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VEGF INVOLVEMENT IN PSORIASIS

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Abstract

Vascular endothelial growth factor (VEGF) is a key growth factor, regulating the neovascularization, during embryogenesis, skeletal growth, reproductive functions and pathological processes. The VEGF receptors (VEGFR) are present in endothelial cells and other cell types, such as vascular smooth muscle cells, hematopoietic stem cells, monocytes, neurons, macrophages, and platelets.

Angiogenesis is initiated by the activation of vascular endothelial cells through several factors. The excess dermal vascularity and VEGF production are markers of psoriasis.

The pathological role of VEGF/VEGFR signaling during the psoriasis onset and evolution makes it a promising target for the treatment of psoriasis. Antibodies and other types of molecules targeting the VEGF pathway are currently evaluated in arresting the evolution of psoriasis.

Keywords: VEGF, VEGFR, psoriasis

VEGF signaling and expression

Vascular endothelial growth factor (VEGF) is a 40–45 kDa dimeric glycoprotein containing a cysteine knot motif [1,2]. The superfamily of VEGF proteins in mammals contains 5 types: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PLGF) [3,4]. The VEGF-A is the main component of the VEGF family and usually referred to VEGF. The human VEGF gene is located on chromosome 6p21.3 [4].

There are three receptors for VEGF: VEGFR-1, VEGFR-2 [5] and VEGFR-3 [6]; all are tyrosine kinase receptors (RTKs), with high affinity. Neuropilins (NRPs, NRP-1 and NRP-2) are transmembrane receptors with non-tyrosine kinase activity, specific marker for ECs, which present also high-affinity in binding VEGF [6,7].

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VEGFR-1 is essential for the recruitment of hematopoietic precursors and migration of monocytes, while VEGFR-2 and VEGFR-3 regulate VEGF-induced angiogenesis and lymphangiogenesis, respectively [2,8]. The NRP-1 and NRP-2 could enhance the activities of VEGFR-2, but also signal independently [3]. VEGFR-1 and VEGFR-2 may link with NRP-1/2, and NRP-2 could bind VEGF-C or co-express with VEGFR-3 [9,10,11].

VEGFR-1 and -2 are activated by VEGF binding and differ considerably in signaling properties [12,13]. There are also non-signaling co-receptors which modulate VEGF RTKs signaling [3]. VEGFR-1 acts during embryogenesis for normal blood vessel development, VEGFR-2 determines the proliferation and the migration of ECs as well as the increased vascular permeability [3,7,14]. Making more complex the situation, there are isoforms of VEGF-A which presents either a pro- or an anti-angiogenic effect [15].

Initially considered to target specifically the ECs,

now it is proved that VEGF acts on many stromal cells [16]. Except VEGFR-3 confined to lymphatic endothelial cells, VEGFR-1 and VEGFR-2 are also present on various cell types such as vascular smooth muscle cells [17,18], hematopoietic stem cells [14], monocytes [19], neurons [20], macrophages [21], and platelets [22], but do not have significant levels in endocrine cells [23].

All layers of the epidermis are positive for VEGFRs and NRPs, except for the most superficial stratum corneum [19,24]. The basal keratinocytes and the keratinocytes in the lower stratum spinosum express on their cytoplasmic membrane VEGFR-1 and VEGFR-2 [25]. Also VEGFR-3 and the neuropilins NRP-1 and NRP-2 are expressed in a uniform pattern in all epidermic layers, except the stratum corneum [6]. When pretreated with VEGFR-2 neutralizing antibody [6], keratinocytes in cell culture showed enhanced proliferation and migration due to secondary treatment with different VEGF concentrations. These data support the idea that VEGFR and NRP expression on the keratinocytes membrane surface may regulate the activity and epidermic cell signaling in an autocrine manner [6,19,26].

VEGF and VEGFR-2 were also detected in epidermal appendages: hair follicle, sebaceous glands, and eccrine sweat glands [27]. An elevated VEGF expression on follicular keratinocytes was correlated with angiogenesis during hair growth cycle [28]. Besides, VEGF-induced follicular cell proliferation is mainly mediated by VEGFR-2 expressed on hair follicle outer root sheath cells and dermal papilla cells [29,30].

VEGF involvement in psoriasis

Psoriasis is a chronic inflammatory disease, which affects skin and small joints. It has an autoimmune mechanism, the autoantigen was not even determined. It can affect 2–4% of the population of Caucasian origin [31]. Most of the patients present psoriatic lesions on scalp, elbows and knees [32].

