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The Role of Angiogenesis in the Pathogenesis of Psoriasis: Mechanisms and Clinical Implications

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Abstract

Psoriasis is a complex multisystemic skin disease characterized by the recurrent apparition of erythematous plaques often covered by silvery scales. In recent years, the importance attributed to angiogenesis in psoriasis by the scientific community has grown significantly. The vascular network found within these lesions is highly altered, especially in the papillary dermis which is infiltrated by a large number of tortuous and dilated capillaries. Also, endothelial cells composing these vessels are activated and express many adhesion molecules promoting leukocyte recruitment (ICAM-1, VCAM-1, Thy-1, E- and P-selectin). Thus, this pathological angiogenesis is not a mere consequence of the disease, but a key component promoting leukocyte accumulation, inflammation and therefore, skin lesions. This review presents the current understanding and the clinical implications of angiogenesis in psoriasis. Psoriatic skin cells, particularly keratinocytes, promote the expansion of the vascular network through the secretion of pro-angiogenic factors such as VEGF and angiopoietins. Moreover, pro-inflammatory cytokines such as TNF-α, which exert pro-angiogenic action as well as activation of endothelial cells, also contribute to this process. It was demonstrated by *in vivo* models that angiogenesis, activation of vascular endothelium, inflammation and skin lesions are all closely related in psoriasis. Indeed, angiogenesis promoted by VEGF-secreting keratinocytes leads to local inflammation and skin lesions mimicking psoriasis. From a clinical perspective, most psoriatic treatments have direct, or at least indirect, anti-angiogenic impact, suggesting that their clinical efficacy might be partly explained by these properties. Altogether, these findings identify angiogenesis and the activation of endothelial cells as novel pharmacological targets against psoriasis.

Keywords: Angiogenesis; Psoriasis; VEGF, Skin; Endothelial cells

Abbrevations: Ang: Angiopoietins; EGF: Epidermal Growth Factor; HIF: Hypoxia-Inducible Factors; ICAM-1: Intercellular Adhesion Molecule-1; IFN-Γ: Interferon-Γ; IL-1β: Interleukin-1β; NOS: Nitric Oxide Synthases; Nuvb: Narrowband Ultraviolet B; PASI: Psoriasis Area and Severity Index; PEDF: Pigment Epithelium-Derived Factor; PMN: Polymorphonuclear Leukocytes; PUVA: Psoralen–Ultraviolet A; TGF-B1: Transforming Growth Factor- B1; TNF-A: Tumor Necrosis Factor- A; VCAM-1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor

Introduction

Psoriasis is a complex immune-mediated chronic skin disease affecting approximately 2% of the worldwide population [1]. This disease is characterized by the recurrent apparition of erythematous plaques often covered by silvery scales. These lesions have several histological hallmarks, including epidermal hyperplasia, infiltration of leukocytes and a highly developed vascular network composed of dilated and prominent blood vessels [2]. There have been major advances in our understanding of psoriasis pathogenesis in recent years, particularly surrounding the immunological and genetic components [3].

A complex interplay between cells from the skin and the immune system leads to chronic inflammation within the skin [4,5]. The undeniable importance of an abnormal T lymphocytes CD4+ activity within skin lesions was demonstrated by several murine models, as well as the mechanisms of action for several treatments like cyclosporine [6-8]. The formation and perpetuation of psoriatic plaques result from an imbalance between pro-inflammatory mediators that promote the infiltration of leukocytes and the proliferation of keratinocytes. Moreover, links between genetic predisposition and the inflammatory activity in this disease are becoming clearer as many susceptibility loci identified concern either T cell's activation or differentiation [1].

On the other hand, vascular alterations observed in lesions are now considered to be an important feature of the disease. Indeed, they would not only be a consequence of the disease, but in fact a key component as it would promote skin inflammation through recruitment of leukocytes. An increased angiogenesis caused by psoriatic skin cells and the activation of endothelial cells through pro-inflammatory cytokines therefore form the bridge between the altered epidermis and the immunological component of the disease. This review presents evidences of both the importance of angiogenesis in the pathogenesis of psoriasis and its clinical implications.

