INTRODUCTION

Angiogenesis is the process of de novo formation of blood vessels in an organ or tissue. It has drawn much attention in recent years being one of the most studied scientific topics worldwide. This is due to the fact that about 500 million people on the planet need a therapeutic correction of wide range of pathological processes associated with angiogenesis [1]. Angiogenesis involves the formation of new blood capillaries from pre-existing vessels, formed in an earlier stage of vasculogenesis, and the organization of these new capillaries into the vascular network. The growth of the vasculature continues by continuous sprouting and splitting [2]. Under physiological conditions, angiogenesis plays essential role in the development and growth of tissue, wound healing, and menstrual cycle in women [3]. Pathological angiogenesis is a crucial incident in the transformation of benign tumors into malignant ones. It also plays a key role in tumor metastasis, atherosclerosis, diabetic retinopathy, endometriosis, and proliferative skin diseases. In ischemic conditions such as myocardial infarction and cerebral stroke, the growth rate of new blood vessels is imperfect [4].

Vascular endothelial growth factor (VEGF) is an extremely specific mitogen for vascular epithelial cells and for micro- and macrovascular cells of lymph vessels. Its normal function is to stimulate both vasculogenesis (the de novo formation of the vascular system during embryonic development) and angiogenesis (the growth of new blood vessels...
from pre-existing vasculature) after tissue injury, muscular exercise, and to form new collateral circulation to bypass impeded vessels. It has a strong effect on permeability of blood vessels and is a powerful angiogenic protein in various neovascularization processes in pathological conditions [5]. Recent research has shed light on VEGF as an important modulator of skin function in both health and disease [6-7]. In many skin disorders such as atopic dermatitis, allergic contact dermatitis, psoriasis, phototoxicity and epidermal barrier dysfunction, dysregulated differentiation/proliferation and impaired intercellular communication in keratinocytes are observed [8]. Therefore, there have been exhaustive efforts to clarify the pathogenic role of VEGF in alteration of keratinocyte function and implication in skin diseases [9]. In this review we will discuss the implication of VEGF as a pathogenic biomarker in skin diseases by inspecting the available experimental and clinical evidences for the potential of VEGF in some dermatologic disorders.

THE FUNDAMENTAL CHARACTERISTICS OF VEGF

VEGF isoforms

In 1989, Ferrara and Henzel isolated a releasing endothelial cell-specific protein from cultured bovine pituitary follicular cells. They named it “vascular endothelial growth factor” to indicate the target cell specificity of this molecule [10-11]. In 1997, Muller and co-workers [12] later obtained the crystal structure of VEGF at 1.93 Å resolution. Resolution of the crystal structure of VEGF has shown that VEGF is homodimeric glycoprotein that forms an antiparallel homodimer linked covalently by two disulfide bridges (Fig 1). VEGF is produced by various types of cells and existing in at least 5 isoforms with parallel biological activity, but significantly different in bioavailability. It is part of the system that restores tissue oxygenation in hypoxic conditions [13]. To date, the VEGF family includes 5 members, which are VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF (placental growth factor). Fundamentally, all the VEGF members have 8 conserved cysteine residues at constant positions, which are very similar to the PDGF family such as macrophage colony stimulating factor (M-CSF) and stem cell factor (SCF) [14]. The best studied VEGF sub-family member is VEGF-A which can be determined in plasma and serum in detectable amounts. Due to alternative exon splicing, VEGF-A exists in at least 4 isoforms such as VEGF121, VEGF165, VEGF189, and VEGF206 corresponding to their primary amino acid structure [15], with the major isoform of all VEGF types being the VEGF165 variant of VEGF-A having a molecular weight of 45 kD and exerts the most potent biological activity [11]. VEGF-A is involved in many pathological processes associated with increased angiogenesis and/or vascular permeability. Examples where VEGF-A plays an important role are rheumatoid arthritis and inflammatory bowel disease [16]. Diabetic retinopathy is another condition associated with high intraocular levels of VEGF-A [17].

