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The cutaneous vascular system in chronic skin inflammation

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Abstract

The blood and lymphatic vasculature play an important role in skin homeostasis. Angiogenesis and lymphangiogenesis – the growth of new vessels from existing ones - have received tremendous interest because of their role in promoting cancer spread. However, there is increasing evidence that both vessel types also play a major role in acute and chronic inflammatory disorders. Vessels change their phenotype in inflammation (vascular remodeling). In inflamed skin, vascular remodeling consists of a hyperpermeable, enlarged network of vessels with increased blood flow, and influx of inflammatory cells. During chronic inflammation, the activated endothelium expresses adhesion molecules, cytokines, and other molecules that lead to leukocyte rolling, attachment and migration into the skin. Recent studies reveal that inhibition of blood vessel activation exerts potent anti-inflammatory properties. Thus, anti-angiogenic drugs might be used to treat inflammatory conditions. In particular, topical application of anti-angiogenic drugs might be ideally suited to circumvent the adverse effects of systemic therapy with angiogenesis inhibitors. Our recent results indicate that stimulation of lymphatic vessel growth and function unexpectedly represents a novel approach for treating chronic inflammatory disorders.

INTRODUCTION

Inflammation is one of the body's major defense mechanisms against pathological insults such as infection, physical or chemical injury. Acute inflammation is terminated by well understood mechanisms restoring homeostasis. In contrast, chronic inflammatory diseases are self-perpetuating conditions which often result in a generalized systemic inflammation affecting several different organs.

Blood and lymphatic vessels play pivotal roles under physiological conditions: the cardiovascular network is the first organ system to develop. Its major functions include the supply of oxygen and nutrients, and the disposal of metabolic waste products. In the adult, physiological angiogenesis is indispensable for the normal wound healing process, the

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Conflict of Interest:

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menstrual and hair cycle, the response to ischemia and for endometrial growth (Carmeliet, 2003). The lymphatic vasculature is involved in intestinal fat absorption and immune surveillance, and it drains excess tissue fluid back to the blood circulation. The formation of new capillaries from preexisting vessels - angiogenesis and lymphangiogenesis - has received tremendous interest, mainly because of the presumed role in enhancing tumor progression and metastasis (Carmeliet, 2003; Hirakawa *et al.*, 2005b; Karpanen and Alitalo, 2008; Mumprecht and Detmar, 2009). However, vascular remodeling is also a hallmark of many inflammatory diseases including chronic airway inflammation, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, and the chronic inflammatory skin disease psoriasis (Bainbridge *et al.*, 2006; Baluk *et al.*, 2005; Danese *et al.*, 2006; Detmar *et al.*, 1994). In these conditions, levels of the angiogenic growth factor vascular endothelial growth factor (VEGF)-A are elevated in the inflamed tissue (Detmar *et al.*, 1994; Kanazawa *et al.*, 2001; Koch *et al.*, 1994). Interestingly, the main vascular changes during inflammation consist of vascular enlargement, whereas tumor growth is mainly associated with sprouting angiogenesis. However, vascular hyperpermeability and endothelial cell proliferation are common to both types of angiogenesis. The effect of blocking VEGF-A and angiogenesis is extensively investigated in human cancers but warrants further investigation in inflammatory processes.

BLOOD AND LYMPHATIC VESSELS UNDER PHYSIOLOGICAL CONDITIONS

The cutaneous blood vascular architecture consists of a lower and an upper horizontal plexus. The capillary loops extend from the latter (Braverman, 1989). The lymphatic vessels of the skin also form two plexuses in vicinity of the blood vascular plexuses. Branches from the superficial lymphatic vessel plexus protrude into the dermal papillae and drain into larger lymphatic vessels in the lower dermis and the superficial zone of the subcutaneous tissue. For more details regarding the cutaneous vessel anatomy please see (Skobe and Detmar, 2000). The structure of blood vascular endothelial cells varies with their anatomical location (Aird, 2007). The resting cutaneous blood vessels contain a continuous monolayer of endothelial cells with a continuous basement membrane (Figure 1). The blood vascular endothelial cells are covered with pericytes and form tight and adherens junctions. Under non-activated conditions, quiescent endothelial cells do not interact with leukocytes and inhibit coagulation, and there is no major extravasation of blood proteins into the surrounding tissue (Poerber and Sessa, 2007).

