



# ACTAS Derma-Sifiliográficas

Full English text available at  
[www.actasdermo.org](http://www.actasdermo.org)



## REVIEW

# Angiogenesis in Dermatology – Insights of Molecular Mechanisms and Latest Developments



N.A. Richarz\*, A. Boada, J.M. Carrascosa

Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Received 17 May 2016; accepted 18 December 2016

Available online 2 February 2017

### KEYWORDS

Vascular endothelial growth factor;  
Angiopoietin;  
Psoriasis;  
Melanoma;  
Antiangiogenic therapy

### PALABRAS CLAVE

Factor de crecimiento vascular endotelial;  
Angiopoietina;  
Psoriasis;  
Melanoma;  
Terapia antiangiogénica

**Abstract** Angiogenesis is the growth of new blood vessels from pre-existing vessels. It is a biological process essential in physiological wound healing or pathological inflammation and tumor growth, which underlies a complex interplay of stimulating and inhibiting signals. Extracellular matrix, cells of innate and adaptive immunity and endothelial cells itself are a major source of angiogenic factors that activate or inhibit specific receptors and consequently influence intracellular signaling pathways.

Most inflammatory and neoplastic diseases in dermatology are characterized by excessive angiogenesis, such as psoriasis, atopic dermatitis, as well as melanoma, non-melanoma skin cancer, but also benign vascular neoplasia. In this article we describe current knowledge of angiogenesis and its most relevant mechanisms in different dermatological disorders with particular emphasis on the angiogenic factors (vascular endothelial growth factor) and angiopoietins as a target of current and future directions of anti-angiogenic therapy.

© 2017 AEDV. Published by Elsevier España, S.L.U. All rights reserved.

### Angiogénesis en Dermatología – Nuevos aspectos en mecanismos moleculares y últimos avances

**Resumen** La angiogénesis es el desarrollo de nuevos vasos a partir de estructuras vasculares preexistentes. Es un proceso biológico esencial en la cicatrización de las heridas, pero también en la inflamación y el crecimiento tumoral y es controlado por una compleja red de factores inhibitorios y estimulantes. La matriz extracelular, las células del sistema inmune innato y adaptativo así como las células endoteliales son fuente de factores angiogénicos que pueden estimular o inhibir receptores específicos y modificar la respuesta de distintas vías de señalización intracelular.

La mayoría de las enfermedades inflamatorias y neoplásicas dermatológicas se caracterizan en general por un exceso de angiogénesis, como por ejemplo en la psoriasis, la dermatitis atópica, o el melanoma, así como en el cáncer cutáneo no melanocítico pero también en las

\* Corresponding author.

E-mail address: [richarznina@gmail.com](mailto:richarznina@gmail.com) (N.A. Richarz).

neoplasias vasculares benignas. En este artículo de revisión describimos los conocimientos actuales del proceso de angiogénesis y sus mecanismos más relevantes en las diferentes enfermedades dermatológicas haciendo especial énfasis en los factores proangiogénicos como el factor de crecimiento vascular endotelial y las angiopoyetinas como potenciales dianas terapéuticas.

© 2017 AEDV. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

## Introduction

Angiogenesis is the process in which tissue recruits blood vessels to form a neovasculature to guarantee blood supply necessary for the perfusion with oxygen and removal of waste. In most physiological and pathological processes angiogenesis occurs together with vasculogenesis, which is defined as *in situ* formation of new vessels from endothelial precursor cells derived from bone marrow, attracted to the developing tissue by migration signals.

The development of a mature vascular network is a process characterized by subsequent steps on a molecular basis that rely on a balanced interaction of cells, extracellular matrix and angiogenic factors.<sup>1</sup> The process usually initiates on a stimulus such as low tissue oxygen tension with upregulation of hypoxia inducible factor (HIF-1) transcription regulator family, which induces the transcription of different cytokines and angiogenic factors. Activation of endothelial cells by these factors regulates vasodilation and hyperpermeability with subsequent degradation of basement membrane through matrix-metalloproteinases (MMP-2 and MMP-9) followed by extravasation of plasma proteins. In response to stimulation by cytokines, growth factors (p.e.: vascular endothelial growth factor – VEGF, basic fibroblast growth factor – bFGF, platelet derived growth factor – PDGF) or cell–matrix interactions, endothelial cells migrate out of the vessel lumen and together with attracted endothelial cell precursors form into a tube, which “sprouts” from the old capillary. Endothelial cells proliferate, in response to stimulating factors and may branch into further vessel tubes, which sprout into the remodeling extracellular matrix. A new lumen is formed, blood flow can begin, and the endothelial cell tube matures forming a new basement membrane. Pericytes, pluripotential cells of mesenchymal origin with smooth muscle cell characteristics, are involved in the last step of vessel formation and maturation by direct interaction with endothelial cells. The function of pericytes in these pathways is influenced by BB isoform of PDGF and activation of Tie-2 receptor by Angiopoietin 1 and 2 (Ang-1 and Ang-2). Pericytes invest the forming endothelial cell tube and decrease vessels ability to regress or to remodel, hence counteract the high degree of remodeling in a growing vascular network of a rapidly proliferating tumor. Quantity and maturity of the developing vessels is highly regulated by cytokines and growth factors secreted in the endothelial cell environment by keratinocytes and the immune cell infiltrate present in most inflammatory and neoplastic skin disease. An imbalance of angiogenic factors can lead to a leaky and unstable neovasculature uncovered by pericytes and prone to constant remodeling.<sup>2,3</sup>

Over 33 years have passed since Harold Dvorak firstly described a “vascular permeability factor”, later called

VEGF, but the different and complex function of this disulphide-linked homodimer are still not fully understood.<sup>4</sup> Five subtypes of VEGF (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor) have been described with different affinity to three different VEGF receptors VEGFR-1, VEGFR-2 and VEGFR-3, all of them tyrosine kinase receptors (RTKs). Activation of VEGFR-2, present on many cell types (blood endothelial cells, vascular smooth muscle cells, hematopoietic stem cells, monocytes, neurons, macrophages, platelets, keratinocyte) by VEGF-A seems to be the most relevant step in physiological and tumor angiogenesis. VEGFR-3 activation by VEGF-C and VEGF-D on lymphatic endothelial cells has been related to lymphangiogenesis. In the last years signaling pathways downstream from VEGF/receptor binding and VEGF interaction with the endothelial cell environment have been in the focus of investigation, offering a better understanding of pathogenesis in inflammatory and neoplastic disease.<sup>5</sup> Many current treatment options in skin disease already interfere in angiogenesis and influence on angiogenic factor transcription and secretion.