Histopathological markers of skin in psoriasis include: the infiltration of multiple immune cells, keratinocyte hyperplasia, activated mast cells, and accentuated vascularity in the dermis [5,33]. Psoriasis is also commonly associated with a prominent permeability barrier abnormality, and excess VEGF production [32].

One of pathogenetic mechanisms in psoriasis is represented by the VEGF-induced angiogenesis. The psoriatic patients have high serum levels of VEGF and endothelial cell stimulating angiogenesis factor (ESAF) and the psoriatic severity is correlated with the VEGF serum levels [34,35,36]. Other facts that support the VEGF role in psoriasis are the strong correlation between the polymorphisms of a single nucleotide of the VEGF gene and the psoriasis pathogenesis [37,38] and the overexpression of VEGFR-1/2/3 in the epidermis of psoriatic patients [39]. Moreover, VEGFRs were strongly labeled in non-lesional, perilesional, and lesional psoriatic keratinocytes in all epidermal strata *in vivo*.

The balance between pro- and anti-angiogenic factors regulates the genesis of new blood vessels. The physiologically neovascularization occurs transiently, for example in wound healing or pregnancy. In pathological processes such as tumor growth or chronic inflammation angiogenesis facilitates the disease progress [40,41].

Several factors with pro-angiogenic effect are expressed at high levels in the psoriatic skin: TNF, TGF-α, VEGF, ESAF, hypoxia inducible factor (HIF), interleukin (IL)-8, IL-17 and angiopoietins [34,40,42]. Combined action of these factors stimulate ECs from dermis to form new blood vessels [43]. The interactions between the pro-angiogenic mediators are very complex; for example, TNF has pro- and anti-angiogenic actions, through inducing others pro-angiogenic factors in ECs, such as basic fibroblast growth factor (bFGF), IL-8 and VEGF [44].

There is a vicious circle: the angiogenic factors bFGF and VEGF activate the ECs, which proliferate and migrate, forming a lumen [45,46], but, at the same time, the extracellular matrix (ECM) is degraded and releases these stored stimulating factors for angiogenesis [5], closing the circle.

The overexpression of VEGF in the skin biopsies of psoriasis patients [43] represents an argument for the important role of VEGF in maintaining the normal functioning of epidermis barrier [47] and for a link existing between epidermal VEGF and keratinocytes hyperplasia. Therefore, it may be sustained that VEGF is involved in keratinocyte proliferation [6,47]. It has been shown by Detmar et al. (1994) that VEGF stimulates *in vitro* the mitotic activity of keratinocytes and upregulates in both ECs and keratinocytes the VEGFR-1 and VEGFR-2 expression [48]. VEGFR-1 and -2 are detectable in skin lesions of psoriatic patients [6]. Thus, because VEGF increases the expression of VEGFR in keratinocytes and the keratinocytes regulate the VEGF expression, we can support the idea that VEGF has an autocrine action on keratinocyte proliferation [49,50].

Only the epidermal barrier disruption alone does not suffice to produce psoriasis. Other dysfunctions in the immune system contribute to establishing the full psoriatic phenotype [49,50]. There is also a perpetuation of the inflammation process in psoriasis [43]: VEGF increases the expression of cell adhesion molecules from capillaries in formation and increase vessel permeability, thereby favoring the leukocytes migration into the psoriatic skin [51]; this process leads to increased oxygen consumption, activation of hypoxia-induced angiogenic transcription factors such as HIF-1, and perpetuation of this angiogenic/inflammatory cycle of psoriasis [43].

VEGF induces several biological effects on ECs: gene expression, survival, proliferation, migration, nitric oxide (NO) and prostacyclin (PGI2) production, increased permeability, tubulogenesis [52,53]. The important

integration between signaling cascades occurs at several points [52]. NO and prostanoids link the post-receptor signaling to biological functions, playing therefore paracrine and autocrine roles [52]. The keratinocyte's VEGF production is upregulated by oxidized phospholipids, which stimulate angiogenesis via autocrine mechanisms involving VEGF, IL-8, and COX-2-generated prostanoids [54]. VEGF alone does not activate endothelium to induce cell adhesion molecules expression; VEGF "sensitizes" ECs to cytokines, increasing selective pro-inflammatory responses [55]. The autocrine/paracrine cycle contributes to psoriatic angiogenesis and epidermal hyperplasia [56]. In genetically modified mice, the overexpression of VEGF can produce a psoriasiform phenotype, with acanthosis, parakeratosis, subepidermal inflammatory infiltrate, tortuous and dilated dermal capillaries, and epidermal microabscesses [56].

