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Advancements in Psoriasis Research: Skin Microcirculation and Its Prognostic Significance

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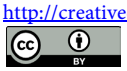

Abstract

Psoriasis, a chronic and recurring inflammatory skin disorder, is distinguished by the excessive proliferation of keratinocytes, immune cell infiltration, and angiogenesis. Ever since the observation of microvascular hyperplasia in psoriatic lesions, there has been a growing focus on exploring the intricate relationship between microcirculation and psoriasis. Furthermore, the potential utility of microcirculatory changes as prognostic indicators for psoriasis has garnered significant attention. This paper provides a comprehensive review of the role of skin microcirculation in psoriasis pathogenesis and its potential application as a clinical prognostic indicator.

Keywords

Psoriasis, Microcirculation, Angiogenesis, Prognosis

1. Introduction

The vascular network of psoriasis patients is very developed, especially in the dermal papillae of edema, the number of capillaries increases, the tube diameter expands, and the capillary loops are prolonged and twisted into clusters, similar to the structure of glomerulus. Microvascular abnormalities have a characteristic significance in the pathological changes of psoriasis and play a fundamental role in the occurrence and development of the disease, providing nutrients for proliferating keratinocytes and tissues, and promoting the migration of inflammatory cells [1]. At the same time, the immune response and inflammation generated by inflammatory cells are also inducers of angiogenesis [2].

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2. Microangiogenesis Related Mechanism

Angiogenesis is the process of the formation of new blood vessels, which sprout from pre-existing blood vessels. The process is complex and involves several key steps, including growth factor stimulation of endothelial cells, proteolytic enzyme degradation of extracellular stroma, endothelial cell migration and proliferation, and capillary formation [3] [4] [5]. It is currently believed that pro-angiogenic factors and anti-angiogenic factors play a crucial role in this process Based on the balance of pro- and anti-angiogenic factors, new vasculature formation is the main cause of most physiological events such as embryogenesis, organ regeneration, body growth and development, skin renewal and wound healing [6] [7] [8]. In the skin, angiogenesis is reactivated during skin renewal, wound healing and tissue repair. However, when the balance between angiogenesis-promoting and angiogenesis-inhibiting factors is faulty, pathological angiogenesis is induced, which in turn triggers a variety of diseases, such as age-related macular degeneration, arthritis, tumors, psoriasis, atopic dermatitis (AD), systemic sclerosis (SSc) and skin cancer [9] [10] [11] [12].

Angiogenic factors mainly include vascular endothelial growth factor (VEGF), angiopoietin (Ang), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and basic fibroblast growth factor (bFGF). Hyun Ji Lee *et al.* [13] summarized the roles of different vascular growth factors, such as the combination of VEGF and VEGFR-2, which can induce angiogenesis, increase vascular permeability and promote endothelial cell proliferation. The combination of Ang-1 and tie-2 can maintain angiogenesis and endothelial cell stability. PDGF and PDGFR combine to maintain angiogenesis by recruiting parietal cells (mainly pericytes). TGF-β can up-regulate vascular endothelial growth factor. bFGF can induce angiogenesis.

3. Angiogenesis Associated with Psoriasis

3.1. VEGF-VEGFR2 Signaling Pathway

Vascular endothelial growth factor (VEGF) is a 40 - 45 kda dimeric glycoprotein containing a cysteine knot motif that regulates neoangiogenesis during embryonic development, skeletal growth, reproductive function, and pathology [14]. The VEGF protein superfamily in mammals contains 5 types: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth coefficient (PLGF), and VEGF-A is believed to be a key regulator of homeostasis and angiogenesis during disease. There are three receptors for VEGF: VEGFR-1, VEGFR-2, and VEGFR-3; all are tyrosine kinase receptors (RTKs) with high affinity. VEGFR-2 is mainly expressed in vascular endothelial cells and is closely related to psoriasis angiogenesis, with roles in mediating inflammatory angiogenesis in psoriasis, leading to vasodilatation and dilatation, promoting endothelial cell proliferation, and enhancing vasodilation and vascular permeability [15].