![Fig 1. A top-down view of the VEGF dimeric protein molecule as represented in ribbon model. The two VEGF monomers are shown in blue and red. The termini of both monomers are labeled. (Adapted from: Muller YA, De Vos AM. Vascular endothelial growth factor refined to 1.93 angstroms resolution. PDB ID 2VPF, DOI: 10.2210/pdb2VPF/pdb).](image)

VEGF receptors

VEGF binds to type V tyrosine kinase family of receptors (RTK) with high affinity and selectivity, resulting in intracellular signaling [18]. The VEGFRs are characterized by having extracellular part consisting of 7 domains resembling that of the human immunoglobulin molecules, a single transmembrane spanning region, and an intracellular part containing a split tyrosine-kinase component [18]. They are predominantly expressed on endothelial, hematopoietic, and connective tissue cells [19]. To date, 3 subtypes of VEGFRs are defined, which are VEGFR-1, VEGFR-2, and VEGFR-3 [18]. Different VEGF sub-family members interact with these receptors with variable affinity and selectivity (Fig 2).
Studies have also shown that the neuropilin receptors (NRP-1 and 2) can act also as co-receptors to enhance VEGF signaling by modulating the VEGF-VEGFR interaction [20]. The general mechanistic pathway of VEGFR signaling is analogous to typical RTK signaling of known growth factors, such as PDGF, in regulating cell differentiation, proliferation and migration [21]. VEGFR-1 is thought to play critical roles in the development of embryonic vascular system (vasculogenesis) as a result of its activation by VEGF-A and B. VEGFR-2 is thought to be responsible for mediating a wide array of angiogenic actions such as endothelial proliferation, migration, and microvascular permeability by binding with VEGF-A. VEGFR-3 is predominantly located in lymphatic vascular tree, and promotes lymphangiogenesis by binding with VEGF-C and D [19, 22].

**Role of VEGF in angiogenesis**

The main mechanism regulating the process of angiogenesis is the release of angiogenic factors which activate receptors on endothelial cells present in pre-existing blood vessels. The activated endothelial cells start releasing proteolytic enzymes that degrade the basement membrane to allow endothelial proliferation and migration into the adjacent matrix to form new sprouts connecting the neighboring vessels. The new vascular growth is determined by the balance between stimulating and inhibiting factors (Table 1). With a low ratio of stimulants to inhibitors of vascular formation, angiogenesis is halted or proceeds in slow rate, but at high ratios, angiogenesis is actively triggered [23].

Normally, VEGF is found in tissues in detectable amount. Cells that express this cytokine include macrophages, fibroblasts, lymphocytes, polymorphonuclear leukocytes, osteoblasts, endothelial and smooth muscle cells, mesangial cells of the kidneys, platelets, and keratinocytes [24]. On the other hand, these cells express VEGFRs to recognize and respond to VEGF in a mutual way. The transcription of VEGF mRNA is induced by various growth factors and cytokines including PDGF, EGF, tumor necrosis factor (TNF)-α, TGF-β, IL-1β,
and IGF-II [25]. VEGF level in human serum progressively decreases after birth and remains low in most adult tissues beyond sites of active angiogenesis, such as ovaries, uterus, skin and its appendages [26]. However, VEGF expression is re-induced at times of pathological angiogenesis. In patients with tumors, VEGF can cause significant changes in hemopoiesis and lymphopoiesis at the level of bone marrow and thymus. It is believed that the increased levels of this factor creates the basis for development of immunodeficiency and helps the tumor escape from immune surveillance [27]. Addition of VEGF to rat T lymphocytes that are stimulated by a mitogen or antigen caused an increase in interferon (INF)-γ production and a decrease in IL-10 [28].

