevent autoimmune disorders (5).

Treg cells are a subpopulation of lymphocytes responsible for suppressing an excessive or autoreactive immune response. They have the ability to interact directly through membrane receptors for immune cells (effector T-lymphocytes, memory and natural killer [NK] cells, B lymphocytes, antigen presenting cells) by creating suppressing cytokines (IL-10, IL-35, TGF- β , galectin-1) or by direct cytotoxic action (granzyme B and perforin release) (6–8). The important feature of Treg cells is a high expression of the IL-2 receptor chain (CD25), which is responsible for maintenance of tolerance to self-antigen because Treg cells bind IL-2 and decrease levels of IL-2, causing inhibition of T cells (9). Phenotypically, Treg cells express FOXP3, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), certain members of toll-like receptors, CD103 (α E β 7 integrin), glucocorticoid-induced TNF receptor family-related gene (GITR), lymphocyte activation gene-3, programmed death receptor-1, and neurophilin on their surface (9, 10). FOXP3 is a more specific marker of Treg cells than CD4 and CD25, and it is very important for the development and activity of Treg cells. Moreover, the expression of FOXP3 induces GITR, CD103, and CTLA-4 (11).

Some studies have shown that approximately 5% of Th cells in the blood express FOXP3, and about 20% of Th cells in the skin of adults. More than 95% of FOXP3-positive Th cells in the skin express CD45RO, but 75–80% are FOXP3-negative (12, 13).

Treg cells are a heterogeneous population consisting of cells with a variety of immunophenotypes: CD4⁺CD25⁺FOXP3⁺T cells

with characteristic expressions of the FOXP3 transcription factor with high CD25 expression and deficiency in expression of IL-7 α subunit receptor (IL7R- α or CD127); CD8⁺CD25⁺FOXP3⁺ T lymphocytes, an analogous subpopulation to the previously mentioned one, are found among CD8⁺ T cells; Treg type 1 (Tr1) are cells with the CD25⁺FOXP3⁺CD4⁺ phenotype that secrete significant amounts of interleukin 10 (IL-10) and transforming growth factor (TGF- β); Th3 are phenotypically similar to Tr1 (CD25⁺FOXP3⁺CD4⁺), but their main modulator is TGF- β ; and CD8⁺CD28⁻ lymphocytes do not express FOXP3 (7, 11, 14).

Treg cells consist of naturally developed cells (nTreg) in the thymus, and inducible Treg cells (iTreg), which transform into Treg cells in the periphery (11). Although iTreg resemble nTreg in phenotype and function, there are differences in epigenetic status and stability (12). Lymphocyte iTreg are Tr1 and Th3, which arise in the periphery from naive T cells under the antigen that is presented by immature dendritic cells with exposition of TGF- β and IL-10 (11, 15). IL-10 is necessary to induce or suppress lymphocyte Tr1 and Th3, which depend on TGF- β . Some Treg cells can induce the formation of other Treg cells under the influence of IL-35 (iTr35). IFN- γ inhibits their activity (11, 15).

The best-known CD4⁺Tregs are FOXP3⁺Tregs and FOXP3⁺Tr1. The mechanisms of FOXP3⁺Tregs and Tr1 action on adaptive immune responses is understandable, but is still ambiguous on innate immunity (16). Yao et al. observed that Tr1 can have a beneficial influence on disease-associated inflammasome activation by IL-10. Lymphocyte Tr1 inhibited the transcription of pro-IL-1 β mRNA, inflammasome-mediated activation of caspase-1, and secretion of mature IL-1 β (16).