In contrast to blood vascular endothelial cells, the endothelial cells of lymphatic capillaries overlap, lack tight junctions and mural cells, have only a rudimentary or no basement membrane, and are linked to the extracellular matrix by fibrillin-containing anchoring filaments (Figure 1). Therefore, tissue fluid - containing cells and macromolecules - can directly enter the lymphatic capillaries. The lumen of lymphatic vessels is significantly wider and the wall is thinner than that of blood vessels. The fluid entering the initial lymphatic capillaries is drained to pre-collecting and collecting lymphatic vessels which contain a basement membrane, smooth muscle cells, and backflow-preventing valves (similar to veins). Finally, the fluid is returned to the blood circulation in the jugular region.

BLOOD AND LYMPHATIC VESSELS IN INFLAMMATION

Blood vessels and, to a lesser extent, lymphatic vessels contribute essentially to the cardinal signs of inflammation: dilated blood vessels with increased flow underlie the “rubor” and “calor”; the excess exudate caused by hyperpermeable blood vessels exceeding the drainage capacity of fluid by lymphatic vessels results in “tumor”. Finally, “dolor” and “functio laesa” are subsequent processes following vascular activation and influx of leukocytes.

Activation of the endothelium by inflammatory mediators (such as VEGF-A, TNF- α , IL-6, IL-1 β and others) leads to the up-regulation of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell-adhesion molecule-1 (VCAM-1), which enables the interaction with leukocytes (Jackson *et al.*, 1997). In chronic inflammatory diseases, the vasculature remains activated, enlarged and hyperpermeable, and it sustains the accumulation of fluid (edema) and cells. Considerable amounts of plasma proteins extravasate from the blood into the tissue during inflammation (Feng *et al.*, 1999). Increased interstitial fluid pressure in inflamed skin leads to the opening of the overlapping lymphatic endothelial cells and to the entry of cell- and macromolecule-rich fluid. The mechanisms controlling the widening of the lymphatic lumen are currently unknown, as is the function of dilated lymphatic vessels. Lymphatic vessels remained dilated in a mouse model of chronic airway inflammation even when inflammation was resolved (Baluk *et al.*, 2005). Therefore, it remains unclear whether the increase in interstitial pressure is the sole driving force of lymphatic vessel dilation. Lymphatic vessels are also a direct source of cytokines and chemokines (Gunn *et al.*, 1998).

INFLAMMATORY SKIN DISEASES WITH VASCULAR INVOLVEMENT

A multitude of diseases are linked to an insufficient or overactive vasculature (Carmeliet, 2003). Among them are many inflammatory diseases (Table 1). The inflammatory skin diseases associated with prominent remodeling of the vasculature range from UV damage, bullous pemphigoid, contact dermatitis to rosacea and psoriasis (Brown *et al.*, 1995; Gooma *et al.*, 2007; Kunstfeld *et al.*, 2004; Yano *et al.*, 2002). Vascular remodeling is controlled by pro- and anti-angiogenic mediators. An imbalance leads to vessel growth or regression.

Psoriasis

Psoriasis is probably the chronic inflammatory skin condition for which changes in the vasculature are best described. The finding that microvascular abnormalities are a characteristic feature, and happen at the onset of psoriasis has been recognized since more than 50 years (Braverman, 1972; Szodoray, 1955; Telner and Fekete, 1961). Already before the epidermal hyperplasia develops, the skin capillaries become tortuous and expanded. The redness of the skin lesions is caused by the close vicinity of the tortuous vessels in regions of thinned epithelium. The lymphatic vasculature is also dilated in the superficial dermis, as recognized by electron microscopy, and recently by the detection of specific markers for lymphatic vessels (Braverman, 1972; Kunstfeld *et al.*, 2004).