The VEGF-VEGFR2 signaling pathway are as follows [16] [17] [18]: 1) VEGF binds to the immunoglobulin-like structural domains on the extracellular segment

of VEGFR2; 2) VEGFR2 undergoes dimerization, which triggers the phosphorylation of tyrosine residues on the intracellular segment; and 3) phosphorylated tyrosine residues activate downstream signaling molecules, such as extracellular signal-regulated kinases (ERK1/2), mitogen-activated protein kinases (P38), and signal transducing and activating factors of transcription (STAT3), etc., which are activated to participate in psoriasis lesion development.

The expression level of VEGF-A in skin lesions of psoriasis patients is higher than that in non-lesional or healthy skin, and its expression level correlates with disease severity [13]. VEGF stimulates the phosphorylation of tyrosine residues of VEGFR2, which activates the downstream pathway Raf-1/MEK/ERK cascade and promotes angiogenesis [19] [20]. Phosphorylation of activated ERK1/2, P38 and STAT3 can promote the mRNA expression of keratin K6, K16 and K17 [17]. High expression of K6, K16, and K17 is a characteristic marker of hyperproliferation and abnormal differentiation of keratinocytes (KCs) [21]. However, dysplasia of keratinocyte proliferation may lead to epidermal thickening. In addition, activated ERK1/2 can mediate Th17 cells to produce IL-6, IL-17 and other inflammatory cytokines that participate in the inflammatory cascade of psoriasis. Activated STAT3 not only plays an important role in psoriatic KCs, but also promotes the secretion of IL-17A and IL-17F [22]. At the same time, it also causes the impaired function of regulatory T cells (Tregs) in psoriatic patients, thus leading to the imbalance of Th17/Treg cells and participating in the chronic inflammatory response of psoriasis [23]. Studies have shown that the ERK1/2 inhibitor JSI287 (A compound was screened from a database of small molecules targeting ERK kinase and was the most specific for ERK kinase binding) can reduce the epidermal thickness of psoriasis, relieve epidermal congestion, edema and inflammatory cell infiltration, and reduce the secretion of inflammatory cytokines such as IL-6, IL-12 and IL-17A. Therefore, JSI287 may be an effective potential drug treatment for psoriasis [24]. BIRB796, a P38-specific inhibitor, reduced psoriasis related gene expression in both recombinant IL-17A-stimulated human keratinocytes *in vitro* and in isolated psoriatic skin specimens [25]. Therefore, BIRB796 mitigated the development of psoriatic dermatitis in mice induced by Anisomycin. To sum up, the in-depth study of VEGF-VEGFR2 signaling pathway helps to clarify the pathogenesis of psoriasis, and then may develop more effective psoriasis treatment drugs, pointing out a new direction for the treatment of psoriasis.

3.2. PI3K/AKT/FOXO Signaling Pathway

Phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) signaling pathways mainly regulate a variety of important cellular physiological functions, such as cell metabolism, protein synthesis, cell survival/inhibition of apoptosis, cell cycle progression, cell proliferation, growth and angiogenesis [26] [27]. The forkhead box O (FOXO) transcription factor is negatively regulated by the PI3K/AKT signaling pathway and is thought to inhibit cell proliferation. It was

found that the expression of PI3K and AKT in keratinocytes in psoriatic lesions was significantly higher than that in normal and non-lesional skin, and the PI3K activity in psoriatic skin lesions was 6.7 times higher than that in normal skin [28]. The link between PIK3/AKT/FOXO signaling pathway and VEGF has been gradually discovered in recent years. Studies [29] have found that FOXO1 plays a role in VEGF-mediated endothelial cell migration and proliferation, and FOXO1 deficiency in endothelial cells leads to altered expression of many genes related to vascular development. Therefore, the PI3K/AKT/FOXO signaling pathway may be involved in psoriasis angiogenesis by altering VEGF expression, but whether the PI3K/AKT/FOXO pathway acting in psoriasis improves the expression of VEGF remains to be further investigated.