Vascular Alterations

The size of capillaries within psoriatic lesions has been demonstrated to be higher than in normal skin or even uninvolved psoriatic skin [9,10]. Many studies confirm that those capillaries are wide, dilated, tortuous and leaky [9,10]. These alterations would be more important within the papillary dermis than the upper reticular dermis [11]. Whether these vascular alterations precede or succeed epidermal alterations is unclear because contradictory results were published [12,13]. However, such alterations are an early event resulting from the expansion of the existing blood vessels, not from sprouting angiogenesis [10,14].

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Angiogenesis in psoriasis

Angiogenesis in psoriasis is caused by high local concentration of vascular endothelial growth factor (VEGF), the $VEFG_{121}$ isoform being predominant [14-16]. Surprisingly, this isoform is also found in higher concentration within uninvolved skin, as compared to skin from healthy donors [17]. Interestingly, this particular isoform has a lower mitogenic potency on endothelial cells than other isoforms like $VEGF_{165}$ [18]. Also, $VEGF_{121}$ causes an extensive vasodilation and increased permeability of existing vessels, but not the sprouting of new vessels [19]. Both these descriptions correspond to the observations made of blood vessels within psoriatic lesions, supporting the finding that $VEGF_{121}$ is the predominant isoform, and might be the main promoter of angiogenesis in psoriatic scales.

The source of VEGF in psoriatic lesions is keratinocytes [15]. A wide variety of factors contribute to this pathologically increased secretion by keratinocytes, from genetic predispositions to pro-inflammatory cytokines secreted by leukocytes. For instance, genetic studies have associated several VEGF SNPs to early-onset psoriasis [−2578(C/A), −460(C/T) and +405(C/G)] [20, 21]. Young *et al*. found that the production of VEGF by peripheral blood mononuclear cells depended on the genotype, whereas production by keratinocytes did not [22]. Aside from genetic predispositions, many factors found in high concentration within scales, such as epidermal growth factor (EGF), transforming growth factor- β1 (TGF-β1) and tumor necrosis factor- α (TNF-α), contribute to the high concentration of VEGF by promoting its secretion [23]. Up regulation of VEGF by pro-inflammatory cytokines could explain the expansion of the vascular network following the injection of activated immunocytes within the skin of xenotransplantation animal model (severe combined immunodeficient mouse: human skin chimeric) [24]. More recently, it was found that the vasoactive intestinal peptide can stimulate VEGF production by keratinocytes, and that this capacity is enhanced by pro-inflammatory cytokines found in psoriasis, such as TNF-α and interferon-γ (IFN-γ) [25]. This is particularly interesting considering that these cytokines are key components in the inflammatory reaction occurring within scales, and also considering the growing importance attributed to neuropeptides in the pathogenesis of psoriasis [26]. Indeed, the promotion of VEGF secretion, and thus angiogenesis, would be linking both neuronal contribution and pro-inflammatory cytokines together, making angiogenesis a central process in the disease.

To investigate the role of VEGF overexpression by keratinocytes, Detmar et al. developed a transgenic mice model in which basal epidermal keratinocytes express constitutively VEGF (K14-VEGF transgenic mice) [27]. They observed an extended vascular network, as well as increased rolling and adherence of leukocytes on endothelial cells. These mice developed an inflammatory skin condition mimicking psoriasis both by its phenotype and the immunological mediators secreted [28,29]. This model gave several important insights into the role of angiogenesis in the disease, and also potential mechanism causing it. Indeed, secretion of VEGF by keratinocytes was enough to significantly alter angiogenesis in skin. Moreover, it resulted in the activation of endothelial cells, leading to persistent inflammation within the skin. Considering the high similitude between inflammations within this transgenic model and the one observed in psoriasis, the overexpression of VEGF by keratinocytes probably has a cornerstone function in the disease. Identifying the mechanisms responsible for VEGF secretion in psoriatic scales is therefore crucial.