Treg cells and psoriasis

The amount of Treg cells in psoriasis

Treg cells play a crucial role in psoriatic inflammation (5, 17). Interleukin-6, which is needed for the differentiation of Treg cells, inhibits the activation and proliferation of Th17, and leads to normalization of Treg cells and Th17 balance (1). Some researchers

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have found deviations in CD4⁺CD25⁺FOXP3⁺Treg, and Furuhashi et al. (18) have noted the presence of CD4⁺FOXP3⁺ in the peripheral blood of patients with psoriasis. Some authors have confirmed dysfunctional CD4⁺CD25⁺FOXP3⁺Treg activity as a reason for hyperproliferation of T effectors in vivo. Karamelic et al. (5) have demonstrated a lower amount of CD4⁺CD25⁺Treg in the blood of psoriatic patients compared to a control group, but there was no correlation with the severity of the disease (psoriasis areas severity index, PASI). Similarly, a Polish study by Pawlaczyk et al. (19) has shown a statistically significant decrease in Treg cells in flow cytometry in psoriasis patients with PASI > 12.

The literature shows many contradictory reports. Saito et al. (20) and Furuhashi et al. (18) did not find any difference in the percentage of Treg cells between psoriatic and healthy patients. Zhang et al. (21) even reported a greater amount of Treg cells in the blood of patients with acute psoriasis than in the control group.

FOXP3⁺ cells were seldom present in healthy epidermis and dermis. Fujimura et al. (22) found more CD3⁺, CD4⁺, and CD25⁺FOXP3⁺Treg in psoriatic epidermis than in the dermis. Leite Dantas et al. (23) described an inducible psoriasis-like arthritis by human TNF in transgenic mouse. The skin lesions were characterized by keratinocyte hyperproliferation, a high amount of pro-inflammatory cytokines with macrophages, and Th1 and Treg cell infiltration as in the psoriasis-like phenotype. Treg cells inhibit the pro-inflammatory activity of macrophages, which are the major immune effector cells in TNF-mediated psoriasis.

Keijsers et al. (24) examined biopsies from patients with chronic plaque psoriasis (n = 9): the center and margin of the lesion, and perilesional and non-lesional skin. They observed a significant increase of CD3⁺, CD4⁺, and FOXP3⁺ cells from non-lesional skin compared to psoriatic skin. In seven of nine patients, the FOXP3⁺Treg/CD4⁺ T cell ratio was higher in non-lesional skin than in perilesional and lesional skin, even in healthy skin. What is more, the expression of IL-17 was correlated with mast cells, but not with CD4⁺ cells. The high FOXP3/CD4 ratio in the non-lesional skin of psoriatic patients showed active mechanisms of immune tolerance, whereas in perilesional and non-lesional skin the high activity of effector cells exacerbated the inflammation (24).

Differences in the amount of Treg cells may depend on the type of psoriasis. Yan et al. (25) have shown a greater number of FOXP3⁺Treg in plaque efflux compared to skin lesions in the guttate form. Another study showed a decrease in CD39⁺FOXP3⁺, especially in the pustular and erythrodermic forms of psoriasis, and their number increased with the duration of the disease. It is questionable whether this can be connected with different pathogenic mechanisms for different types of psoriasis (26).

Dysfunction of Treg cells in psoriasis

The divergences of the studies cited above indicate that not the amount of Treg cells but their dysfunction may be significant in the pathogenesis of psoriasis. It has been found that Treg cells separated from the lesions or peripheral blood of psoriatic patients cannot properly suppress T effector responses due to alloantigen-specific or polyclonal TCR stimulation (12, 27). Sugiyama et al. (27) have observed their decreased cytotoxic activity, but only three patients were assessed. CD4⁺CD25⁺Treg isolated from psoriatic lesions are not capable of suppressing effector activities of Th1 in the skin of people with psoriasis. In contrast, those isolated from non-psoriatic patients' peripheral blood are able to inhibit hyperactive psoriatic Th1 in vitro (6, 28–30). Thus, hyperproliferation of

psoriatic pathogenic cells in vivo is a consequence of abnormal Treg cell activity in the blood and psoriatic lesions (12, 27).