Specific antibodies against VEGF (e.g.: Bevacizumab) and its receptors as well as molecules that inhibit the VEGF/VEGFR activation have been designed to neutralize the pro-angiogenic effects in tumors, but might also be of interest in inflammatory disease with angiogenesis excess. Nevertheless the latter of adverse events of these therapies currently limit its use to intravitreal treatment for retinopathy or life-prolonging cancer therapy and the only dermatological disease so far in clinical trials for these agents is advanced melanoma.<sup>6,7</sup> Dermatologists might be more familiar with the cutaneous adverse effects that occur in 90% of patients treated with antiangiogenic agents for other neoplastic disease.<sup>8</sup>

Another target of potential anti-angiogenesis therapy, although less known are the angiopoyetins (Ang-1 and Ang-2) and its receptor. Both Ang-2 and Ang-1 bind to the same endothelial cell membrane tyrosine kinase receptor Tie-2 (also known as TEK) and stimulate similar signaling cascades.<sup>9</sup> Ang-1 acts as an agonist for Tie-2 and mediates vessel maturation, whereas Ang-2 seems to act as a partial Tie-2 agonist causing vessel leakage and expression of adhesion molecules at endothelial cell membrane promoting angiogenesis, especially in the presence of VEGF.<sup>10,11</sup> Several drugs targeting Ang-1, Ang-2 or both, are in late-stage clinical trials for non-dermatological cancer therapy.<sup>12</sup>

## Angiogenesis in psoriasis

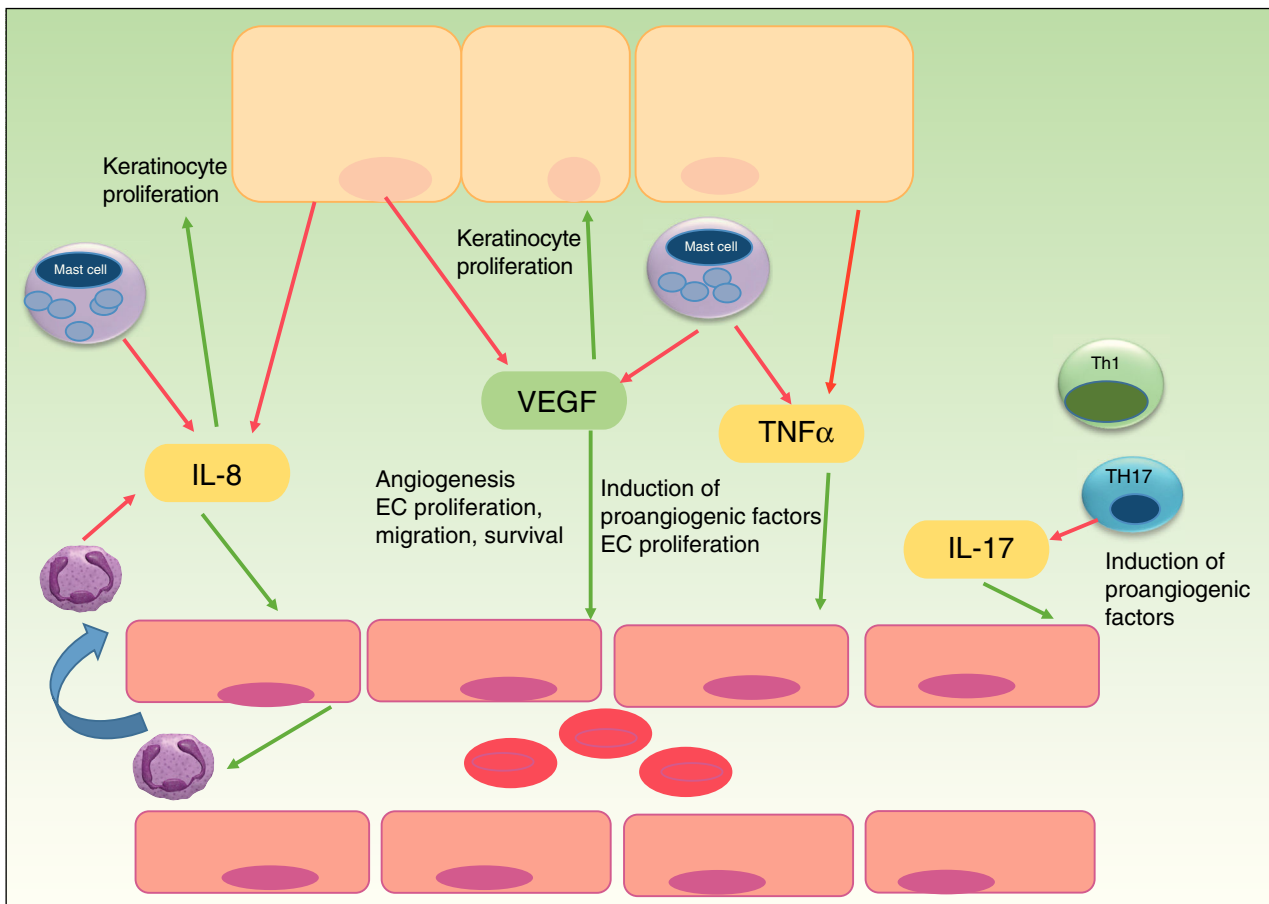
Histological hallmarks of psoriatic skin include the infiltrate of multiple immune cells, abnormal keratinocyte proliferation and increased dermal vascularity. The erythema

of psoriatic plaques, evaluated by PASI score together with induration and scaling, reflects vascular permeability and capillary density in papillary dermis. Classically, the increased vascularity can be demonstrated clinically by ‘Auspitz sign’ where scraping scale from psoriatic plaques leads to pin-point bleeding.