Given that VEGF is stress-induced protein, its regulation is influenced by tissue oxygen status; therefore, physiological and pathological angiogenesis can be considered as a regulatory response to oxygen deficiency [29]. There is an activation of metabolic pathways regulated by proteins such as hypoxia-induced factor 1 (HIF-1), which leads to an increase in the expression of pro-angiogenic factors, including VEGF and fibroblast growth factor (FGF) [30]. At the moment when the action of pro-angiogenic factors exceeds the effect of anti-angiogenic factors, endothelial cells pass from the usual dormant state to the active one. Following turning on angiogenesis, degradation of vascular basement membranes and liquefaction of the extracellular matrix by increased activity of matrix metalloproteinase (MMP) facilitate the migration of endothelial cells into the extravascular space, where they begin to multiply and organize to form new capillary network. During this process, pericytes are attracted to the newly formed vessels and stabilize them [2-4].

In this way, VEGF functions in dynamic orchestration with cytokines, their soluble receptors and inhibitors, and proteolytic enzymes to regulate endothelial cell migration and proliferation during angiogenesis.

The importance of VEGF-A for tumor growth was clearly demonstrated by using VEGFR-2 antagonists to block tumor cell proliferation [31]. As a result, interfering with VEGF-A function has become a major interest for the development of drugs aimed at blocking angiogenesis and metastasis. Currently, more than 110 pharmaceutical companies worldwide are developing such antagonists. Their approaches include antibodies against VEGF-A or antagonists to VEGFR-2 [32]. In general, the targeting of VEGF signaling can be of great therapeutic value for many diseases and serve as the basis for the development of future antiangiogenic therapies.

### VEGF EXPRESSION AND SIGNALING PATHWAYS IN KERATINOCYTES

The expression of VEGF in keratinocytes of rodent skin during wound repair was first observed by Brown and co-workers in 1992 [33]. Following this observation, the cellular source of cutaneous VEGF was extensively investigated. Both epidermal keratinocytes and dermal fibroblasts are capable of expression of VEGF, but interestingly, keratinocytes were shown to be the principal source of cutaneous VEGF. In cultured human keratinocytes, significant expression of VEGF was observed after stimulation with serum, EGF, TGF-β1, TNF-α, or IGF [34-35]. It was recently found that epidermal keratinocytes and dermal fibroblasts were able to express the three main VEGF isoforms (VEGF121, VEGF165, and VEGF189) in co-culture. Moreover, these

| Angiogenic stimulators                  | Angiogenic inhibitors                  |
|----------------------------------------|----------------------------------------|
| Vascular endothelial growth factor (VEGF) | Endostatin                              |
| Fibroblast growth factor (FGF)         | Soluble VEGF receptors (sVEGF-R)        |
| Epidermal growth factor (EGF)          | Thrombospondin                          |
| Platelet-derived growth factor (PDGF)  | Angiostatin (plasminogen fragment)      |
| Transforming growth factor-beta (TGF-β) | Vasostatin                              |
| Insulin-like growth factors I and II (IGF-I &II) | MMP inhibitors |
| Interleukin (IL)-1α & IL-8             | Delta-like ligand 4 (DII4)              |
| Non-specific factors such as matrix metalloproteinase (MMP) |
factors were expressed in much higher levels in epidermal keratinocytes than dermal fibroblasts [7]. Cutaneous VEGF serves as a potent and specific mitogen for dermal microvascular endothelial cells and a crucial mediator for increased angiogenesis and vascular permeability during the process of wound repair [36] and hair growth [37]. It has also main contribution in many cutaneous pathological conditions including cutaneous inflammation [38], skin cancer [39] and psoriasis [40].

Various growth factors and cytokines are known to up-regulate VEGF expression in epidermal keratinocytes, including ILs, TGF-α and β, TNF-α, EGF, and PDGF [base, nm]. Contribution of intracellular signaling kinases, including phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) to VEGF synthesis in keratinocytes are also well-documented [41-42]. Transcriptional regulation of VEGF in keratinocytes is also shown to be mediated by transcription factors such as activation protein (AP)-1 and 2, HIF, and nuclear factor kappa-B (NFkB) [43-45]. Additionally, skin exposure to ultraviolet irradiation promotes up-regulation of VEGF expression in keratinocytes either by direct induction of transcriptional pathways or by release of soluble cytokines [46-47].

