INTRODUCTION

The interest on skin has been increased both in pharmaceutical and cosmetic industries. Epidermal tissue composes of a physical barrier structure, maintaining homeostasis by preserving water and protecting inner organs against various external stresses including chemicals, microbial products, and UV irradiation. Keratinocytes are the main components of epidermis, and play active roles in skin function. In many skin problems such as allergic contact dermatitis, atopic dermatitis, psoriasis and phototoxicity, serious damage and functional impairment such as epidermal barrier dysfunction, impaired differentiation/proliferation and dysregulated intercellular communication in keratinocytes are observed (Kubo et al., 2012; Hänel et al., 2013). There have been intensive efforts to elucidate the pathogenic alteration of keratinocytes and identify new biomarkers for keratinocytic damage during skin diseases (Enerbäck, 2011; Bernard et al., 2012). Here we will discuss if vascular endothelial growth factor (VEGF) has a potential as a biomarker for dermal impairment. Experimental and clinical evidences for induction of keratinocytic VEGF under pathological conditions will be reviewed.

BASIC CHARACTERISTICS OF VEGF AND VEGFR

VEGF, a dimeric heparin-binding glycoprotein of approximately 40 kDa in its active form, is known to be a main regulator of physiological and/or pathological angiogenesis. Since it was first described as vascular permeability factor (VPF) (Senger et al., 1983; Keck et al., 1989), several VEGF sub-family members and isoforms have been reported. Although the existence of VEGF-E and -F is newly suggested (Suto et al., 2005; Takahashi and Shibuya, 2005), it is generally accepted that VEGF sub-family consists of five members, VEGF-A, B, C, D and placenta growth factor (PLGF) in mammals (Olsson et al., 2006). Due to the alternative splicing of the original mRNA transcript, VEGF is occurring in isoforms with different biological activities. In case of VEGF-A, at least four isoforms of VEGF-A121, 165, 189 and 206 exist (Tischer et al., 1991; Gille et al., 2000). The bioactivity of VEGF sub-family members is also affected by proteolytic processing which enables specific interactions with different receptor types (Lee et al., 2005).

VEGF selectively binds to high affinity tyrosine kinase receptors (RTKs) that are predominantly expressed on endothelial cells (ECs) (de Vries et al., 1992; Olsson et al., 2006), resulting in receptor activation and intracellular signal transduction.
There are three types of VEGF receptors, which are VEGFR-1 (fms-like tyrosine kinase-1 or Flt-1), VEGFR-2 (kinase insert-domain containing receptor (KDR) or fetal liver kinase (Flk-1)), and VEGFR-3 (Flt-4) (Skobe et al., 1999; Carmeliet, 2000). VEGF receptors usually form homodimers, but heterodimeric complexes of VEGF receptor are also expressed. With different affinities and selectivities, each of VEGF sub-family members binds to distinct VEGFRs (Ruiz de Almodovar et al., 2009).

Specific interaction between VEGF sub-family members and VEGFR is shown in Fig. 1. The neuropilin receptors (NRP-1 and 2) are known to enhance VEGF signaling by modulating VEGF-VEGFR interaction as co-receptors (Geretti et al., 2008).

The overall regulatory mechanism of VEGF receptor signaling is similar to typical RTK signaling of other growth factors, such as cellular signaling in cell migration, proliferation and survival (Leung et al., 1989; Ruiz de Almodovar et al., 2009). Besides these typical roles, the unique bioactivity of VEGF receptor is to transduce signals for angiogenesis and lymphangiogenesis, and to regulate permeability (Ferrara et al., 2003; Olsson et al., 2006). VEGFR-1 mainly binds to VEGF-A and B, and plays key roles in developmental/embryonic angiogenesis. The majority of angiogenic activities of VEGF, such as EC proliferation, migration, and microvascular permeability, are mediated by VEGFR-2 following binding with VEGF-A. Meanwhile, VEGFR-3 is predominantly found in lymphatic ECs, and promotes lymphangiogenesis by binding with VEGF-C and D (Jeltsch et al., 1997; Hicklin and Ellis, 2005; Olsson et al., 2006; Zgraggen et al., 2013).