Even though VEGF has been demonstrated to be important in the pathological angiogenesis observed in psoriasis, several other less studied factors also seem to contribute significantly: angiopoietins, hypoxia-inducible factors (HIF-1α, -2α, et -3α) and nitric oxide synthases (iNOS, eNOS and nNOS) [23,30,31]. Recently, polymorphisms of eNOS have been associated with psoriasis, although other independent studies are necessary to confirm this finding [32].

The overexpression of Tie2 in involved psoriatic skin, a receptor for angiopoietins Ang-1 and -2, led to the conception of an interesting transgenic mice model led to the conception of an interesting transgenic mice model [33]. These mice, which have both endothelial cells and keratinocytes expressing Tie2, develop psoriasis-like lesions that were characterized by hypervascularization, epidermal hyperplasia and leukocytes accumulation [33]. More importantly, these pathological features could be partially reversed by treating the mice with cyclosporine, an immunosuppressive drug used against psoriasis. It was later demonstrated that the overexpression of Tie2 by keratinocytes, not by endothelial cells, is responsible for the apparition of the psoriasis-like lesions [34]. This is somewhat surprising because the expression of Tie2 by either endothelial cell or keratinocytes resulted in increased angiogenesis, but lesions were only present when keratinocytes expressed Tie2. Another difference between the two is that only keratinocyte-Tie2 mice had an increased level of VEGF, once again suggesting that VEGF is a cornerstone in the pathogenesis of psoriasis. Regarding the inflammatory reaction occurring in these mice, it was found that the secretion of several Th-1 and -17 cytokines implicated in psoriasis immunogenesis was increased in this model, and they were once again downregulated following cyclosporine treatment.

Endothelial cells contribution to inflammation

Endothelial cells plays an essential role in skin inflammation, which is the recruitment of leukocytes [35]. Indeed, the expression of adhesion molecules and the secretion of chemokines by activated endothelial cells is a crucial step required for leukocyte migration towards inflammation sites [35]. As presented in table 1, many adhesion molecules involved in this process are overexpressed by endothelial cells within psoriatic lesions: intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), Thy-1, E- and P-selectin [36-40].

	Functions	Main ligands	References
ICAM-1 (CD54)	Leukocyte adhesion, facilitates leukocyte transmigration	LFA-1 and Mac-1	[36, 64, 80-82]
VCAM-1 (CD106)	Leukocyte adhesion	VLA-4	[36, 80, 83]
Thy-1 (CD90)	Leukocyte adhesion, secretion of IL-8 and MMP-9 by neutrophils	Mac-1	[40]
E-selectin (CD62E)	Rolling of leukocytes on blood vessels	Sialyl Lewis^A and Sialyl Lewis^X	[36, 38, 82, 83]
P-selectin (CD62P)	Rolling of leukocytes on blood vessels	PSGL-1	[36]

Table 1: Adhesion molecules expressed by endothelial cells in psoriasis

The expression of most of these molecules can be induced through the activation of endothelial cells by various pro-inflammatory cytokines such as TNF-α, however the exact mechanisms involved in psoriasis are not fully known [36].

An interesting example is Thy-1 (CD90), a counterreceptor of Mac-1 expressed by polymorphonuclear leukocytes (PMN) [41]. Its expression is up regulated by interleukin-1β (IL-1β) and TNF-α, both of which are overproduced in psoriasis [42-44]. Thy-1 is over expressed by dermal endothelial cells of psoriatic scales [40]. Interestingly, psoriatic PMNs also have a higher adhesion to Thy-1 than healthy PMNs. Although ICAM-1 is also a counter receptor of Mac-1, this increased adherence is specific to Thy-1. Following binding of Thy-1/Mac-1, neutrophils secrete IL-8 and MMP-9, thus attracting even more PMNs and allowing extracellular matrix degradation to facilitate their migration within tissue [45]. These studies suggest that the binding of Mac-1 to Thy-1 facilitates PMNs migration to skin lesions, therefore this binding could be very important in psoriasis.