Angiogenesis in psoriasis—It is of interest that the main drivers of angiogenesis in psoriasis are derived from the epidermis (Malhotra *et al.*, 1989). Macrophages and fibroblasts are additional sources of angiogenic factors, including VEGF-A. VEGF-A is probably the most important growth factor leading to blood and lymphatic vascular remodeling in psoriasis, and is currently the best described inducer of inflammation-driven vascular remodeling (Detmar *et al.*, 1994; Ferrara *et al.*, 2003). Additional angiogenic mediators, including hypoxia-inducible factor, TNF- α , IL-1, IL-6, IL-8, IL-17, IL-18, angiopoietins, and many others are involved (Bernardini *et al.*, 2003; Heidenreich *et al.*, 2009). Table 2 summarizes the differential pro- and anti-angiogenic effects of important cytokines and chemokines involved in the pathogenesis of psoriasis. VEGF-A binds to VEGFR-1 and VEGFR-2. VEGFR-1 is expressed on blood vessels, whereas VEGFR-2 is expressed on both blood and lymphatic vessels (Figure 1). VEGFR-1 can be expressed by monocytes / macrophages, whereas VEGFR-2 is expressed at least by a subset of T-cells (Edelbauer *et al.*, 2010; Sawano *et al.*, 2001). Hence, VEGF-A can directly lead to blood and lymphatic vessel activation, and directly affects the attraction of inflammatory cells. The receptor tyrosine kinase VEGFR-2 is thought to be the main mediator of VEGF-A-driven endothelial cell proliferation, differentiation, and sprouting (Adams and Alitalo, 2007). In contrast, the role of VEGFR-1 in the adult organism is less clear. In embryogenesis, VEGFR-1 - which has a higher affinity for VEGF-A than VEGFR-2 but lower kinase activity - likely sequesters VEGF-A to prevent excess signaling and increased angiogenesis through VEGFR-2 (Fong *et al.*, 1995; Hiratsuka *et al.*, 1998).

Thus, the remodeling of the vasculature in lesional psoriatic skin might depend on factors derived from the epidermis, whereas blood vascular remodeling is essential for nutrients supply of the overlying, hyperproliferative epidermis. Indeed, epidermal *vegfa*^{-/-} mice do not show epidermal hyperplasia after repeated tape stripping (Elias *et al.*, 2008). Targeting both the epidermis and the dermal vasculature might therefore represent a valuable treatment strategy for psoriasis. VEGF-A serum levels correlate positively with disease severity in psoriasis patients, and negatively with the treatment success of standard therapies, implicating a role of VEGF-A in disease maintenance and progression (Bhushan *et al.*, 1999; Mastroianni *et al.*, 2005; Nielsen *et al.*, 2002). Therefore, VEGF-A could serve as a biomarker for psoriasis activity.

Besides the morphological changes in the cutaneous vasculature, it has been increasingly recognized that these vessels are activated, and that they have an increased expression of adhesion molecules such as VCAM-1, ICAM-1 and E-selectin (Springer, 1994), sustaining the accumulation of infiltrating inflammatory cells.

Angiogenesis in mouse models of inflammation—Many insights into the proinflammatory role of VEGF-A stem from animal models: Homozygous keratin 14 (K14)/VEGF-A transgenic (Tg) mice - that overexpress mouse VEGF-A₁₆₄ in the epidermis - spontaneously develop a chronic inflammatory skin disease with many features of human psoriasis at an age of approximately 6 months (Xia *et al.*, 2003). Besides the vascular changes, the homozygous K14-VEGF-A Tg mice also show epidermal hyperplasia, altered keratinocyte differentiation, the typical infiltration of CD11b⁺ and CD4⁺ cells, the intraepidermal localization of CD8⁺ T cells, the presence of corneal microabscesses, and the

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typical Koebner phenomenon (Xia *et al.*, 2003). Importantly, the K14-VEGF-A Tg mice are sensitive to standard anti-psoriatic therapies such as treatment with betamethasone and cyclosporine A, and they develop a Th17-like disease phenotype, similar to human psoriasis (Canavese *et al.*, 2010; Hvid *et al.*, 2008). Interestingly, many current treatment modalities for psoriasis have anti-angiogenic effects, such as targeted phototherapy with a laser, vitamin D3 analogues, TNF- α antagonists, methotrexate, cyclosporine A, and corticosteroids (Avramidis *et al.*; Canete *et al.*, 2004; Cornell and Stoughton, 1985; Hernandez *et al.*, 2001; Hirata *et al.*, 1989; Oikawa *et al.*, 1990), whereas their effect on the lymphatic vasculature remains elusive. Indeed, the vasoconstrictive potency of corticosteroids was even shown to correlate with clinical activity in psoriasis (Cornell and Stoughton, 1985).