**VEGF SYNTHESIS IN KERATINOCYTES**

Following the initial in vivo observation of expression of VEGF mRNA in the newly generated epithelium (Brown et al., 1992), the source of cutaneous VEGF was extensively studied. It is possible that VEGF during wound repair can be induced by macrophages or fibroblast (Nissen et al., 1998, Trompezienski et al., 2004), but keratinocytes are found to be one of the main sources of cutaneous VEGF. In cultured human keratinocytes, significant up-regulation of VEGF was observed after stimulation with serum, epidermal growth factor (EGF), transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), insulin-like growth factor-2, or keratinocyte growth factor (Frank et al., 1995; Kim and Kim, 2005). Three major spliced forms of VEGF can be synthesized in human keratinocytes that are the secreted 121 and 165 isoforms and cell-associated 189 isoform (Ballaun et al., 1995). Acting as a key mediator for cutaneous angiogenesis and vascular permeability, keratinocytic VEGF is a potent and selective mitogen for dermal microvascular ECs during physiological processes such as wound repair (Wilgus et al., 2005) and hair growth (Yano et al., 2001), and pathological conditions including cutaneous inflammation, skin cancer (Brown et al., 1992) and psoriasis (Detmar et al., 1994).

**SIGNALING PATHWAYS IN VEGF INDUCTION IN KERATINOCYTES**

Generally, the expression of VEGF is tightly regulated at the transcriptional level and also at the post-transcriptional level (Ruiz de Almodovar et al., 2009). Various growth factors and cytokines are known to induce VEGF expression in keratinocytes, including interleukins (ILs), TGF-α, TGF-β, TNF-α, EGF, and platelet-derived growth factor (PDGF) (Frank et al., 1995; Cohen et al., 1996; Gille et al., 1997; Kozlowska et al., 1998; Ma et al., 2014). Contribution of signaling kinases including phosphatidylinositol 3-kinase (PI3K) or mitogen-activated protein kinase (MAPK; p42/p44 MAPK) to VEGF synthesis in keratinocytes are well-established (Nakai et al., 2009; Yu et al., 2010). Transcription factors of activation protein (AP)-1, AP-2, hypoxia-induced factors (HIFs), specificity protein (SP)-1 and nuclear factor κB (NFκB) are found to mediate transcriptional...
regulation of VEGF in keratinocytes (Forsythe et al., 1996; Finkenzeller et al., 1997; Gille et al., 2000, Brenneisen et al., 2003; Scortegagna et al., 2008). Several pathological conditions such as hypoxia or UV irradiation induce up-regulation of keratinocytic VEGF (Detmar et al., 1997; Gille et al., 2000; Brenneisen et al., 2003; Weir et al., 2011), either by direct activation of transcriptional pathways or by secretion of cytokines.

### UP-REGULATION OF VEGF IN SKIN DAMAGE

Although it is clear that VEGF can be expressed in keratinocytes, it is still controversial whether cutaneous VEGF is restorative or aggravative for skin damage. In normal epidermis, blood vessels are generally quiescent and angiogenesis is hardly occurring. Consistently, the level of VEGF in normal epidermis is found to be low (Weninger et al., 1996). However, in many skin conditions such as psoriasis, contact dermatitis, wound healing and cutaneous neoplasia that are closely associated with angiogenesis or chronic inflammation, there is prominent induction of VEGF in epidermal keratinocyte (Detmar, 1996; 2000) suggesting that increased VEGF plays key roles in these skin problems. The evidences and the suggested roles of up-regulated VEGF in abnormal skin condition are summarized in Table 1.

### Cutaneous inflammation

Inflammation is basically a self-defense innate immune response against harmful stimuli including infectious agents, physical or chemical challenges. For infiltration of inflammatory cells to inflamed tissue, change in vascular permeability is inevitable. Besides the hyper-permeability, the close association between angiogenesis and inflammation is reported in various skin diseases that require vascular remodeling (Detmar et al., 1994; Karkkainen and Petrova, 2000). Angiogenesis and lymphangiogenesis occur in chronic cutaneous inflammations in atopic dermatitis and psoriasis (Detmar et al., 1994; Zhang et al., 2006; Elias et al., 2008; Huggenberger and Detmar, 2011). Hyper-permeability and angiogenesis/lymphangiogenesis are mainly mediated by VEGF, therefore it is convincing that VEGF is up-regulated in lesions with cutaneous inflammation (Detmar et al., 1994; Elias et al., 2008; Zhang et al., 2006). It is also interesting that pro-inflammatory cytokines up-regulate VEGF in keratinocytes. Temporal expression profile of cytokines in epidermal keratinocytes is important in the orchestration of inflammatory responses (Kataru et al., 2009). IL-1, 6, 8 and TNF-α are known to be potent inducers for keratinocyte-derived VEGF-A (Detmar et al., 1995). VEGF-C induction associated with up-regulated VEGF-3 and dermal lymphangiogenesis were observed in the lesion of atopic dermatitis in IL-4 transgenic mouse (Shi et al., 2012), supporting the role of VEGF in IL-mediated lymphangiogenesis and inflammation. The role of VEGF as a chemotactic factor in skin inflammation was also reported (Suzuki et al., 2014).