Whereas in normal skin, capillary loops show an arterial phenotype, they exhibit characteristic features of venous capillaries such as a single or multilayered basement membrane and bridged fenestrations of the endothelium in psoriasis plaques. Several angiogenic mediators like VEGF, HIF, angiopoietins and pro-angiogenic cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-8 and IL-17, are up-regulated in psoriasis development.<sup>13</sup> Most of the cytokines are released directly, or transcription is upregulated indirectly, by the inflammatory infiltrate of Th17, Th1, mast cells, macrophages and neutrophils in psoriatic lesions. Furthermore, even psoriatic keratinocytes have shown to overexpress VEGF and its receptors,<sup>13,14</sup> CXCL8/IL-8 and TNF alpha<sup>15</sup> and thereby promote angiogenesis. TNF alpha produced by mast cells, macrophages, keratinocytes and lymphocytes seems to up-regulate the expression of IL-8, VEGF, bFGF, angiopoietins and the Tie-2 receptor in endothelial cells.<sup>16,17</sup> Th17 cells produce IL-17 that not only promotes

angiogenesis directly but also upregulates the expression of other angiogenic factors (VEGF, IL-8) (Fig. 1).<sup>18,19</sup>

Successful antipsoriatic treatment was accompanied by noticeable reduction of angiopoietin 2 and VEGF expression in psoriatic skin as well as VEGF serum level reduction, suggesting a key role for these two factors in controlling vascular proliferation in psoriatic plaques.<sup>20,21</sup> An intense crosstalk between immune cells, keratinocytes and endothelial cells seems to establish an interactive cytokine network, responsible for development and maintenance of psoriatic lesions with characteristic capillary proliferation. Xia et al. in 2003 could firstly demonstrate the importance of VEGF and its receptors in the development of psoriasis in a transgenic mouse model with overexpression of VEGF in basal keratinocytes.<sup>22</sup> Histopathological evaluation showed the typical features of psoriatic skin lesions with high number of capillaries, high expression of VEGFR-1 and 2 in keratinocytes and an inflammatory infiltrate. Interestingly clinical as well as histopathological features were reversible by treatment with a VEGF inhibitor. In another in vitro study VEGF has shown to enhance the proliferation and migration of keratinocytes and these effects were partially inhibited by pretreatment with VEGFR-2 neutralizing antibody, thus suggesting an important influence on keratinocyte activity



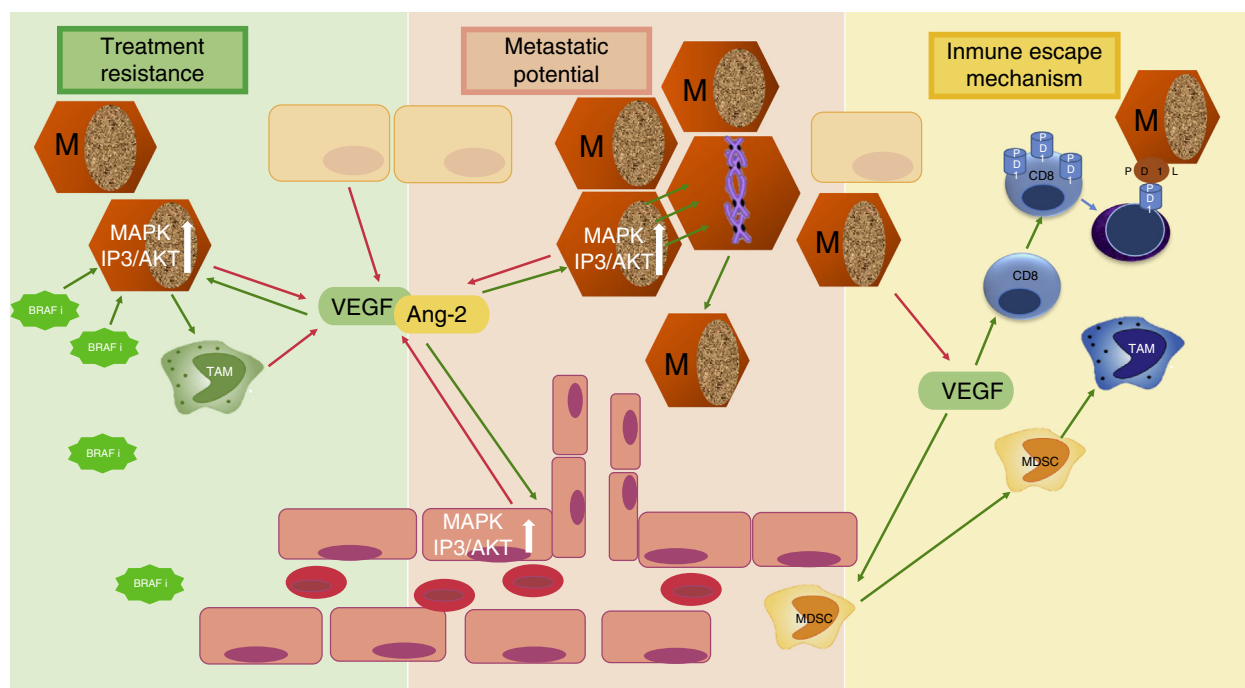
**Figure 1** The role of angiogenesis in the pathogenesis of psoriasis. Keratinocytes, immune cells and endothelial cells activate and maintain the inflammatory skin condition of psoriasis by secretion of different pro-angiogenic factors and cytokines. VEGF, vascular endothelial growth factor; IL, interleukin; TNF, tumor necrosis factor; EC, endothelial cell; red arrows indicate secretion; green arrows indicate activation or attraction.

by VEGF in a possible autocrine manner.<sup>14</sup> VEGF gene polymorphisms may increase predisposition to develop psoriasis as patients with severe disease, and those with onset of psoriasis between the ages of 20 and 40, showed significantly increased frequency of the +405 CC genotype and the C allele.<sup>23</sup> Different case reports with angiogenesis-inhibitors given for cancer therapy in patients with psoriasis have been published. Sunitinib (Sutent), a potent VEGFR – inhibitor in the treatment for renal cell carcinoma, could almost clear chronic large psoriatic plaques in a patient, as reported in 2007 by Keshtagarpour and Arkadius.<sup>24</sup> In 2009 another report of a patient presenting complete remission of chronic psoriasis while receiving Bevacizumab (anti-VEGF Ab) for colon cancer therapy was published.<sup>25</sup> Sorafenib, another oral multi-kinase inhibitor that acts upon the tyrosine kinase component of VEGFR, has shown in 2010 to clear chronic psoriatic lesions of a 78 year-old male treated for renal cell carcinoma.<sup>26</sup> Antiangiogenesis therapy subsequently appeared in the focus of investigation in psoriasis therapy, even though it has not yet developed into the clinical setting, because anti-TNF alpha therapy and other newer anti IL17 and anti p40 IL12/IL23 treatments proved to be effective with fewer adverse events than anti-angiogenic therapy available at this time. Current treatment strategies already interfere in the complex cytokine network that promotes angiogenesis in psoriasis. Anti-TNF treatment with Infliximab of 16 patients with moderate-severe psoriasis could significantly reduce levels of VEGF, Ang-2, TNF alpha and mRNA expression by PCR of Ang1 and Tie-2 receptor in cutaneous biopsies.<sup>27</sup> The anti-angiogenic effect of NB-UVB could be demonstrated by Chen, showing decreased levels