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In hemizygous K14-VEGF-A Tg mice, chronic inflammatory skin lesions can be induced by delayed-type hypersensitivity reactions (Kunstfeld *et al.*, 2004), and we have previously used this model to discover that topical application of a small molecule inhibitor of VEGF receptor (VEGFR) kinases results in potent anti-inflammatory effects that were subsequently also found in other models of inflammation (Halin *et al.*, 2008). Specific inhibition of VEGF-A also ameliorated psoriasis-like symptoms in a mouse model of psoriasis - where the epidermal specific deletion of *c-Jun* and *JunB* leads to the disease (Schonthaler *et al.*, 2009). Besides VEGF-A, another member of the same family of growth factors, namely placental growth factor (PlGF), also plays a major role in cutaneous angiogenesis, inflammation, and edema formation (Oura *et al.*, 2003). K14-PlGF Tg mice are characterized by an increased inflammatory response, with more pronounced vascular enlargement, edema, and inflammatory cell infiltration as compared with wild-type mice. In contrast, mice deficient in PlGF show less inflammation, diminished inflammatory angiogenesis, and edema (Oura *et al.*, 2003). Last but not least, the importance of angiogenesis for inflammation is underscored by the finding that deficiency of the endogenous angiogenesis inhibitor thrombospondin-2 resulted in prolonged and enhanced cutaneous delayed-type hypersensitivity reactions (Lange-Asschenfeldt *et al.*, 2002). Together, these results indicate an important role of angiogenesis and blood vascular activation in sustaining chronic inflammation. In contrast, the role of the lymphatic vasculature in chronic inflammation has remained unclear.

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Lymphangiogenesis in psoriasis—Lymphatic vessels are the conduit for leukocytes from the site of inflammation to secondary lymphoid organs. The current literature suggests that chemokines expressed by lymphatic vessels (in particular CCL21) lead the way of leukocytes to lymphatic vessels, and that the migration in the interstitium depends on forward flow of polymerizing actin but is integrin independent (Alvarez *et al.*, 2008; Lammermann *et al.*, 2008; Ohl *et al.*, 2004; Pflücke and Sixt, 2009).

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It has been reported that the lymphatic vasculature plays an active role in corneal and kidney transplant rejection, in part by facilitating dendritic cell transport to draining lymph nodes (Cursiefen *et al.*, 2004; Kerjaschki *et al.*, 2004). On the other hand, specific blockade of VEGFR-3, a receptor for the lymphangiogenic growth factors VEGF-C and VEGF-D, which is mainly expressed on the lymphatic endothelium in the adult (Kaipainen *et al.*, 1995), enhanced the mucosal edema in a mouse model of chronic airway inflammation (Baluk *et*

et al., 2005), increased the severity of inflammation in a mouse model of chronic inflammatory arthritis (Guo *et al.*, 2009), and also prolonged the course of inflammatory ear swelling in a mouse model of chronic skin inflammation (Huggenberger *et al.*, 2010). Additionally, the inhibition of VEGF-C/-D by sVEGFR-3 significantly decreased lymph flow in a model of bacterial skin inflammation (Kataru *et al.*, 2009), whereas the genetic overexpression of soluble VEGFR-3 in the skin of mice resulted in a lymphedema-like phenotype (Makinen *et al.*, 2001a).

Interestingly, the deficiency of the chemokine receptor D6 in mice – that is expressed on lymphatic vessels, and likely degrades pro-inflammatory chemokines – leads to a chronic inflammatory skin disease resembling human psoriasis after treatment with phorbol esters (Jamieson *et al.*, 2005; Nibbs *et al.*, 2001).

Lymphatic vessels also have an increased density in arthritic joints of mice and men, and are further increased after standard infliximab therapy (Polzer *et al.*, 2008; Zhang *et al.*, 2007). In inflamed tissues, the lymphangiogenic growth factors VEGF-C and VEGF-A are secreted by immune cells such as macrophages, and by resident tissue cells such as keratinocytes and fibroblasts. After proteolytic processing of the propeptides, the mature VEGF-C also binds and activates VEGFR-2 which, besides its expression on the blood vascular endothelium, is also expressed on lymphatic vessels (Joukov *et al.*, 1997; Kriehuber *et al.*, 2001; Makinen *et al.*, 2001b; Wirzenius *et al.*, 2007). Inflammation-induced lymphangiogenesis can be directly regulated by VEGF-A/VEGFR-2 and VEGF-C/VEGF-D/VEGFR-3 signaling, and might be modulated by the attraction of inflammatory cells secreting lymphangiogenic factors (Baluk *et al.*, 2005; Kataru *et al.*, 2009; Wuest and Carr, 2010). However, VEGF-A-induced lymphatic vessels might be less functional than those induced by VEGF-C or VEGF-D/VEGFR-3 signaling (Kajiyama *et al.*, 2006; Nagy *et al.*, 2002). Recently, it was reported that the inflamed lymphatic endothelium expresses ICAM-1, and that it might directly interact with CD11b expressing dendritic cells, resulting in a reduced capacity of dendritic cells to stimulate T-cell proliferation (Podgrabinska *et al.*, 2009). These results highlight the active participation of lymphatic endothelial cells in regulating inflammatory processes.