There is also an involvement of TNF-α in psoriatic angiogenesis [57]. TNF-α up-regulates the genetic transcription of VEGF [48,58] and increase keratinocyte's production of pro-inflammatory cytokines, such as IL-8 [59]. Also, it has been proved that TNF-α inhibitors improve endothelial dysfunction [60] and, in the psoriatic plaque, down-regulate levels of many inflammatory cytokines, including angiopoietins and their receptor [61].

Others cells with potential involvement in psoriasis are the mast cells, which can also produce angiogenesis factors (bFGF, VEGF, IL-8) [33,62]. Mast cells are numerous in the dermis (about 7,000/mm^3) and nearby small skin vessels. T cell - mast cell interactions determine degranulation of mast cells [63], but also a cytokine production [64], thus the mast cells are regulating the attraction of polymorphonuclear leukocytes into inflammation sites, in response to infiltrating T1 cells, which plays a central role in the pathogenesis of psoriasis [33].

Recentl findings on T-cell populations (Th17 and regulatory T cells), dendritic cells, macrophages, keratinocyte signal transduction, novel cytokines (IL-22, IL-23, IL-20) suggest that psoriasis pathogenesis consists of distinct stages, each with a specific cell as dominant [50].

VEGF as a pharmacological target in psoriasis

The current therapies for psoriasis have two target points: the immune response and the inhibition of neoangiogenesis factors [32]. Patients with history of malignancies might benefit more from a primarily anti-angiogenic approach [65].

Several VEGF inhibitors were clinically tested in several malignancies as a strategy for the prevention of angiogenesis and vascular leakage [3]. Pharmacological blockade of VEGF signaling to inhibit tumor angiogenesis is clinically approved but the survival benefit is limited as patients invariably acquire resistance [16].

Increasing experimental data have shown the effectiveness of anti-VEGF therapy for the treatment of psoriasis; this therapy can reverse a psoriasis-like skin phenotype. The antibody G6-31, which is potently against human and murine VEGF, demonstrated a therapeutic effect in a mouse model which had psoriasis-like skin inflammation [66].

Bevacizumab, a monoclonal antibody against VEGF, used in the treatment of solid cancers (breast, colorectal, renal cell carcinoma) [67,68] is effective also for psoriasis, which validates the consensus that VEGF signaling plays a crucial role during the pathogenesis of psoriasis [69,70]. Akman *et al*. (2009) described a patient with complete remission of psoriasis under bevacizumab therapy for metastatic colon cancer [70].

Other types of molecules have been developed to target the VEGF pathway including monoclonal antibodies and small molecule inhibitors against VEGFRs. Ramucirumab, a human IgG1 monoclonal antibody (MAb) targeting VEGFR-2, exhibits effectiveness at eliciting tumor responses [71]. Tanibirumab is another fully human IgG1 MAb and demonstrates successful blocking of VEGF in preclinical studies [72].

The inhibitors of VEGFR, used in cancer patients, may also have positive clinical effects in some psoriatic patients, but are recommended to be used in topical forms to limit the toxicities [73]. At present the following are evaluated for psoriatic ameliorating effects: Sunitinib [73], which inhibits VEGFR-2, platelet derived growth factor receptor (PDGFR) and fibroblast growth factor receptor [74,75] and Pazopanib, which inhibits VEGFR-1, -2, -3, and PDGFR [76].

In transgenic mice treated with Aflibercept (VEGF-inhibitor, a soluble chimeric decoy receptor for VEGF), the epidermal structure was restored and blood vessels number was reduced [56].

Retinoids, commonly used as systemic therapy in psoriasis, can stop the VEGF production. The all-trans retinoic acid (RA) produces the inhibition of VEGF keratinocytes' production in a genotype-dependent manner [38].

Conclusions

VEGF has an important role in initiating the psoriasis phenotype. The pathological role of VEGF/VEGFR signaling during the psoriasis onset and evolution makes it a promising target for the psoriasis treatment.

Angiogenesis is a central process in the evolution of psoriasis, but it is still under evaluation how effective the anti-angiogenic treatments of psoriasis are.

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