of IL-8 and VEGF after therapy.<sup>28</sup> Other treatment options in psoriasis such as retinoids seem to inhibit VEGF and MMP expression.<sup>29,30</sup> A more specific inhibition of the angiogenic checkpoints with new anti-angiogenic agents might offer advantages over current therapies with less immunosuppression but other potential side effects that have to be evaluated carefully before clinical trial.

### Angiogenesis in melanoma

Melanoma is the third most common skin cancer, but has by far the worst prognosis and outcome in terms of survival. The factors that make melanoma such a lethal cancer is its propensity to metastasize, its ability to decrease immunologic response and the early resistance of metastatic tumors to current anti-cancer treatment. All three of these adverse prognostic factors are related to angiogenesis (Fig. 2). Tumor angiogenesis in Melanoma as in other cancers is not only limited to the previously described mechanism of “endothelial sprouting” but other, alternative mechanisms of tumor vascularization seem to play an important role in melanoma, such as including intussusceptive angiogenesis,<sup>31</sup> vascular co-option,<sup>32</sup> mosaic vessels,<sup>33</sup> vasculogenic mimicry,<sup>34</sup> and seeding and incorporation of bone marrow-derived endothelial cell progenitors.<sup>35</sup> How these complex mechanisms of angiogenesis independent vascularization can be activated and in response to which stimuli they occur is still under investigation and beyond the scope of this article.



**Figure 2** Three mechanisms of melanoma aggressiveness related to angiogenic factors. The secretion of pro-angiogenic factors and other cytokines by melanoma cells confers metastatic potential, inhibits immune response and favors resistance to targeted therapy. VEGF, vascular endothelial growth factor; Ang-2, angiopoietin 2; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cells; PD1, programmed cell death protein 1; BRAFi, BRAF inhibitor; M, Melanoma cell; red arrows indicate secretion; green arrows indicate activation or attraction.

## Metastatic potential

Tumor angiogenesis is closely related to lymphangiogenesis in the spread of cancer cells from the primary neoplasm to other tissues and organs and usually first occur via the sentinel lymph node.<sup>36</sup> Nevertheless, melanoma tumor cells can bypass the lymph-node system and metastasize to distant organs by gaining direct access to blood circulation. Depending on the angiogenic potential of the tumor cells trapped in secondary organ capillary beds, metastatic tumor growth can be favored by increased induction of neovascularization.<sup>37</sup> Some authors therefore suggest that tumor angiogenesis is associated with poor prognostic outcome and increased rate of relapse in melanoma.<sup>38-40</sup> Pro-angiogenic factors such as VEGF-A, IL-8, PDEGF, bFGF, Ang-2 and MMP, necessary for tumor angiogenesis can be generated in part by melanoma cells.<sup>41,42</sup> Therefore, the clinical utility of VEGF serum determination in melanoma patients has been under investigation as circulating serum levels of VEGF in some studies have shown to be directly related to Breslow depth and number of mitosis,<sup>43</sup> whereas other authors cannot confirm such direct correlation,<sup>44</sup> but point out the utility of VEGF as a marker of progression-free survival.<sup>45</sup> In addition to VEGF, the serum blood vessel destabilizing Tie-2 receptor ligand Ang-2 seems to play an important role in melanoma angiogenesis, as Helfrich demonstrated, analyzing serum levels and biopsies of 98 melanoma patients.<sup>42</sup> A statistically significant correlation could be observed between circulating Ang-2 serum levels, tumor progression and patient survival. Analysis of serum samples during the transition from stage III to IV identified an increase of Ang-2 up to 400% and could demonstrate a potential role for Ang-2 as a predictive marker over the established marker S100beta.<sup>42</sup>

## Decrease of immunologic response

In reaction to the developing tumor with higher vessel density, immune cells infiltrate the tumor microenvironment and initially release cytokines that inhibit tumor proliferation and survival. However melanoma cells may exert immunosuppressive mechanisms in the tumor microenvironment via cytokines and pro-angiogenic factors, and thereby regulate the composition of inflammatory cell infiltrate and their cytokine expression.<sup>46</sup> The role of VEGF-A seems to be critical in the so called "immune escape" of tumor cells, as it acts on different cell populations. VEGF-A seems to inhibit effective immune tumor response by induction of T-regulator cell (T-reg) proliferation and inhibition of dendritic cell maturation to functional dendritic cells capable of presenting tumor antigens and inducing a T cell response directed against tumor antigens.<sup>47-49</sup> VEGF-A has shown to induce PD-1 (programmed death receptor 1) expression on the surface of tumor infiltrating CD8 cells and thus ameliorate immune response by increased induction of apoptotic signaling pathways on binding PD-L1 (programmed death receptor ligand 1) of melanoma cells.<sup>50</sup> Furthermore VEGF-A increases the attraction of immature myeloid cells from bone marrow and myeloid derived suppressor cells (MDSC) to tumor site favoring the development of tumor-associated macrophages