Several studies have shown that Treg cells' function in psoriasis was inversely correlated with human CD127 expression (31–33). These disorders may be the result of abnormal CD127 expression in CD4⁺CD25⁺lymphocytes (18). Zhao et al. (34) found strong expression of miR-210 (microRNAs: endogenous, noncoding RNAs) in CD4⁺ cells, which inhibited expression of FOXP3, thereby causing Treg cell dysfunction and not reducing their numbers. In addition, it led to increased production of IFN- γ and IL-17, and the decrease of IL-10 and TGF- β in T CD4⁺. In contrast, Wang et al. (35) discovered the dysfunction of Treg cells by CD18 knockout (CD18hypo PL/J mice) as a causal factor of pathogenic T cell hyperproliferation in psoriasis. This reduced CD18 expression on CD4⁺CD25⁺CD127⁺ Treg, compared to a wild type, which led to weak function and proliferation of Treg cells. The abnormal function of Treg cells can be reversed by transfer of CD18 Treg cells into mice with a CD18 defect, causing psoriasis improvement. Yang et al. (36) revealed that psoriatic Treg cells show a predominant STAT3 phosphorylation pathway that leads to overproduction of pro-inflammatory cytokines (IL-6, IL-21, IL-23), resulting in T effector activation. In addition, Treg cells isolated from psoriatic patients could produce IFN- γ , TNF- α , and IL-17.

Th17 and Treg cells

Hyperactivation of Th17 is responsible for abnormalities of the Th17/Treg balance in psoriasis (1). Priyadarssini et al. (37) showed abnormalities in T cell phenotypes with an increase in Th1/Th17 and a relative decrease in Th2/Treg in psoriasis compared to healthy patients. They observed a linear trend of the Th1/Th17 percentage together with PASI increasing. These outcomes proved an immune-dysregulation in psoriasis, and connection between the Th1/Th17 phenotype and severity of the disease (37).

Lymphocyte Th17 development is functionally linked to the development of FOXP3⁺Treg and they share the requirement for TGF- β to develop from naive T cells. When activated in the presence of TGF- β or TGF- β /IL-6, naive T cells start to simultaneously upregulate both FOXP3 and ROR γ t, and it has been shown that these transcription factors can directly interact with each other (38, 39). Thus, the competition of Treg cells with Th17 for their reciprocal development from this common precursor can already be seen as a way to control Th17 or Treg cell development, respectively (38, 39). In patients with psoriasis, the impaired function of Treg cells causes the hyperactivation of Th1 and Th17, which causes psoriatic inflammation (5, 40, 41). Zhang et al. (21) revealed an increasing amount of Th17 and FOXP3⁺Treg in the blood and lesions in psoriatic patients and a positive correlation with severity of the disease. The correlation of Th17/Treg ratio in skin lesions with PASI was inverse, but in blood it was positive.

However, Bovenshen et al. (28) discovered that FOXP3⁺Treg isolated from psoriatic lesions can easily differentiate into a strong proinflammatory IL-17A-positive Th17, which expresses three cell surface markers, IL-17A⁺, FOXP3⁺, and CD4⁺. They might significantly contribute to the disease development. These cells produce IL-17A and IL-22, and show ROR γ t expression. In severe psoriasis, the expression of ROR γ t is increased, and FOXP3 of the Treg marker decreases, which may suggest that Treg cells take part in perpetuating the inflammatory process rather than in suppressing it (28, 42).

Treg cells and psoriasis therapy

Treg cells are up-regulated by drug therapy in psoriasis. The long-term remission is connected with normalization of the Treg cells and pathogenic memory/effector cell balance (10). After an effective monoclonal antibody therapy (infliximab, etanercept, and efalizumab), an increase of CD4⁺CD25⁺FOXP3⁺ cells in the blood of psoriatic patients is observed as well as in the previously affected skin after treatment with adalimumab (17, 24, 43). Quaglino et al. (43) noted Th1/Th17 hyperactivity with Treg cell down-regulation at baseline, and after etanercept treatment the normalization of their activity. Therefore, stimulating Treg cell activity can be dependent on the anti-TNF mechanism (17). Alefacept inhibits T effectors by apoptosis of T cells (releasing granzymes by the NK cells). The apoptosis is enhanced by Treg cells and causes remission of the disease in responding patients (10). Furuhashi et al. (18) evaluated the amount of Treg cells in blood before treatment and after photochemotherapy treatment. For patients that achieved PASI 90, the amount of Treg cells was significantly higher than for those that did not have PASI 90. Moreover, UVB can induce Treg cell production (10). Similarly, Kubo et al. (44) proved that bath-PUVA (psoralen and UVA) therapy significantly increases the number of Treg cells and restores Treg cell function to almost normal in most patients with psoriasis. Variations of Treg