We have recently found that the establishment of chronic inflammatory skin lesions is associated with impaired lymphatic function and concomitantly decreased lymph flow using an in vivo near-infrared imaging approach in mice (Huggenberger *et al.*, 2010). More importantly, we found, for the first time, that specific activation of lymphatic vessels by Tg overexpression of VEGF-C or of the VEGFR-3-specific ligand mVEGF-D, as well as the intradermal injection of the VEGFR-3-specific mutant VEGF-C156S protein, inhibited chronic skin inflammation in the K14-VEGF-A Tg mouse model (Huggenberger *et al.*, 2010). The reduction in skin inflammation was accompanied by a decreased inflammatory cell infiltrate and normalized epidermal differentiation. It will be of great interest to see whether the application of VEGF-C and activation of lymphatic vessels also exert anti-inflammatory effects in other chronic inflammatory diseases, such as arthritis and inflammatory bowel disease.

Inflammation-induced lymphangiogenesis might therefore represent an endogenous counter-regulatory mechanism aimed at limiting edema formation and inflammation.

Rosacea

Besides psoriasis, rosacea is also characterized by pronounced vascular alterations. The potential mechanisms contributing to the pathogenesis of rosacea include innate immunity, reactive oxygen species, UV radiation, microbes, and vascular alterations (Yamasaki and Gallo, 2009). Blood flow is increased and dermal dilation of blood vessels is visible in lesional rosacea skin (Marks and Harcourt-Webster, 1969; Sibenge and Gawkrödger, 1992). VEGF-A levels, angiogenesis, and lymphangiogenesis have been reported to be increased in lesional skin of rosacea patients (Gomaa *et al.*, 2007). This is in line with the clinical flushing episodes and the erythema observed in patients. Interestingly, UV irradiation exacerbates rosacea, likely by stimulating keratinocytes to produce VEGF-A (Brauchle *et al.*, 1996). In contrast, the role of lymphatic vessels in rosacea is currently unknown. A number of patients show skin edema reminiscent of lymphedema, and at the phymous stage, there is a pronounced lymphedema of the skin. Together, these findings implicate an important role of impaired lymphatic function in rosacea pathogenesis.

Cutaneous UVB damage

A single dose of ultraviolet B (UVB; 290–320 nm) irradiation induces epidermal thickening, dilation, and hyperpermeability of blood vessels, edema, and erythema (Berton *et al.*, 1997; Pearse *et al.*, 1987). UVB irradiation up-regulates several pro-angiogenic molecules, such as basic fibroblast growth factor, interleukin-8, and VEGF-A, whereas the anti-angiogenic proteins such as thrombospondin-1 are down-regulated (Bielenberg *et al.*, 1998; Kramer *et al.*, 1993; Strickland *et al.*, 1997; Yano *et al.*, 2004). The repeated exposure of human skin to UVB radiation results in the degradation of extracellular matrix, increased elastosis, a reduction of dermal blood and lymphatic capillaries, wrinkle formation, and ultimately in an increased risk for epithelial skin cancers (Chung *et al.*, 2002; Kajiya *et al.*, 2007; Kligman, 1979, 1989; Kripke, 1994). The reduction of blood and lymphatic vessels most likely is the consequence of extracellular matrix degradation that no longer supports the vessel maintenance (Chung and Eun, 2007; Kajiya *et al.*, 2007).

Mice that overexpress VEGF-A are more sensitive to UVB irradiation than wild-type mice (Hirakawa *et al.*, 2005a). Conversely, we previously found that systemic blockade of VEGF-A reduces UVB-induced inflammation and vascular enlargement without inhibiting tissue repair (Hirakawa *et al.*, 2005a). In line with these findings, overexpression of the angiogenesis inhibitor thrombospondin-1 in epidermal keratinocytes of Tg mice potently prevented UVB-induced photodamage (Yano *et al.*, 2002). These data underscore a damage-mediating role of angiogenesis and blood vascular hyperpermeability in UVB-induced skin damage.