(TAM), which are able to promote tumor growth and angiogenesis.<sup>51</sup>

## Resistance to current anti-cancer treatment

Another reason why advanced melanoma is so difficult to treat and survival rates of current treatment options are still far away from optimum, is melanoma's mechanism of resistance to anticancer therapy. Interestingly, pro-angiogenic factors such as VEGF-A, MMP-9 or angiopoietins secreted by melanoma cells and by different cells of the microenvironment seem to be directly implicated in treatment resistance to BRAF inhibitors. On binding VEGF to VEGFR-2 on melanoma cells not only the intracellular MAPK pathway, but also the mTOR pathway are activated with subsequent stimulation of proliferation and growth.<sup>52</sup> The single inhibition of MAPK pathway might favor cell lines with higher activation of mTOR pathway. In fact, BRAF inhibitor resistant melanoma cell lines were found to be more invasive and to secrete higher levels of VEGF-A and MMP-9 than non BRAF resistant cell lines. BRAF inhibitor resistant melanoma cells also interact with immune cells in the microenvironment and stimulate VEGF production of co-cultured macrophages that conversely has an activating effect on MAPK signaling pathway of melanoma cell line, inducing tumor growth.<sup>53</sup>

Additionally, Helfrich showed that human melanoma-isolated tumor cells were Tie-2 receptor positive and could be stimulated by high levels of Ang-2. Interestingly Ang-2 was secreted either by tumor associated endothelial cells and or by melanoma cells themselves, suggesting an autocrine angiopoietin/Tie-2 loop that might be implicated in AKT activation necessary for the change from horizontal to vertical growth in melanoma.<sup>42,54,55</sup>

Recent clinical phase II studies for unresectable stage III and IV melanoma, that show the potential of anti-VEGF therapy with bevacizumab combined with nab-paclitaxel, have proven safety and could demonstrate interesting results for overall survival which might be related to the direct down-regulation of VEGF activity.<sup>56,57</sup> Nevertheless other studies in different non-melanoma cancers already have shown resistance mechanisms to current antiangiogenesis agents (anti VEGF, VEGFR inhibitor, MMP inhibitors, angiopoietin antagonist). These mechanisms seem to be related not only to the selection of advantaged tumor subpopulations and tumor associated cells under new environmental conditions, but also to the up-regulation of alternative proangiogenic pathways and the activation of angiogenesis independent vascularization mechanisms, not dependent on the classical interaction of cytokine and angiogenesis factor stimuli.

## Angiogenesis in vascular lesions

Hemangioma is the most common benign vascular tumor found in 1% of all births and up to 10% of premature infants. It is characterized by a rapid growth with subsequent spontaneous involution together with endothelial cell apoptosis and later replacement by a connective tissue scar. Besides angiogenesis, vasculogenesis, or the in situ development of new vessels from progenitor or primitive mesenchymal cells (CD 133+) seems to be implicated in genesis and growth of hemangioma.<sup>58</sup> VEGF serum concentrations are significantly

correlated with lesion size and oral propranolol treatment significantly decreased VEGF serum levels 4 weeks after treatment of infantile hemangioma.<sup>59</sup> Propranolol seems to induce in vitro regression of hemangioma derived endothelial cells via the inhibition of cell cycle progression, invasion, and tube formation, concomitantly with decreased nitric oxide (NO) and VEGF levels.<sup>60</sup> Tie-2 receptor and its ligands Ang-1 and Ang-2 also seem to be implicated in the pathogenesis of hemangioma;<sup>61</sup> in fact, Tie-2 receptor blockade showed a decrease of hemangioma growth in vivo, but direct inhibition of Ang-2 production could even more effectively abolish hemangioma growth.<sup>62</sup> The use of direct anti-angiogenic agents, such as anti-VEGF antibody has not yet been described for benign vascular lesions. In aggressive vascular tumors such as angiosarcomas however, vascular targeted agents like Bevacizumab (anti-VEGF antibody) have shown some promising results in different case reports either in monotherapy or in combination with chemotherapy.<sup>63–65</sup>

Another endothelial malignancy, Kaposi's sarcoma, has been related to the overexpression of VEGF and its receptor, during the proliferative phase, activated by a viral oncoprotein, secondary to HHV-8 infection. Interestingly, Kaposi's lesions associated to immunosuppression in solid organ transplant recipients disappear on switch from calcineurin inhibitors to mTOR inhibitor Sirolimus which is known to have an anti-angiogenic activity related to VEGF expression.<sup>66</sup> Acquired vascular disorders such as rosacea can be treated with tetracycline class antibiotics, which inhibit matrix metalloproteinases,<sup>67</sup> or by drugs such as metronidazole, which inhibits reactive oxygen involved in induction of angiogenesis.

### Angiogenesis in non-melanoma skin cancer

Basal and squamous cell carcinomas represent the most common skin cancers, curable through local excision in most

of the times. However, some can show more aggressive behavior and even metastatic potential in certain settings such as organ transplant patients, or carcinomas arising in scars or ulcers.

Angiogenic factors, such as increased levels of VEGF, but also up-regulation of bFGF expression in keratinocytes seem to play an important role in progression of both tumors.<sup>68</sup> UVB exposure, a well-known risk factor for cancerous skin lesions, is known to modulate the balance of angiogenic factors favoring increased endothelial cell proliferation within existing blood vessels by up-regulation of bFGF and VEGF while it decreases anti angiogenic IFN beta.<sup>69</sup>

There might exist a different expression pattern of VEGF by tumor epithelial cells of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), as BCC has shown to predominantly overexpress VEGF at the invasive tumor front, while SCC tends to express VEGF in a more widespread pattern.<sup>70</sup>

Upregulation of Ang-2 in squamous cell carcinoma during early stage of carcinogenesis seems to promote tumor growth by counteracting the inhibitory role of Ang-1, which favors a stable number of vessels and low VEGF m-RNA expression and VEGF-R2 phosphorylation.<sup>71</sup>

Parallel to the role of infiltrating immune cells on angiogenesis in melanoma, there might exist an influence on angiogenesis by immune cells in the tumor microenvironment of non-melanoma skin cancer (NMSC). NMSC samples of renal transplant recipients have shown a higher proportion of microvessel density, but also less VEGF-A positive leukocytes than in immunocompetent controls; this finding suggests a suppressive role for VEGF-A positive peritumoral leukocytes on NMSC.<sup>72</sup> A higher number of tumor associated macrophages (TAM) in BCC has shown to be associated with invasion, angiogenesis and poor prognosis, subsequent to a higher release of MMP-9 and increased bFGF and VEGF-A secretion.<sup>73</sup>