Kinase, is a key downstream target of PI3K and a central mediator of the PI3K pathway. It has multiple downstream effector factors, shares the same structural homology in its catalytic domain, and participates in a variety of cellular processes. There are three subtypes of AKT: AKT1, AKT2, and AKT3. When activated by GFR tyrosine kinase, PI3K mediates the synthesis of phosphatidylinositol 3-phosphate (PIP3) on the plasma membrane. PIP3 binds to the PH structural domain of AKT, causing AKT to accumulate at the cell membrane. Further involvement of the PIP3-dependent kinase (PDK) leads to full activation of AKT [30]. Upon activation, AKT moves to the nucleus and cytoplasm, further activating downstream factors thereby regulating cellular functions. When PI3K/AKT signaling is activated, it promotes FOXO nuclear output and blocks FOXO transfer to the nucleus, thereby inhibiting FOXO-dependent transcription. Conversely, when growth factor receptor signaling is missing, AKT activity is reduced, FOXO phosphorylation is missing, and FOXOs accumulates in the nucleus. In the nucleus, FOXO triggers apoptosis and inhibits proliferation by inducing the expression of genes associated with cell death and growth. Therefore, the expression of PI3K and AKT is up-regulated in keratinocytes of psoriasis patients, the PI3K/AKT signaling pathway is activated, FOXO is retained in the cytoplasm, and its transcriptional program is inhibited, thus promoting the proliferation of keratinocytes. It has been found that FOXO1 expression is predominantly exists in the nuclei of keratin-forming cells in psoriatic non-lesional skin and normal skin, and that FOXO1 expression is significantly suppressed in psoriatic lesions; whereas FOXO1 expression is reactivated during the treatment of patients with psoriasis [31].

Phosphatase and tensin homolog (PTEN), a key upstream molecule of the PI3K/AKT pathway, is a tumor suppressor gene that inhibit cell proliferation and induce apoptosis. PTEN dephosphorylates PIP3 to produce PIP2 and negatively regulates the PI3K/AKT pathway, and its inactivation leads to continued activation of PI3K/AKT [32]. Li *et al.* [33] found that compared with normal skin, the mRNA level and protein expression of PTEN in psoriasis lesions were decreased, which confirmed that the down-regulation of PTEN expression was related to the over-activation of PI3K/AKT pathway.

Mammalian target of rapamycin (mTOR) is the main downstream regulator of PI3K/AKT pathway, which can negatively regulate FOXO activity, inhibit FOXO transcription, promote excessive proliferation and inhibit differentiation of keratinocytes [34]. It has been reported that the role of IL-17 and IL-22, which are associated with the psoriasis cascade, depends on the PI3K/AKT/mTOR signaling pathway [35] [36].

3.3. Oxidative Stress

Oxidative stress (OS), often considered as a redox imbalance originating from the overproduction of pro-oxidants (e.g., ROS, RNS, NO, and lipid peroxides) or deficiencies in antioxidants/antioxidant enzymes (e.g., SOD, CAT, and GPx), is the cause and consequence of many vascular disorders, and one of the biomarkers of these diseases [37] [38]. In addition, new evidence supports that oxidative stress and angiogenesis play an important role in many skin diseases such as psoriasis, atopic dermatitis and skin tumors [4].

Pro-angiogenic factors associated with psoriasis include VEGF, HIF-1α, TNF, angiopoietin, IL-8, il-17 and TGF-α [2]. VEGF expression was significantly increased in serum and skin lesions of patients with psoriasis. The expression of HIF-1α is mainly regulated by oxygen levels, and hypoxic conditions can promote HIF-1α expression [39] [40]. Upregulation of HIF-1α in the psoriatic epidermis promotes the proliferation and abnormal differentiation of keratinocytes, contributing to the progression of angiogenesis and skin inflammation. Reactive oxygen species (ROS) induce the release of VEGF from different cell types, which in turn promotes endothelial cell migration and proliferation by increasing intracellular reactive oxygen species [41] [42]. Therefore, the VEGF pathway may be a key link between oxidative stress and angiogenesis in psoriasis, and in particular the HIF-1α/VEGF signaling pathway plays a synergistic role in new angiogenesis in psoriasis. By up-regulating the expression of cell adhesion molecules, VEGF can enhance the migration of white blood cells to psoriatic skin and increase oxygen consumption, further activate HIF-1α and perpetuate the angiogenesis and inflammatory cycle of psoriasis [43] [44].