Clinical significance of angiogenesis in psoriasis

Skin vascular parameters can be assessed *in vivo* by non-invasive techniques [23]. Some researchers have therefore sought to demonstrate the correlation between hypervascularization and the patient`s state of disease. For instance, Rosina *et al.* observed a significant reduction of capillaries per mm^2 and a reduction in their diameter following 30 days of treatment with topical calcipotriol and betamethasone dipropionate [46]. Those vascular parameters correlated with psoriasis area and severity index (PASI) score.

VEGF could also be a biomarker of the disease. Indeed, VEGF was found in higher concentration in serum of psoriatic patients in comparison to healthy patients [47,48]. There is a correlation between VEGF concentrations and PASI scores both before and after treatments with psoralen–ultraviolet A (PUVA) and acitretin [47]. Topical treatments for 14 days with 5% salicyl ointment for desquamation and then with 0.3% dithranol ointment also reduced VEGF concentrations in psoriatic patients [48]. These treatments having a positive impact on dermis microcirculation within scales are not an exception. In fact, most psoriatic treatments have demonstrated influence on the vascular network.

Anti-psoriatic drugs improving vascular alterations

Most clinically used treatments for psoriasis have anti-angiogenic proprieties, even though they do not target it specifically. The table 2 presents psoriatic treatments with such proprieties. A very good example is anti-TNF-α treatments, which were a major breakthrough in the clinical management of psoriasis. TNF-α is a pro-inflammatory cytokine of major importance in the pathogenesis of psoriasis. It has pleiotropic effects on a vast number of cells, including the promotion of angiogenesis [49]. It also has a role in the induction of adhesion molecules in psoriasis, as discussed earlier [36]. Therefore, anti-TNF-α could have anti-angiogenic proprieties in psoriatic patients, which could partly explain their clinical efficacy.

It was demonstrated in a small prospective study that infliximab therapy in combination with methotrexate had impact on the vascular network of skin [50]. The authors found a reduced number of blood vessels in the dermis. Also, the expressions of several adhesion molecules within involved skin (ICAM-1, VCAM-1 and E-selectin) were reduced after 4 weeks of treatment. Several studies were able to associate Tie2 receptor and angiopoietins to TNF-α-induced angiogenesis in other related pathologies such as rheumatoid arthritis [51,52]. Markham et al. were able to demonstrate that patients treated with infliximab have a reduced expression of Ang1 and Tie2 [53]. Moreover, immunohistochemical staining revealed lower presence of Ang2, VEGF, Tie2 and TNF-α within scales after 12 weeks of treatment. Similar studies regarding the impact of etanercept on microcirculation of psoriatic were also conducted [54,55]. It was found to decrease angiogenesis and promote the regression of already altered networks. Altogether, these studies demonstrate the importance of TNF-α in the pathological angiogenesis occurring in psoriasis, and suggest clinical efficacy of anti-TNF-α drugs might be linked to the regression of the vascular network.

Leukocytes accumulated within scales, which are crucial in the pathogenesis of psoriasis, necessarily transited through blood vessel walls. Therefore, leukocytes recruitment by adhesion molecules is an early event in the formation of lesions, making it an attractive pharmacological target. Efalizumab, a recombinant humanized monoclonal antibody that binds to CD11a, thus blocking LFA-1/ICAM-1 interaction, was used to treat psoriasis (withdrawn from the market in 2009 for serious side effects) [56]. Its clinical efficacy demonstrated the therapeutic potential of a pharmacological strategy targeting the inhibition of leukocytes recruitments, although its efficacy can also be partly explained by the inhibition of T cells interaction with dendritic cells [1]. Another way to achieve this pharmacological goal would be to suppress the expression of adhesion molecules by endothelial cells. A better understanding of the mechanisms promoting these expressions by endothelial cells in psoriasis is necessary, although TNF-α seems very important in this process. As mentioned before, this could also contribute to the clinical efficacy of anti-TNF-α agents [57].