**Table 1** The role of VEGF/Angiopoietins in distinct dermatological disease.

	VEGF/VEGF-R	Angiopoietin/TIE-R
Psoriasis	Overexpression of VEGF and VEGF-R in keratinocytes <sup>13</sup> TNF alpha and IL17 upregulate VEGF expression <sup>16,18</sup> VEGF serum level correlates with PASI <sup>21</sup>	TNF alpha upregulates Ang/TIE expression <sup>17,27</sup> Reduction of Ang-2 expression in tissue after successful antipsoriatic treatment <sup>20</sup>
Melanoma	VEGF and microvessel density involved in potential to metastasize <sup>40</sup> VEGF serum levels as a potential marker of progression-free survival <sup>44</sup> VEGF influence on immune cell infiltrate – “immune escape” <sup>47,49,50</sup> VEGF involvement in treatment resistance <sup>51–53</sup>	Significant increase of serum Ang-2 in progression from stage III–IV <sup>42</sup> Stimulation of melanoma cells by an autocrine Ang/Tie2 loop <sup>42</sup> Tie2 receptor activation in melanoma cells might lead to AKT activation necessary for the change from horizontal to vertical growth in melanoma. <sup>42,54,55</sup>
Hemangioma	VEGF serum levels correlate with lesion size in IH <sup>56</sup> VEGF serum level decrease by Propranolol treatment in IH <sup>57</sup>	Direct inhibition of Ang-2 production could abolish hemangioma growth <sup>60</sup>
NMSC	Different expression pattern of VEGF between BCC and SCC <sup>68</sup> Interaction with immune cell infiltrate <sup>71</sup>	Ang-1 enhances tumor vessel maturation and inhibits tumor growth in SCC <sup>69</sup>

Ang – angiopoietin, BCC – basal cell carcinoma, IL – interleukin, IH – infantile hemangioma, NMSC – non-melanoma skin cancer, PASI – psoriasis area and severity index, SCC – squamous cell carcinoma, VEGF – vascular endothelial growth factor.

Imiquimod, a topical treatment of superficial NMSC, has an antiangiogenic effect by increasing local production of interferon. Intralesional treatment of locally advanced basal cell carcinoma with Bevacizumab (anti-VEGF antibody) has been investigated as an adjuvant treatment to immunocryosurgery with promising results.<sup>74</sup>

## Summary

Angiogenesis is an important molecular mechanisms contributing to the development and persistence of many dermatological diseases (Table 1). The inflammatory infiltrate, endothelial cells, keratinocytes and melanocytes are in close contact and stimulate each other's proliferation and development by a network of angiogenic factors and cytokines. The pro-angiogenic factors VEGF and angiopoietins secreted by keratinocytes, melanocytes, endothelial cells and different immune cells play a key role in the development of blood vessels but also influence the microvessel environment with direct effects on the different cell population. A better understanding of molecular mechanisms and the interaction of angiogenic factors with the endothelial cell environment might allow the development of new therapeutic strategies for inflammatory or neoplastic skin disease.

## Ethical responsibilities

**Protection of people and animals.** The authors state that no experiments have been performed on humans or animals for this research.

**Confidentiality of data.** The authors state that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors state that no patient data appears in this article.

## Conflict of interests

The authors declare that they have no conflict of interest.

## References

- Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285:1182–6.
- Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science.* 1989;246:1306–9.
- Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med.* 2000;6:389–95.
- Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science.* 1983;219:983–5.
- Weis SM, Cheresh DA. Pathophysiological consequences of VEGF-induced vascular permeability. *Nature.* 2005;437:497–504.
- Von Moos R, Seifert B, Simcock M, Goldinger M, Gillessen Sochsenbein A, et al. First-line temozolomide combined with bevacizumab in metastatic melanoma: a multicentre phase II trial (SAKK 50/70). *Ann Oncol.* 2012;23:531–6.
- Spitler LE, Boasberg P, O'Day S, Hamid O, Cruickshank S, Mesko S, et al. Phase II study of nab-paclitaxel and bevacizumab as first-line therapy for patients with unresectable stage III and IV melanoma. *Am J Clin Oncol.* 2015;38:61–7.
- Ara M, Pastushenko E. Antiangiogenic agents and the skin: cutaneous adverse effects of sorafenib, sunitinib and bevacizumab. *Actas Dermosifilogr.* 2014;105:900–12.
- Yuan HT, Khankin EV, Karumanchi SA, Parikh SM. Angiopoietin 2 is a partial agonist/antagonist of Tie2 signaling in the endothelium. *Mol Cell Biol.* 2009;29:2011–22.
- Daly C, Pasnikowski E, Burova E, Wong V, Aldrich TH, Griffiths J, et al. Angiopoietin-2 functions as an autocrine protective factor in stressed endothelial cells. *Proc Natl Acad Sci U S A.* 2006;103:15491–6.
- Holash J, Maisonpierre PC, Compton D, Boland P, Alexander CR, Zagzag D, et al. Vessel cooption, regression and growth in tumors mediated by angiopoietins and VEGF. *Science.* 1999;284:1994–8.
- Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2014;15:799–808.
- Detmar M, Brown LF, Claffey KP, Kocher O, Jackman RW, Berse B, et al. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. *J Exp Med.* 1994;180:1141–6.
- Man XY, Yang XH, Cai SQ, Yao YG, Zheng M. Immuno-localization and expression of vascular endothelial growth factor receptors (VEGFRs) and neuropilins (NRPs) on keratinocytes in human epidermis. *Mol Med.* 2006;12:127–36.
- Heidenreich R, Rocken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. *Int J Exp Pathol.* 2009;90:232–48.
- Yoshida S, Ono M, Shono T, Izumi H, Ishibashi T, Suzuki H, et al. Involvement of interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor in tumor necrosis factor alpha-dependent angiogenesis. *Mol Cell Biol.* 1997;17:4015–23.
- Scott BB, Zaratini PF, Colombo A, Hansbury MJ, Winkler JD, Jackson JR. Constitutive expression of angiopoietin-1 and -2 and modulation of their expression by inflammatory cytokines in rheumatoid arthritis synovial fibroblasts. *J Rheumatol.* 2002;29:230–9.
- Numasaki M, Fukushi J, Ono M, Narula SK, Zavodny PJ, Kudo T, et al. Interleukin-17 promotes angiogenesis and tumor growth. *Blood.* 2003;101:2620–7.
- Numasaki M, Watanabe M, Suzuki T, Takahashi H, Nakamura A, McAllister F, et al. IL-17 enhances the net angiogenic activity and in vivo growth of human non-small cell lung cancer in SCID mice through promoting CXCR-2-dependent angiogenesis. *J Immunol.* 2005;175:6177–89.
- Kuroda K, Sapadin A, Shoji T, Fleischmajer R, Lebwohl M. Altered expression of angiopoietins and Tie2 endothelium receptor in psoriasis. *J Invest Dermatol.* 2001;116:713–20.
- Nofal A, Al-Makhzangy I, Attwa E, Nassar A, Abdalmoati A. Vascular endothelial growth factor in psoriasis: an indicator of disease severity and control. *J Eur Acad Dermatol Venereol.* 2009;23:803–6.
- Xia YP, Li B, Hylton D, Detmar D, Yancopoulos GD, Rudge JS. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. *Blood.* 2003;102:161–8.
- Young HS, Summers AM, Bhushan M, Brenchley PE, Griffiths CE. Single-nucleotide polymorphisms of vascular endothelial growth factor in psoriasis of early onset. *J Invest Dermatol.* 2004;122:209–15.
- Keshtagarpour M, Arkadius ZD. SU-011248, a vascular endothelial growth factor receptor-tyrosine kinase inhibitor, controls chronic psoriasis. *Transl Res.* 2007;149:103–6.