Importantly, we recently found that chronic UVB exposure of mouse skin results in dilated lymphatic vessels that are leaky (Kajiya *et al.*, 2006). Furthermore, inhibition of the lymphatic endothelium-specific VEGFR-3 by a monoclonal antibody significantly prolonged UVB-induced inflammatory edema formation and cell infiltration (Kajiya and

Detmar, 2006), whereas activation of VEGFR-3 by the specific activator VEGF-C156S or mouse VEGF-D reduced edema and inflammation (Huggenberger *et al.*, 2011; Kajiya *et al.*, 2009). While VEGF-A is up-regulated after UVB irradiation, VEGF-C is down-regulated (Kajiya *et al.*, 2009). This finding might explain the increased permeability of blood vessels, and the reduced lymphatic drainage function after UVB exposure. Together, these data indicate that inhibition of blood vessel activation / angiogenesis or stimulation of lymphatic function might represent novel approaches to prevent cutaneous photodamage.

CONCLUSIONS AND OUTLOOK

There are numerous drugs for the treatment of inflammatory disorders but none of these drugs was intentionally developed to directly modulate the vascular endothelium, although many clinically used therapeutics also target the vasculature. There is now extensive evidence that targeting the activated, remodeled blood vessels might represent a novel and promising therapeutic approach for treating chronic inflammatory diseases – not only of the skin. The status of vascular activation might also be used as a biomarker for the intensity and activity of inflammatory diseases. Importantly, our recent findings indicate that activation of lymphatic vessels might serve as a novel strategy for treating chronic inflammatory disorders such as psoriasis, rosacea, chronic airway inflammation, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, and others.

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Abbreviations

K14	keratin 14
Tg	transgenic
VEGF(R)	vascular endothelial growth factor (receptor)

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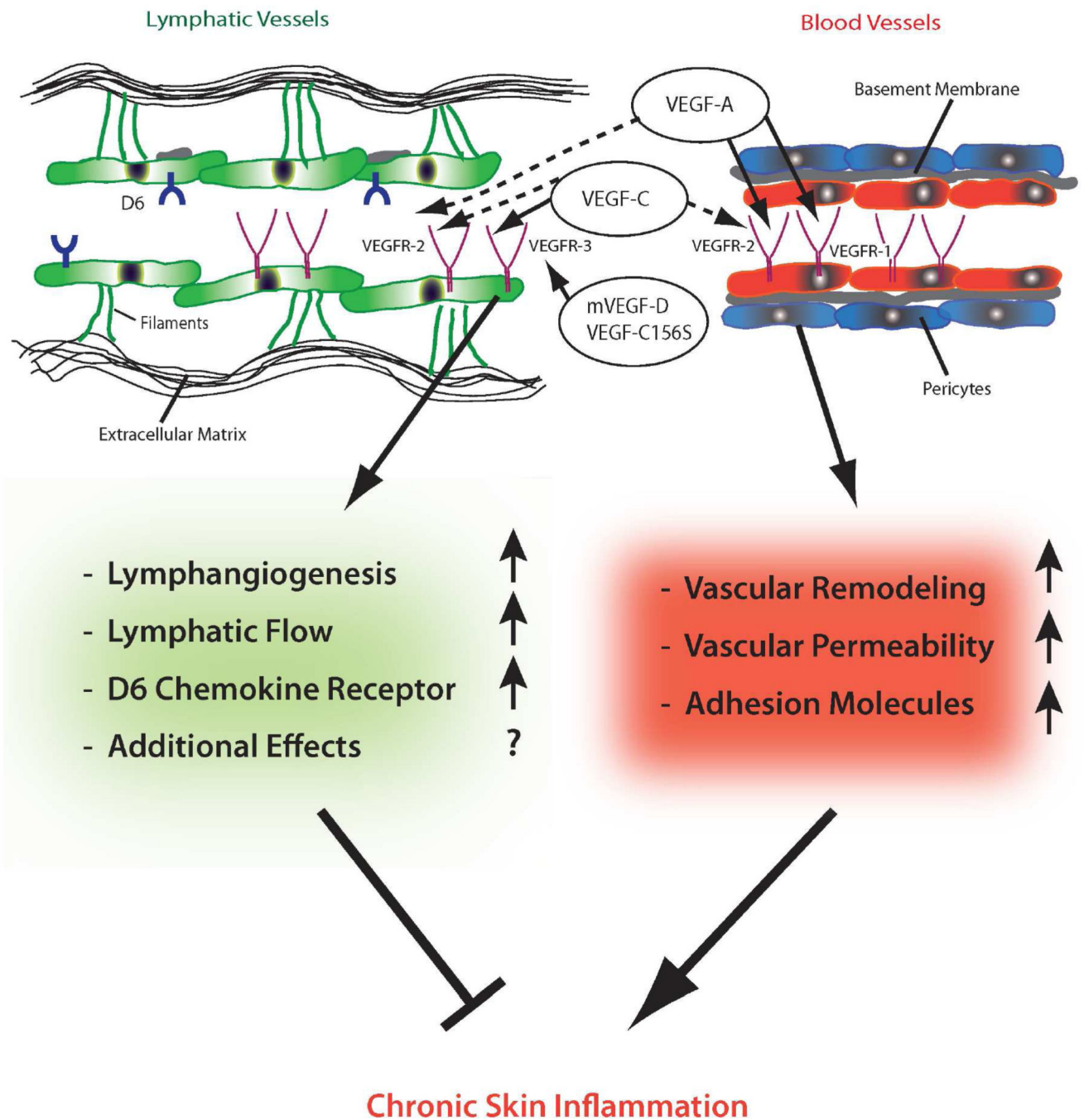
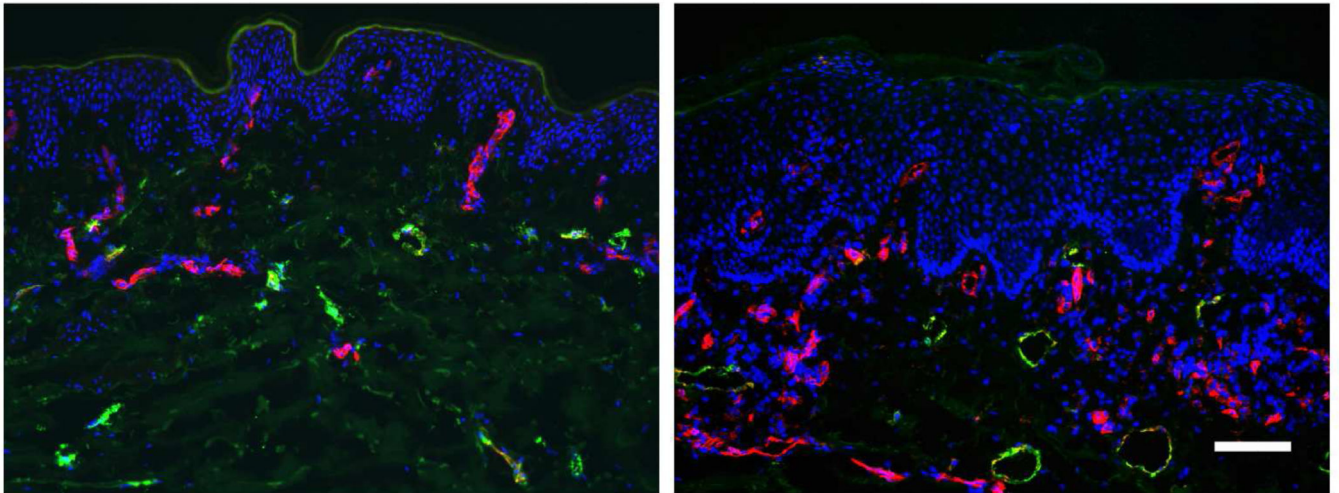