The expression of VEGF by keratinocytes in monoculture is downregulated by retinoid, suggesting a similar action *in vivo* [58]. Furthermore, it was demonstrated in a pharmacogenomic study that the −460(C/T) polymorphism of VEGF have predicting values for treatment with acitretin [22]. It means that the clinical efficacy of acitretin is at least partly due to its inhibiting activity on VEGF expression, because VEGF polymorphisms could not affect acitretin efficacy if that was not the case. These findings support that VEGF and angiogenesis contribute to the psoriasis pathogenesis and have a potential as a pharmacological target.

Vitamin D3 analogues also have recognized anti-angiogenic effect. Indeed, they would have an antiproliferative activity on endothelial cells, although they would be more potent to inhibit it on tumor-derived cells [59]. Also, they inhibit VEGF-induced angiogenesis *in vitro* and have a demonstrated anti-angiogenic effect *in vivo* [60, 61]. Most of these studies focus on oncology, but considering the importance of angiogenesis (and VEGF-induced angiogenesis) in psoriasis, it is likely that topical vitamin D analogues exert this effect on lesions too, and that it contributes to their efficacy.

Methotrexate was first used for its effects on keratinocytes such as inducing cellular differentiation *in vitro* [62]. Low dose methotrexate also exerts anti-proliferative effects on endothelial cells [63]. It was later suggested that the efficacy of low dose methotrexate resided in its anti-inflammatory action on T lymphocytes. This hypothesis remains, but the mechanism explaining this effect is very pertinent to this review. Indeed, methotrexate inhibits the expression of adhesion molecules by both T lymphocytes and endothelial cells [64-66]. It demonstrates that although angiogenesis by itself is important, the expression of adhesion molecules by endothelial cells is a crucial step in the recruitment of leukocytes, and therefore the perpetuation of the skin inflammation.

The immunosuppressive action of cyclosporine is also believed

Treatment	Main mechanisms of action	Vascular impact	References
Anti-TNF-α (infliximab, etanercept and adalimumab)	Bind soluble TNF-α (immunosuppressant)	Inhibit TNF-α induced angiogenesis and the expression of adhesion molecules	[36, 49, 50, 53]
Anti-CD11a (efalizumab)	Block LFA-1 (inhibition of T cell activation by dendritic cells)	Block leukocyte adherence to endothelium *via* ICAM-1	[1, 56]
Retinoids (acitretin)	Retinoic acid receptors agonist (antiproliferative and promotion of epidermal differentiation)	Downregulate VEGF secretion by keratinocytes	[22, 47, 58]
Vitamin D3 analogues (calcitriol, calcipotriol and tacalcitol)	Vitamin D receptor agonist (antiproliferative and promotion of epidermal differentiation)	Inhibit VEGF-induced angiogenesis and has antiproliferative activity on endothelial cells	[59-61]
Methotrexate	Dihydrofolate reductase inhibitor (antiproliferative and immunosuppressant)	Inhibit the expression of adhesion molecules and has antiproliferative activity on endothelial cells	[50, 62-66]
Cyclosporine	Inhibit calcineurin causing a downregulation of IL-2 (immunosuppressant)	Inhibit VEGF-induced angiogenesis	[67, 68]
Phototherapy (PUVA, nUVB)	Damage DNA (antiproliferative and lymphotoxic)	Downregulate VEGF secretion and has antiproliferative activity on endothelial cells	[47, 69, 70]

Table 2: Impact of psoriatic treatment on the vascular endothelium

to yield its clinical efficacy. However, it also has an impact on skin microcirculation of psoriatic lesion [67]. It is interesting to note that in one small scale study, microcirculation parameters and clinical outcomes seem to be closely related. Also, as it was the case for vitamin D analogues, cyclosporine inhibits VEGF-induced angiogensis [68].

Even phototherapy exerts anti-angiogenic effects. *In vitro*, it reduces endothelial cells proliferation and promotes apoptosis [69]. Whether these effects also apply *in vivo* is unclear. However, it was observed in patients that PUVA and narrowband ultraviolet B (nUVB) therapy reduced circulating level of VEGF [70]. Also, as mentioned above, there is a correlation between VEGF concentrations and PASI scores both before and after treatments with PUVA and acitretin [47].