cell amounts during various therapies may explain why some of them (methotrexate and cyclosporine) resulted in very short remissions, and others (alefacept and UVB) in long-term ones (10). Therefore, one should ask whether, after determining Treg cells, it is possible to predict a good response to the treatment (17, 18).

Mattozzi et al. (41) also described the relationship between vitamin D and Treg cells in psoriasis. They assessed whether vitamin D status is correlated with circulating Treg cells and PASI. In contrast, low titer encourages the activity of Th1, Th17, and Th22. The immune modulator properties of vitamin D are mediated in part through its effects on Treg cells.

Interesting research findings were shown by Ma et al. (45). They analyzed patients during anti-TNF treatment with manifestation of psoriasis-like disease. They noticed that the neutralization of TNF- α did not cause the production of proinflammatory cytokines (IL-1 β , IL-6, IL-17, IL-21, and IL-22), but it suppressed FOXP3 expression in the skin with reduction of FOXP3⁺Treg (45) (Table 1).

Interleukin-10 and psoriasis

IL-10 has an anti-inflammatory effect, inhibiting the production of pro-inflammatory cytokines such as IFN- γ , IL-2, IL-3, TNF- α , or GM-CSF. It is produced by Treg lymphocytes, but also by macrophages, dendritic cells, and B lymphocytes (46, 47). Interleukin-10 inhibits

Table 1 | Psoriasis and Treg disorders.

Category / Study	Examined	Finding
Amount of Treg cells in blood		
Karamehic et al. (5)	↓ CD4 ⁺ CD25 ⁺ Treg	Decrease in peripheral blood, no correlation with PASI
Pawlaczyk et al. (19)	↓ Treg	Decrease in peripheral blood, correlation with PASI > 12
Saito et al. (20)	Treg	No differences between psoriatic and healthy patients
Furuhashi et al. (18)	Treg	No differences between psoriatic and healthy patients
Zhang et al. (21)	↑ Treg	Greater amounts in peripheral blood of patients with acute psoriasis than in the control group
Amount of Treg cells in psoriatic lesion		
Fujimura et al. (22)	CD3 ⁺ , CD4 ⁺ , CD25 ⁺ FOXP3 ⁺ Treg	More in psoriatic epidermis than in dermis
Keijsers et al. (24)	CD3 ⁺ , CD4 ⁺ , CD25 ⁺ FOXP3 ⁺ Treg	Significant increase in non-lesional skin compared to psoriatic lesions
Yan et al. (25)	FOXP3 ⁺ Treg	Greater number in chronic plaques compared to skin lesions in the guttate form
Zhang et al. (26)	CD39 ⁺ FOXP3 ⁺	Decrease in the pustular and erythrodermic psoriatic lesions
Dysfunction of Treg cells		
Sugiyama et al. (27)	CD4 ⁺ CD25 ⁺ Treg	Decreased cytotoxic activity of Treg cells from psoriatic lesions Not capable of suppressing Th1 in psoriatic lesions Isolated from non-psoriatic patients' peripheral blood, able to inhibit hyperactive psoriatic Th1 in vitro
Sugiyama et al. (27)	Treg	Hyperproliferation of psoriatic pathogenic cells in vivo is a consequence of abnormal Treg cell activity in blood and psoriatic lesions
Zhang et al. (26)		
Bovenschen HJ et al. (28)		
Zhao et al. (34)	CD4 ⁺ CD25 ⁺ Treg	Strong expression of miR-210, which inhibited expression of FOXP3, thereby causing Treg cell dysfunction, not reducing their numbers and leading to increased production of IFN- γ , IL-17, and the decrease of IL-10, TGF- β in T CD4 ⁺
Wang et al. (35)	CD4 ⁺ CD25 ⁺ CD127 ⁻ Treg (mice)	Reduced CD18 expression on Treg cells, which leads to weak function and proliferation
Yang et al. (36)	Treg	Predominant STAT3 pathway in psoriatic Treg cells leads to overproduction of IL-6, IL-21, IL-23, resulting in T effectors activation/Treg cells isolated from psoriatic patients could produce IFN- γ , TNF- α , and IL-17
Th17 and Treg cells		
Lochner et al. (38)	FOXP3 ⁺ Treg	Th17 development is linked with FOXP3 ⁺ Treg depending on TGF- β and in psoriasis, the impaired function of Treg cells cause the hyperactivation of Th1 and Th17
Zhou et al. (39)		
Zhang et al. (21)	FOXP3 ⁺ Treg	Correlation of Th17 Treg ratio in skin lesions with PASI was inverse, but in blood it was positive
Bovenshen et al. (28)	FOXP3 ⁺ Treg	Treg cells from psoriatic lesions can differentiate into IL-17A-positive Th17, which express IL-17A ⁺ , FOXP3 ⁺ , and CD4 ⁺ and produce IL-17A and IL-22 Increase of the expression of ROR γ t and FOXP3, which may suggest that Treg cells enhance the inflammatory process, rather than suppress it