PATHOLOGICAL ROLE OF VEGF IN SKIN DISEASES

The cellular and molecular mechanisms underlying physiological and pathological angiogenesis are now being extensively studied in the field of dermatology. Recent studies show that VEGF plays key roles in wound healing, psoriasis, contact dermatitis, lichen planus, alopecia, and skin carcinogenesis. Although it is now established that VEGF is significantly expressed in keratinocytes and dermal fibroblasts, it is still debated whether cutaneous VEGF is restorative or exacerbative for abnormal skin conditions.

Psoriasis

Studying the mechanisms of formation of psoriatic plaque, the main morphological feature of the disease, showed the role of dermal vascular changes [48]. They appear earlier than epidermal changes and persist for a longer time after treatment. Moreover, dermal vascular changes are detected in the clinically healthy skin of patients and their first degree [49]. During recovery, only epidermal disorders are normalized while the inflammatory process persists in the dermis, especially in blood vessels. In situ hybridization and immunohistochemistry of skin biopsies from psoriatic patients showed marked up-regulation of VEGF mRNA and protein expression in keratinocytes [50] and increased expression of VEGFR-1 and -2 on endothelial cells of the dermal papillae [51]. It was shown that serum levels of VEGF and the soluble form of VEGFR-1 in patients with conventional psoriasis significantly exceeded the values in the control group and correlated significantly with the Psoriasis Area and Severity Index (PASI) [52]. Additionally, a close correlation was found between the initial values of the PASI index and the concentration of VEGF in the blood serum of patients with exudative psoriasis [40]. Overexpression of VEGF in skin lesions of psoriatic patients showed also a positive correlation with TNFα, MMP-2, and HIF [40]. In the early stages of psoriatic arthritis, the content of VEGF and TGF-β in the synovial fluid is also increased [40]. Studies have documented the possibility of induction of psoriasis under the influence of VEGF and both IGF-I and II, which are powerful autocrine-paracrine regulators of cell growth and differentiation [53].

Recent studies on the dynamics of the progression of the psoriatic process have shown that one of the key factors determining the pathogenesis of this disease is dysregulated angiogenesis [54]. VEGF is recognized as a crucial pro-angiogenic mediator responsible for the de novo formation of blood vessels in psoriatic plaques [40]. The involvement of angiogenesis in the development of psoriasis has been proven with the discovery of gene polymorphism in relation to VEGF. In patients with severe psoriasis, a systemic dysregulation of VEGF was observed due to polymorphic variants of VEGF receptors in activated keratinocytes [55]. Assessment of the state of angiogenesis in children suffering from psoriasis revealed a significant increase in the expression level of VEGF and IGF-I; however, the increase in IGF-II in all age groups was not confirmed [56].

Additional evidence of the pathogenic role of VEGF in psoriasis is provided by the effect of therapy. Treatment of psoriasis with topical steroids leads to significant decrease in the concentration of serum VEGF, especially in patients with severe disease (PASI > 20), and an increase in the concentration of soluble VEGFR-1 in patients with mild disease activity (PASI < 10) [57]. Moreover, the serum levels of
VEGF and MMP-9 in patients with psoriasis vulgaris decreased after 4 weeks of treatment with the cytostatic drugs, methotrexate [58] while therapy of patients with psoriasis according to the Goeckerman method reduced the levels of VEGF and FGF that were significantly high before treatment [59]. Studies have also shown that infliximab has a positive effect by suppressing the VEGF/angiopoietin/Tie-2 signaling pathway [60]. Another evidence of the importance of anti-angiogenic therapy for psoriasis is obtained by studying retinoids that become biologically active as a result of their interaction through one of two ways: interaction with their nuclear receptors (retinoic acid receptors) or with the nuclear transcription factor AP-1. There are four AP-1 binding sites in the promoter region of the VEGF gene; the interaction of retinoids with AP-1 blocks the expression of VEGF, therefore, retinoids have anti-VEGF activity [61]. Taken collectively, targeting VEGF and/or VEGFRs has been recently proposed as a new treatment for psoriasis [62-63], since the use of anti-VEGF antibodies in mouse models of psoriasis has shown relief of the symptoms of the disease [64].