25. Akman A, Yilmaz E, Mutlu H, Ozdogan M. Complete remission of psoriasis following bevacizumab therapy for colon cancer. *Clin Exp Dermatol.* 2009;34:202–4.
26. Fournier C, Tisman G. Sorafenib-associated remission of psoriasis in hypernephroma: case report. *Dermatol Online J.* 2010;16:17.
27. Markham T, Golden-Mason L, Bresnihan B, Fitzgerald O, Fearon U, Veale DJ. Resolution of endothelial activation and down-regulation of Tie2 receptor in psoriatic skin after infliximab therapy. *J Am Acad Dermatol.* 2006;54:1003–12.
28. Chen H, Li X, Tang R. Effects of narrow band ultraviolet B on serum levels of vascular endothelial growth factor and interleukin-8 in patients with psoriasis. *Am J Ther.* 2016;23:655–62.
29. Young HS, Summers AM, Read IR, Fairhurst DA, Plant DJ, Campalani E. Interaction between genetic control of vascular endothelial growth factor production and retinoid responsiveness in psoriasis. *J Invest Dermatol.* 2006;126:453–9.
30. Tsang KJ, Crowe DL. Retinoic acid and extracellular matrix inhibition of matrix metalloproteinase 9 expression is mediated by the mitogen activated protein kinase pathway. *Int J Oncol.* 2001;18:369–74.
31. Ribatti D, Nico B, Floris C, Mangieri D, Piras F, Ennas MG, et al. Microvascular density, vascular endothelial growth factor immunoreactivity in tumor cells, vessel diameter and intussusceptive microvascular growth in primary melanoma. *Oncol Rep.* 2005;14:81–4.
32. Welti J, Loges S, Dimmeler Carmeliet P. Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. *J Clin Invest.* 2013;123:3190–200.
33. Zhang S, Guo H, Zhang D, Zhang W, Zhao X, Ren Z, et al. Microcirculation patterns in different stages of melanoma growth. *Oncol Rep.* 2006;15:15–20.
34. Maniotis AJ, Folberg R, Hess A, SefTOR EA, Gardner LM, Pe'er J, et al. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. *Am J Pathol.* 1999;155:739–52.
35. Sun B, Zhang S, Ni C, Zhang D, Liu Y, Zhang W, et al. Correlation between melanoma angiogenesis and the mesenchymal stem cells and endothelial progenitor cells derived from bone marrow. *Stem Cells Dev.* 2005;14:292–8.
36. Pastushenko I, Conejero C, Carapeto FJ. La linfangiogenesis. Sus implicaciones en el diagnóstico, tratamiento y pronóstico del melanoma. *Actas Dermosifiliogr.* 2015;106:7–16.
37. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. *Cell.* 1994;79:185–8.
38. DePasquale I, Thompson WD. Microvessel density for melanoma prognosis. *Histopathology.* 2005;47:186–94.
39. Demirkesen C, Büyükpınarbasılı N, Ramazanoglu R, Oguz O, Mandel NM, Kaner G. The correlation of angiogenesis with metastasis in primary cutaneous melanoma: a comparative analysis of microvessel density, expression of vascular endothelial growth factor and basic fibroblastic growth factor. *Pathology.* 2006;38:132–7.
40. Srivastava A, Laidler P, Davies RP, Horgan K, Hughes LE. The prognostic significance of tumor vascularity in intermediate-thickness (0.76–4.0mm thick) skin melanoma. A quantitative histologic study. *Am J Pathol.* 1988;133:419–23.
41. Rofstad EK, Halsor EF. Vascular endothelial growth factor, interleukin 8, platelet-derived endothelial cell growth factor, and basic fibroblast growth factor promote angiogenesis and metastasis in human melanoma xenografts. *Cancer Res.* 2000;60:4932–8.
42. Helfrich I, Edler L, Sucker A, Thomas M, Christian S, Schadendorf D, et al. Angiopoietin-2 levels are associated with disease progression in metastatic malignant melanoma. *Clin Cancer Res.* 2009;15:1384–92.
43. Tas F, Duranyildiz D, Oguz H, Camilica H, Yasasever V, Topuz E. Circulating levels of vascular endothelial growth factor (VEGF), matrix metalloproteinase-3 (MMP-3), and BCL-2 in malignant melanoma. *Med Oncol.* 2008;25:431–6.
44. Pelletier F, Bermont L, Puzenat E, Blanc D, Cairey-Remonay S, Mouglin C, et al. Circulating vascular endothelial growth factor in cutaneous malignant melanoma. *Br J Dermatol.* 2005;152:685–9.
45. Ascierto PA, Leonardi E, Ottaiano A, Napolitano M, Scala S, Castello G. Prognostic value of serum VEGF in melanoma patients: a pilot study. *Anticancer Res.* 2004;24:4255–8.
46. Salven P, Heikkilä P, Joensuu H. Enhanced expression of vascular endothelial growth factor in metastatic melanoma. *Br J Cancer.* 1997;76:930–4.
47. Ohm JE, Gabrilovich DI, Sempowski GD, Kisseleva E, Parman KS, Nadaf S, et al. VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. *Blood.* 2003;101:4878–86.
48. Dikov MM, Ohm JE, Ray N, Tchekneva EE, Burlison J, Moghanaki D, et al. Differential roles of vascular endothelial growth factor receptors 1 and 2 in dendritic cell differentiation. *J Immunol.* 2005;174:215–22.
49. Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer Res.* 2010;70:6171–80.
50. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med.* 2015;212:139–48.
51. Varney M, Johansson SL, Singh RK. Tumour associated macrophage infiltration, neovascularization and aggressiveness in malignant melanoma: role of monocyte chemoattractant protein-1 and Vascular endothelial growth factor A. *Melanoma Res.* 2005;15:417–25.
52. Graells J, Vinyals A, Figueras A, Llorens A, Moreno A, Marcoval J, et al. Overproduction of VEGF concomitantly expressed with its receptors promotes growth and survival of melanoma cells through MAPK and PI3K signaling. *J Invest Dermatol.* 2004;123:1151–61.
53. Wang T, Xiao M, Ge Y, Krepler C, Belser E, Lopez-Coral A, et al. BRAF inhibition stimulates melanoma-associated macrophages to drive tumor growth. *Clin Cancer Res.* 2015;21:1652–64.
54. Govindarajan B, Sligh JE, Vincent BJ, Li M, Canter JA, Nickoloff BJ, et al. Overexpression of Akt converts radial growth melanoma to vertical growth melanoma. *J Clin Invest.* 2007;117:719–29.
55. Tsai JH, Lee WM. Tie2 in tumor endothelial signaling and survival: implications for antiangiogenic therapy. *Mol Cancer Res.* 2009;7:300–10.
56. Kottschade LA, Suman VJ, Perez DG, McWilliams RR, Kaur JS, Amatruda TT, et al. A randomized phase 2 study of temozolomide and bevacizumab or nab-paclitaxel, carboplatin, and bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N0775. *Cancer.* 2013;119:586–92.
57. Spitler LE, Boasberg P, O'Day S, Hamid O, Cruickshank S, Mesko S, et al. Phase II study of nab-paclitaxel and bevacizumab as first-line therapy for patients with unresectable stage III and IV melanoma. *Am J Clin Oncol.* 2015;38:61–7.
58. Greenberger S, Bischoff J. Pathogenesis of infantile haemangioma. *Br J Dermatol.* 2013;169:12–9.
59. Ozeki M, Nozawa A, Hori T, Kanda K, Kimura T, Kawamoto N, et al. Propranolol for infantile hemangioma: effect on plasma vascular endothelial growth factor. *Pediatr Int.* 2016;58:1130–5.
60. Pan WK, Li P, Gup ZT, Gao Y. Propranolol induces regression of hemangioma cells via the down-regulation of the PI3/Akt/eNOS/VEGF pathway. *Pediatr Blood Cancer.* 2015;62:1414–20.