4. Microcirculation Changes in Patients with Psoriasis after Treatment

The onset of psoriasis is accompanied by dilation and distortion of superficial dermal capillaries, and this microvascular aspect has been evaluated by different techniques, including dermoscopy, video capillaries, fluorescence angiography, reflection confocal microscopy (RCM), high-frequency ultrasound, and histopathology [45]. Microvascular changes can be regularly monitored during patient treatment follow-up using non-invasive techniques such as dermoscopy, video capillary scopy, and RCM. Regarding the study of vascular changes in psoriasis lesions, G. Stinco [46] investigated the changes in the capillary bed on the surface of psoriasis plaques during cyclosporine treatment by video capillaroscopy.

The study showed that cyclosporine significantly improved clinical symptoms and reduced the size of the vessel diameter. In the following years, this author successively evaluated different drug treatments and reached the same conclusions [47] [48] [49]. In recent years, there are still similar studies, such as using different instruments (e.g., dermoscopy, videocapillaroscopy, and RCM) to assess the changes in vessel diameter and vessel density with various treatments. Most of them have shown improvement in clinical symptoms with drug treatment, with varying degrees of reduction in vessel density and vessel diameter [50]-[59]. And there is a correlation between microvascular changes and the improvement of clinical symptoms, that is, microvascular changes can be used as an observational index to assess the condition and prognosis. In addition to the reduction in vessel diameter and density, some studies have observed a reduction in both dermal and epidermal thickness at the lesions by RCM, high-frequency ultrasound, and histopathology [51] [53] [60] [61], as well as a reduction in dermal papilla diameter and the number of inflammatory cells [50] [62]. It has also been noted that the presence of globular vessels is associated with poorer clinical outcomes, while punctate vessels are associated with better clinical outcomes [63] [64] [65]. The above results suggest that changes in microcirculation are to some extent useful in assessing the prognosis of psoriasis. Since psoriasis is a chronic inflammatory relapsing disease, some patients may experience relapse of the disease after treatment. Regarding psoriasis recurrence, some studies have confirmed that recurrence is associated with the persistence of vascularization or revascularization at the end of treatment [63] [66].

5. Summary and Outlook

Microcirculation is an important histopathological change in psoriasis, which occurs before clinical symptoms and lesions. After effective treatment, microcirculation abnormalities begin to recover gradually, and then clinical symptoms begin to gradually relieve. Therefore, the change of microcirculation can be used as an effective index to evaluate the severity of disease, drug efficacy and disease monitoring. Currently, the treatment of psoriasis includes topical therapy (vitamin D analogues, corticosteroids, and calcineurin inhibitors), phototherapy (NB-UVB, BB-UVB, and PUVA), conventional systemic medications (methotrexate, cyclosporin, Avitamin, and sulfasalazine), and other treatments. Targeted biologics (TNF-α, IL-17 and IL-23 inhibitors) [67] [68]. Most psoriasis is affected by the climate environment has the characteristics of heavy winter and light summer, so psoriasis patients need to strengthen moisturizing skin on weekdays. For patients with mild disease and small lesion range, local external drug treatment can be used. Phototherapy and systemic administration are used for a wide range of lesions, including moderate to severe plaque, erythrodermic pustular, and articular psoriasis. However, for patients with moderate and severe psoriasis whose conventional treatment is ineffective or poorly tolerated, biologics often have better results. Based on the altered vascularity of psoriasis, studies have re-

ported anti-VEGF therapy (using bevacizumab for oncologic reasons), which can alleviate psoriasis [69]. Therefore, inhibition of angiogenesis may be a promising treatment for psoriasis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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