**Lichen planus**

Despite several studies, the exact pathogenesis of lichen planus has not been fully understood [65]. Data in the literature point at involvement of angiogenic process and hypoxia, as well as involvement of inflammatory cells secreting mediators such as TNFα, IL-1, and IGF leading to the induction of VEGF [30, 35, 38]. In such angiogenic dermatoses, overexpression of VEGF mRNA was clearly defined in the upper part of the pricky and granular layers and correlates with the density of microvessels in the papillary dermis [66]. According to the authors, therapy aimed at normalizing the level of VEGF may lead to persistent remission of the disease, especially when the mucous membrane is involved such as oral lichen planus (OLP).

In a study published in 2007, Tao and colleagues investigated the microvascular density and expression of VEGF in patients with OLP, and found that angiogenesis and VEGF expression were closely correlated to the severity of OLP lesions [67]. Similar results were obtained by Scardina and co-workers who reported that 64.2% of OLP samples show significant VEGF expression and considerable neoangiogenesis [68]. Likewise, the serum VEGF level was significantly higher in patients with oral lichen planus compared with the healthy controls [69]. Rhodus and co-workers showed that a panel of pro-angiogenic cytokines, including TNF-α, IL-1, IL-6, and IL-8 are markedly elevated in samples of tissues and oral fluids in patients with OLP [70]. These cytokines can, indeed, lead to overexpression of VEGF and increased VEGF in serum. Taking into consideration the angiogenic abnormalities and the overexpression of angiogenic factors in lichen planus, as occurs in many other inflammatory conditions [71], new therapeutic strategies based on the use of anti-angiogenic medicine could be promising. These medications are already in use for other conditions with chronic inflammatory pathologies and are exhibiting good results [72].

**Inflammatory skin diseases**

Some of the pathological characteristics of inflammation include the infiltration of tissue with acute and chronic inflammatory cells, release of inflammatory mediators and increased vascular permeability. Vascular remodeling is a characteristic feature of chronic inflammatory skin diseases in which angiogenesis and inflammation are closely concomitant [72-73]. Atopic dermatitis is a common, chronic inflammatory skin disease in which, beside immune dysregulation, angiogenesis also plays a key role [74]. Samples from plasma and skin of patients with atopic dermatitis show increased levels of VEGF when compared with control samples [75]. Moreover, the association between polymorphisms of the VEGF/VEGFR genes and atopic dermatitis has been confirmed [76]. Chronic urticaria is another inflammatory condition in which the association with angioedema is present in approximately 40% of patients [77]. Release of histamine and other vasoactive mediators from dermal mast cells causes characteristic skin wheals that are red, raised, and itchy [76]. It has been suggested that VEGF plays a critical role in the increased vascular permeability, edema, and inflammatory cell infiltrates pathognomonic for chronic urticaria [78]. Studies have confirmed the increase of VEGF in plasma and skin samples of patients with chronic urticaria, and these levels are correlated with disease severity [79]. Several cellular types, including mast cells, eosinophils, and basophils contribute to increased levels of VEGF in plasma and skin [79]. Therefore, infiltrating inflammatory cells can play important role in whealing of the skin and tissue edema characteristic of chronic urticaria through the release of
VEGF [78].

**Phototoxicity**

Phototoxicity is a broad term that includes all forms of skin damage induced by ultraviolet (UV) irradiation such as photo-irritation, photo-sensitization, photo-aging, and photo-carcinogenesis. UV irradiation causes generation of reactive oxygen species (ROS) that can induce damage to DNA and cellular macromolecules [80]. UV exposure provokes skin irritation, hyperaemia, hyper-permeability, edema, and angiogenesis, which are closely connected with VEGF. Several studies have shown that UV exposure induces overexpression of VEGF in keratinocytes either directly by activating nuclear transcription factors such as NFκB, AP-1 and AP-2, or indirectly by releasing soluble cytokines such as IL-1 and TNF-α [81-83]. While UVB induced VEGF overexpression in primary human keratinocytes and in premalignant keratinocytes cell line (HaCaT) [82], UVA induced VEGF overexpression only in premalignant keratinocytes cell line [84] suggesting significant contribution of cutaneous VEGF signaling in the premalignant keratinocytes which may promote carcinogenic transformation.