Table 1 | Continued.

Category / Study	Examined	Finding
Treg cells and therapy of psoriasis		
Richetta et al. (17) Keijsers et al. (24) Quaglino et al. (43)	anti-TNF therapy	Increased Treg cells in blood of psoriatic patients
Quaglino et al. (43) Kagen et al. (10)	etanercept alefacept	Normalization of Treg cell activity Stimulating apoptosis of T effectors, which is enhanced by Treg cells and causes remission
Furuhashi et al. (18)	PUVA therapy	Increased Treg cells in blood after successful treatment (PASI 90)
Kubo et al. (44)	bath-PUVA therapy	Increases Treg cells and restores function to almost normal
Kagen et al. (10)	methotrexate, cyclosporine, alefacept, UVB	Variations of Treg cells amounts during different therapies may explain why methotrexate and cyclosporine resulted in very short remissions, but alefacept and UVB resulted in long-term ones
Mattozzi et al. (41)	vitamin D	Level correlates with Treg cells and PASI Low titer encourages the activity of Th1, Th17, and Th22
Ma et al. (45)	anti-TNF therapy	In psoriasis-like disease provoked by TNF-inhibitors: TNF- α neutralization does not cause the production of IL-1 β , IL-6, IL-17, IL-21, and IL-22, but it suppresses FOXP3 expression in the skin with reduction of FOXP3 ⁺ Treg

PASI = psoriasis area severity index, TNF = tumor necrosis factor, IL = interleukin, PUVA = psoralen and UVA.

the production of IL-12 by macrophages, and IL-12 stimulates IFN- γ secretion. Therefore, IL-10 is considered the most important inhibitor of INF- γ activity (46). Moreover, IL-10 inhibits Th1 and promotes Th2 responses, and inhibits Th17 responses in mice (46, 48). It also has the ability to inhibit the expression of co-stimulating molecules and MHC II on dendritic cells and macrophages. In addition, it also blocks NF- κ B activity and is involved in regulating the JAK-STAT signaling pathway (49). IL-10 can inhibit cyclooxygenase-2 (COX-2). Its deficiency causes COX-2 activation and increased production of thromboxane A₂, causing vascular and cardiovascular endothelial dysfunction in mice. Mice with congenital deficiency of IL-10 develop atherosclerotic abnormalities in vessels much faster (49). In psoriatic fibroblast studies that were stimulated with IL-8 and TNF, Głowacka et al. (50) showed that they are not able to produce IL-10, but neutrophils released IL-10 in a very low concentration.