Figure 1. Schematic overview of the proposed role of blood and lymphatic vessels in chronic skin inflammation

Cutaneous blood vessels contain a monolayer of endothelial cells (red) with a continuous basement membrane (gray). Pericytes (blue) cover the blood vascular endothelial cells (BEC). In contrast, lymphatic endothelial cells (LEC, green) lack mural cells and have only a rudimentary basement membrane. They are linked to the extracellular matrix via fibrillin-containing anchoring filaments (green). The lumen of lymphatic vessels is significantly wider and the wall is thinner than that of blood vessels. BEC express VEGFR-1 and VEGFR-2, whereas LEC express VEGFR-2 and VEGFR-3. VEGF-A – which binds both

VEGFR-1 and VEGFR-2 - can directly induce blood and lymphatic vascular remodeling. Chronic stimulation of the blood vasculature by VEGF-A leads to vascular remodeling, increased vascular permeability, increased expression of adhesion molecules and chronic skin inflammation. VEGF-C binds to VEGFR-3 and – after proteolytic processing - might also bind to VEGFR-2 (dashed arrows). In contrast, mouse VEGF-D (mVEGF-D) and VEGF-C156S are specific ligands for VEGFR-3. Stimulation of VEGFR-3 leads to lymphangiogenesis and increases lymphatic flow. An expanded network of lymphatic vessels inhibits chronic skin inflammation. Additional effects of lymphatic vessels – such as binding of chemokines (e.g. to the D6 chemokine receptor) – might contribute to the reduction of chronic inflammation.