**Hair growth and alopecia**

Impairment of the vascularization of hair follicles plays critical role in the pathogenesis of conditions characterized by increased hair loss [85]. Human hair follicles are constantly involved in a cyclic change of growth and regression, which requires appropriate changes in skin vascularization during the life cycle. In the anagen phase, the requirements of hair follicles for energy substrates are significantly increased, therefore, the size of the perifollicular vessels increases, while in the catagen and telogen phases, the size of vessels decreases [85]. VEGF is one of the principal mediators of hair follicle survival, having a direct effect on their vascularization, as well as various cellular functions, including cell lifespan, proliferation, and the formation of nitric oxide and prostacyclin [37]. In vivo VEGF increases microvascular permeability and angiogenesis, promotes mutual adhesion of keratinocytes of the hair, increases the strength, thickness and density of the hair [37, 85]. In dermal papillae of hair follicles, VEGF stimulates the proliferation of matrix and vascular endothelial cells, and synthesis of extracellular matrix material, thus maintaining the follicles in the anagen state [86]. In addition, VEGF enhances the production of nitric oxide by eNOS synthase and increasing cell permeability for the movement of nutrients [87]. In experimental studies on transgenic mice with increased expression of VEGF in keratinocytes, the cells of the dermal papillae displayed enhanced perifollicular vascularization, accelerated hair restoration after depilation, and growth of longer hair [37]. Conversely, VEGF blockade by the systematic administration of neutralizing VEGF antibodies slows down hair growth and reduces the size of hair follicles [37].

For long time, the endogenous androgen dihydrotestosterone (DHT) has been considered responsible for hair loss during androgenetic alopecia [88]. This hormone binds to follicle receptors and inhibits Bcl-2, which leads to cell apoptosis. It has been shown that VEGF plays a critical role in the prevention of premature apoptosis of hair follicle cells, contributing to the suppression of caspase 9 genes and the interaction of Bcl-2 with the Bax and Bad genes, and also provides protection against hypoxia and oxidative stress; therefore, the anagen phase lasts for longer time [37]. Given the pivotal role of VEGF in hair biology, this growth factor can be an effective method in the treatment of conditions characterized by impaired hair growth and miniaturization of hair follicles. Studies have shown that the effectiveness of minoxidil in treatment of hair loss is attributed, at least partially, to its promoting effect on VEGF synthesis and release [89]. It was found that minoxidil activates the expression of VEGF in the cells of the dermal papillae in the anagen phase ensuring sufficient follicular vascularization [90]. In the cells of skin papillae isolated from the hair follicle of the scalp, the addition of minoxidil led to increased expression of VEGF mRNA.

Diphenylcyclopropenone (diphencyprone) is a topically administered experimental drug intended for treating alopecia areata and alopecia totalis [91]. Recent studies have shown that this drug normalizes the ratio of CD4/CD8 cells in the skin that were dysregulated in patients with alopecia areata, and upregulates the expression of survivin, thus prevents premature apoptosis [92]. Diphencyprone also induces the expression of VEGF in keratinocytes of the hair follicles, providing good of nutrients and oxygen [93]. In summary, it is well known that minoxidil and anti-DHT drugs are effective against androgenetic alopecia, and diphencyprone is a promising treatment for alopecia areata. Treatments based
on VEGF enhancing may provide alternative to these treatments, or boost the effect of all the already present therapeutic options.

Conclusion

The present article reviewed the role of VEGF in the pathogenesis of skin diseases. From the data presented in this article, it is clear that studies of the angiogenesis and pathogenic role of VEGF in skin diseases are beginning to be intensively organized. This will pave the road to develop new therapeutic strategies based on molecular understanding of disease pathogenetic processes and signaling proteins interaction in various skin diseases.

Conflict of interest

The author declares that he has no conflict of interest.

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