Relative IL-10 deficiency in serum and skin in patients with psoriasis is an essential factor in pathogenesis (51). The beneficial effects of recombinant human IL-10 treatment have been suggested for psoriasis treatment (46, 51, 52). Clinical trials in psoriatic patients showed improvement in the reduction in relapse rate and good tolerance. Anti-psoriatic action of interleukin-10 inhibits antigen-presenting cells (inhibition of MHC II expression and coagulating molecules) and shifts the ratio between Th1 and Th2 cells, rather than by acting directly on keratinocytes. It promotes the production of cytokines by Th2 through inhibition of IFN- γ and it inhibits Th1 activity through suppression of IL-12 synthesis (51). This causes a decrease in the chemotactic concentration of IL-8 neutrophils in the efflorescence, limiting the formation of microtubules (51, 53). Döcke et al. (46) reported the effect of systemic IL-10 in 7-week therapy in 10 psoriasis patients. In addition to clinical improvement, they also observed the activation of NK cells and an increase in proinflammatory indicators (CRP and soluble IL-2R). Some medications, such as apremilast, a phosphodiesterase inhibitor, can inhibit intracellular cAMP, increasing the amount of IL-10 (54).

Recently, a specific subset of IL-10-producing regulatory B cells was identified as so-called Bregs, which are major negative regulators of the immune response (55, 56). They inhibit differentiation of Th1 and Th17 (57, 58). Psoriasis is characterized by a significant decrease in their amount, although the number of progenitor B

cells is even increased, suggesting that Bregs may be functionally impaired in psoriasis (55, 59). Mavropulos et al. (57) proved that there is a decrease in IL-10⁺B cells and an inverse correlation with PASI, IL-17A⁺CD3⁺, and IFN γ ⁺CD3⁺ T cells.

Recently many studies have been concerned with IL-10 gene polymorphisms in psoriasis, especially the promoter region (60). Studies by Asadullah et al. (61) have shown that IL-10.G13 allele polymorphism is associated with familial predisposition to psoriasis. Asian meta-analysis showed a strong association between psoriasis and the IL-10-1082G allele (62).

Interleukin-10 is an important modulator of HLA-G expression in the CD14⁺ monocytes in blood. HLA-G is a molecule with immunosuppressive properties. Its deficiency in membrane-bound and soluble form can cause abnormalities in immune responses that lead to autoimmune diseases (63, 64).

Aractingi et al. (65) revealed the presence of HLA-G protein in psoriatic lesions, but never in normal healthy skin, such that it can be an inhibitor for T cells. They described lower plasma levels of sHLA-G and IL-10 in psoriatic patients compared to healthy volunteers (63). Borghi et al. (63) showed that treatment of psoriasis leads to suppression of Th1 activation because of sHLA-G secretion by an IL-10.

Transforming growth factor β and psoriasis

TGF- β is an important regulator in maintaining immune homeostasis. Disorders in TGF- β -expression or TGF- β -response play an important role in autoimmune diseases, chronic inflammatory conditions, parasitic infections, neurodegenerative diseases, cancer, and chronic rejections of transplants (66). General administration of TGF- β suppresses the symptoms of autoimmune diseases, whereas anti-TGF- β antibodies cause disease progression (67). Mutations within the TGF- β gene result in a phenotype characteristic for autoimmune diseases (67). TGF- β inhibits macrophage activity, although it can be produced by them. It also inhibits the activity of neutrophils, stimulates fibroblast proliferation and production of extracellular matrix elements by these cells, and activates angiogenesis (68).