Angiogenesis as a Potential Pharmacological Target against Psoriasis

All these studies cannot demonstrate whether this regression of the vascular network is causing clinical improvement or is only its consequence. This is obviously an important question because pharmacological agents targeting angiogenesis would only be efficient if it can indeed improve clinical outcome. Several animal models suggest it might be a viable target.

Adult mice with an epidermal deletion of both JunB and c-Jun develop psoriasis-like phenotype which includes both skin alterations (e.g. parakeratosis and increased vascularization) and arthritic lesions [71]. Also, the inflammatory infiltrate and the various immune mediators found within lesions are similar to those observed in psoriasis lesions. Schonthaler *et al.* demonstrated the efficacy of anti-VEGF antibody in reducing symptoms in these mice [72].

Topical treatments targeting angiogenesis might also be a viable option. This was demonstrated using a mice xenotransplantation model to which a small peptide mimicking pigment epithelium-derived factor (PEDF) was applied topically or injected within the dermis [73]. Analysis revealed a reduction in angiogenesis and reduction of the epidermis thickness.

More recently, it has been demonstrated in xenotransplantation models and transgenic mice with epidermal expression of TGF-β1 (K5. TGF-β1) that antiangiogenic non-viral somatic gene therapy could reduce clinical scores of the disease in those models [74]. The K5.TGF-β1 transgenic mice model is complex since TGF-β1 is a cytokine having pleiotropic effects on a vast number of cells, including cell proliferation and inflammation [75,76]. However, because antiangiogenic gene therapy is successful, it demonstrates that increased angiogenesis is a key component in this model. Considering that the vascular component also seems to be affected in Sano et al. K5.Stat3C transgenic mice, it would be interesting to investigate whether the gene therapy could also control the lesion's apparition in this model [77].

In humans, there have been case reports of clinical improvement following anti-VEGF treatment, but those remain anecdotal [78,79]. Clinical studies are rather limited and so far, these have had poor clinical outcomes, or at least the results did not reach the expectations [23]. Further research might be necessary to truly assess the potential of these treatments. The review of clinical efficacy of such therapy outscopes this article. However, even if these treatments are inefficient, one has to remember that multitherapies are not as frequent in psoriasis as opposed to many other chronic pathologies (e.g. diabetes and hypertension). As discussed above, current drugs used for psoriasis have pleiotropic effects affecting proliferation in the dermis, T cell activity and angiogenesis. These effects could be synergic and result in drug efficacy. It is possible that angiogenesis as a single target might not be enough, and therefore drug combinations might be necessary, or new anti-angiogenic drugs developed against psoriasis should also exert multisystemic effects. Also, the growing understanding of the mechanisms underlying angiogenesis associated with psoriasis should provide new pharmacological targets, giving significant hope that anti-angiogenic treatment might be further developed in the near future.

Conclusion

Angiogenesis is both an important feature of psoriasis and a key component in its pathogenesis. The mechanisms responsible for it are complex and involve secretion by keratinocytes, leukocytes and possibly even neurons. Therefore, angiogenesis is a cornerstone of the disease affected by both the abnormal skin and the inflammation. Moreover, endothelial cells contribute significantly to inflammation by expressing adhesion molecules responsible for leukocytes recruitment. Animal models demonstrate how altered vascularization can lead to skin inflammation and lesions.

Interestingly, many treatments not specifically targeting angiogenesis have an important impact on the vascular network in psoriatic scales. Whether this effect contributes to the clinical efficacy of these treatments or it is only a consequence of lesions going into remission is unclear. However, it does demonstrate the tight relationship between the vascular component of the disease and the clinical symptoms of patients. Therefore, angiogenesis is viewed as

a potential new pharmacological target for psoriasis. Although anti-angiogenic agents in clinical studies have had only limited success so far, animal studies have given promising results. Further development in this area might lead to new treatment which could be complementary to drugs directly targeting inflammation.

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