Normal skin

Psoriatic plaque

Figure 2. Blood and lymphatic vessel expansion in psoriatic skin lesion

The number and size of CD31⁺/LYVE-1⁻ blood vessels (red) is increased in lesional psoriatic skin vs. normal skin of healthy donors. CD31⁺/LYVE-1⁺ lymphatic vessel size (green) is also increased in lesional skin of psoriasis patients. Nuclear staining is shown in blue (Hoechst); bar, 100 μ m.

Table 1

Inflammatory diseases with vascular involvement

Disease state	References
Skin diseases	
Psoriasis	(Braverman, 1972; Kunstfeld <i>et al.</i> , 2004)
Rosacea	(Gomaa <i>et al.</i> , 2007)
Atopic dermatitis	(Agha-Majzoub <i>et al.</i> , 2005; Chan, 2008; Zhang <i>et al.</i> , 2006)
Alopecia areata	(Simonetti <i>et al.</i> , 2004)
UV damage	(Yano <i>et al.</i> , 2002)
Bullous pemphigoid	(Brown <i>et al.</i> , 1995)
Dermatitis herpetiformis	(Brown <i>et al.</i> , 1995)
Erythema multiforme	(Brown <i>et al.</i> , 1995)
Systemic sclerosis	(Abraham <i>et al.</i> , 2009; Distler <i>et al.</i> , 2004)
Others	
Inflammatory bowel disease	(Chidlow <i>et al.</i> , 2007)
Rheumatoid arthritis	(Paleolog, 2002)
Atherosclerosis	(Hansson, 2005)
Asthma	(Bailey <i>et al.</i> , 2009; Feltis <i>et al.</i> , 2006; Ribatti <i>et al.</i> , 2009)

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Table 2

Cytokines and chemokines with potential pro- or anti-angiogenic activity in psoriasis

Name	Pro-angiogenic	Anti-angiogenic	References
Cytokines			
IL-1	+	+	(BenEzra <i>et al.</i> , 1990; Cozzolino <i>et al.</i> , 1990)
IL-2	+	-	(Bae <i>et al.</i> , 2008)
IL-6	+	-	(Fan <i>et al.</i> , 2008; Wei <i>et al.</i> , 2003)
IL-8 (CXCL8)	+	-	(Koch <i>et al.</i> , 1992; Strieter <i>et al.</i> , 1992; Strieter <i>et al.</i> , 1995)
IL-15	+	-	(Angiolillo <i>et al.</i> , 1997)
IL-17	+	-	(Numasaki <i>et al.</i> , 2003)
IL-18	+	+	(Amin <i>et al.</i> , 2010; Cao <i>et al.</i> , 1999; Cho <i>et al.</i> , 2006; Coughlin <i>et al.</i> , 1998; Park <i>et al.</i> , 2001)
IL-19	+	-	(Jain <i>et al.</i> , 2011)
IL-20	+	+	(Heuze-Vourc'h <i>et al.</i> , 2005; Hsieh <i>et al.</i> , 2006)
IL-24	-	+	(Ramesh <i>et al.</i> , 2003)
IFN- γ	-	+	(Fathallah-Shaykh <i>et al.</i> , 2000; Gately <i>et al.</i> , 1994; Ruegg <i>et al.</i> , 1998)
TNF- α	+	-/(+)	(Fajardo <i>et al.</i> , 1992; Frater-Schroder <i>et al.</i> , 1987; Montrucchio <i>et al.</i> , 1994; Patterson <i>et al.</i> , 1996)
Chemokines			
CCL2	+	-	(Keeley <i>et al.</i> , 2008; Salcedo <i>et al.</i> , 2000)
CCL5 (RANTES)	+	-	(Westerweel <i>et al.</i> , 2008)
CXCL1	+	-	(Keeley <i>et al.</i> , 2008; Strieter <i>et al.</i> , 1995)
CXCL2	+	-	(Keeley <i>et al.</i> , 2008; Strieter <i>et al.</i> , 1995)
CXCL3	+	-	(Keeley <i>et al.</i> , 2008; Strieter <i>et al.</i> , 1995)
CXCL5	+	-	(Keeley <i>et al.</i> , 2008; Strieter <i>et al.</i> , 1995)
CXCL9	-	+	(Strieter <i>et al.</i> , 1995)
CXCL10	-	+	(Strieter <i>et al.</i> , 1995)
CXCL11	-	+	(Keeley <i>et al.</i> , 2008)