TGF- β also has the ability to regulate the T lymphocyte subpopulation. It promotes the development of the Th17 response by using peripheral FOXP3⁺Treg while inhibiting the development of

Th1 and Th2 lines (69). In addition, Th3 is produced under high concentrations in the TGF- β microalgae, and when fully mature they secrete large amounts of TGF- β , modulating immunoreactivity (70). TGF- β suppressive effects on T lymphocytes, B lymphocytes, and macrophages, and the effect on T cell effector memory transformation have been demonstrated. Moreover, it cooperates with CTLA-4 to suppress the immune response, and also inhibits the expression of adhesion molecules and thus the adhesion of leukocytes to endothelial cells (70, 71).

The role of TGF- β in psoriasis is still not fully explained. A significant decrease in its receptors in the epidermis has been observed (72, 73). TGF- β 1 is a potent growth inhibitor for keratinocytes, and limiting its signaling increases keratinocyte hyperproliferation in psoriasis. Flisiak et al. (74) reported higher TGF- β 1 expression in the epidermis and serum in psoriatic patients, and TGF- β 1 correlation with PASI (74, 75). In addition, effective treatment resulted in TGF- β 1 serum reduction (76). Moreover, abnormal signaling of TGF- β discovered in psoriasis, even in the presence of higher TGF- β expression, stimulates hyperproliferation of psoriatic keratinocytes (77). The mechanism responsible for increasing TGF- β levels in psoriatic patients' serum may be due to stromal cells (74). Based on clinical data, it is difficult to evaluate whether increased TGF- β 1 is a reason for psoriatic inflammation, or is a result.

In a study by Zaher et al. (78), TGF- β 1 concentration was slightly higher in the healthy skin of the control group compared to the non-lesional skin of psoriatic patients. In contrast, Li et al. (79) suggest that even physiological doses of TGF- β 1 may contribute to the development of psoriasis. Contrary to plasma concentrations, TGF- β 1 levels in psoriasis are still contradictory. TGF- β 1 regulation in psoriatic plaques requires further analysis.

TGF- β 1 is a potent inhibitor of keratinocyte growth and, on the other hand, one can observe its overexpression in psoriatic keratinocytes. The fact that it seemed to react with different growth factors concomitantly with inflammation requires further explanation. Transgenic mice expressing wild-type TGF- β 1 in the epider-

mis develop skin lesions in the form of psoriasis efflux (68). These lesions are characterized by hyperproliferation of the epidermis, massive infiltration of neutrophils, T lymphocytes, and macrophages to the epidermis and superficial dermis, basophilic degradation, and angiogenesis as in Th1-mediated inflammatory skin diseases such as psoriasis (79). After biologic treatment (etanercept and efalizumab), TGF- β 1 levels have been decreased together with PASI in mild psoriasis (68).

Recent research by Litvinov et al. (77) has identified CD109 as a new co-receptor and negative regulator of TGF- β signaling. A decreased expression of TGF- β receptors is observed compared to CD109 release in keratinocytes in vitro in psoriatic epidermis (77).

Another crucial part of the analysis of the role of TGF in psoriasis is assessing its isoforms (TGF- β 1, TGF- β 2, and TGF- β 3), which bind specific receptors (TGF β RI, TGF β RII, and TGF β RIII). Activation of receptors turns on the SMAD intracellular signaling pathway (80). A study by Yu et al. (81) showed lower expression of TGF β RI and SMAD2, SMAD4, and SMAD6 mRNA in lesions and non-lesional skin in psoriasis. SMAD7 mRNA expression was remarkably lower in lesions compared with non-lesional and healthy skin. TGF- β 3 and TGF β RII mRNA were found only in non-lesional skin without differences in TGF- β 1 and TGF- β 2 expression. Processes of TGF- β isoform regulation in psoriatic plaques need more analyses.

Recent studies by Szondy et al. (82) have shown that treatment with anti-TNF- α is not only related to neutralization of the effects of this molecule, but also leads to TGF- β production in macrophages (82).

Conclusion

In the literature, there have been conflicting reports on the role of different types of regulatory cells and anti-inflammatory cytokines in psoriasis and immune tolerance mechanisms. Full understanding of these processes can develop new therapies for this disease.

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