61. Yu Y, Varughese J, Brown LF, Mulliken JB, Bischoff J. Increased Tie2 expression, enhanced response to angiopoietin-1, and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells. *Am J Pathol.* 2001;159:2271–80.
62. Perry BN, Govindarajan B, Bhandarkar SS, Knaus UG, Valo M, Sturk C, et al. Pharmacologic blockade of angiopoietin-2 is efficacious against model hemangiomas in mice. *J Invest Dermatol.* 2006;126:2316–22.
63. Jeng MR, Fuh B, Blatt J, Merrow AC, Hammil A, Adams D. Malignant transformation of infantile hemangioma to angiosarcoma: response to chemotherapy with bevacizumab. *Pediatr Blood Cancer.* 2014;61:2115–7.
64. Rosen A, Thimon S, Ternant D, Machet MC, Paintaud G, Machet L. Partial response to bevacizumab of an extensive cutaneous angiosarcoma of the face. *Br J Dermatol.* 2010;163:225–7.
65. Nespeira-Jato MJ, Peña Panabad C, Quindós-Vareira M, García-Silva J. Unresectable angiosarcoma treated with bevacizumab and paclitaxel. *Actas Dermatosifilogr.* 2014;105:520–2.
66. Stallone G, Infante B, Grandaliano G, Paolo F, Gesualdo L. Kaposi's sarcoma and mTor: a crossroad between viral infection neovascularization and immunosuppression. *Transplant Int.* 2008;21:825–32.
67. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol.* 2006;54:258–65.
68. Arbisier JL, Byers HR, Cohen C, Arbeit J. Altered basic fibroblast growth factor expression in common epidermal neoplasms: examination with in situ hybridization and immunohistochemistry. *J Am Acad Dermatol.* 2000;42:973–7.
69. Bielenberg DR, Bucana CD, Sanchez R, Donawho CK, Fidler IJ. Molecular regulation of UVB-induced cutaneous angiogenesis. *J Invest Dermatol.* 1998;111:864–72.
70. Bowden J, Brennan PA, Umar T, Cronin A. Expression of vascular endothelial growth factor in basal cell carcinoma and cutaneous squamous cell carcinoma of the head and neck. *J Cutan Pathol.* 2002;29:585–9.
71. Hawighorst T, Skobe M, Streit M, Hong YK, Velasco P, Brown LF, et al. Activation of the tie2 receptor by angiopoietin-1 enhances tumor vessel maturation and impairs squamous cell carcinoma growth. *Am J Pathol.* 2002;160:1381–92.
72. Mackenzie KA, Miller AP, Hock BD, Gardner J, Simcock JW, Roake JA, et al. Angiogenesis and host immune response contribute to the aggressive character of non-melanoma skin cancers in renal transplant recipients. *Histopathology.* 2011;58:875–85.
73. Tjju JW, Chen JS, Shun CT, Lin SJ, Liao YH, Chu CY, et al. Tumor-associated macrophage-induced invasion and angiogenesis of human basal cell carcinoma cells by cyclooxygenase-2 induction. *J Invest Dermatol.* 2009;129:1016–25.
74. Gaitanis G, Bassukas I. Intralesional bevacizumab as in-add adjuvant to immunocryosurgery for locally advanced basal cell carcinoma. *J Eur Acad Dermatol Venereol.* 2014;28:1117–21.