### Psoriasis

The link between pathological skin condition and VEGF is well-established in psoriasis by clinical and experimental data (Elías et al., 2008; Schonthaler et al., 2009), and it is even suggested that systemic VEGF antagonist can be a therapeutic option for psoriasis treatment (Canavese et al., 2010; Weidemann et al., 2013). The systemic serum VEGF level (Bhushan et al., 1999; Nielsen et al., 2002), as well as the local level of VEGF in hyperplastic epidermis is significantly increased in psoriasis, along with up-regulation of VEGFRs in ECs (Detmar et al., 1994; Bhushan et al., 1999). The observation that both

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**Table 1. Keratinocyte derived VEGF under pathological conditions in skin**

| Pathological condition | Evidences for VEGF involvement | Suggested roles of VEGF | Refs |
|------------------------|--------------------------------|-------------------------|------|
| Cutaneous inflammation | Increased expression of VEGF/VEGFR in skin lesion of inflammation | Hyper-permeability | Detmar et al., 1994; Elias et al., 2008; Huggenberger and Detmar, 2011; Suzuki et al., 2014; Zhang et al., 2006 |
|                         | VEGF induction by inflammatory cytokines such as ILs and TNF-α | Angiogenesis | |
|                         | VEGF-induced immune cell accumulation in the skin | Lymphangiogenesis | |
| Psoriasis | Increased expression of VEGF/VEGFR in skin lesion of psoriasis | Epidermal hyperplasia | Bhushan et al., 1999; Canavese et al., 2010; Detmar et al., 1994, 1998; Elias et al., 2008; Nielsen et al., 2002; Rogers and D’Amato, 2006; Schonthaler et al., 2009; Weidemann et al., 2013; Xia et al., 2003; Young et al., 2006 |
|                         | Increased level of systemic serum VEGF in psoriasis | Hyper-permeability | |
|                         | Aggravated psoriasis in VEGF transgenic animal | Inflammation | |
|                         | Reduced psoriatic symptoms after systemic antagonism against VEGF-VEGFR | Enragement of lymphatic vessels | |
|                         | Susceptibility change in psoriasis by VEGF genetic polymorphism | | |
| Phototoxicity | Increased VEGF induction in skins and keratinocytes | Hyper-permeability | Blaudschun et al., 2000; Brauchle et al., 1996; Brenneisen et al., 2003; Gille et al., 2000; Hirakawa et al., 2005; Longuet-Perret et al., 1998; Yano et al., 2005 |
|                         | Increased level of VEGF by UV irradiation | Edema | |
|                         | Increased susceptibility to photo-damage by VEGF | Erythema | |
|                         | Increased level of VEGF by UV irradiation | Epidermal hyperplasia | |
|                         | Increased susceptibility to photo-damage by VEGF | Inflammation | |
| Skin cancer | VEGF up-regulation in lesions of skin cancers | Angiogenesis | Alitalo et al., 2013; Detmar et al., 1995; Gille et al., 2000; Hicklin and Ellis, 2005; Mantovani et al., 2008 |
|                         | Reduced invasion by blocking of VEGF-VEGFR | Lymphangiogenesis | |
|                         | Increased invasion by over-expressed VEGF | Inflammation | |
|                         | Increased invasion by over-expressed VEGF | Invasion | |

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systemic and local cutaneous levels of VEGF are increased under psoriasis further warrants the need to investigate the relationship between systemic and local VEGF in skin disorders. The clinical characteristics of psoriasis, which are epidermal hyperplasia, inflammation, hyper-permeable blood vessels, and enlargement of lymphatic vessels (Christensen et al., 2006), are closely associated with bioactivity of VEGF. The contribution of VEGF to psoriatic pathogenesis has been confirmed in experimental models, where typical features of human psoriasis were observed in transgenic mice with increased VEGF levels (Detmar et al., 1998; Xia et al., 2003). Keratinocytic VEGF was induced by vasoactive intestinal peptide (VIP), which is specifically found in psoriatic epidermis (Kakurai et al., 2009; Yu et al., 2010). Interestingly, several studies reported that the susceptibility to psoriasis might be affected by VEGF genetic polymorphism. Single nucleotide polymorphism of the VEGF gene was found to be more frequent in patients with psoriasis compared to healthy individuals, with increased level of VEGF (Young et al., 2006). Promoter variations in the VEGF gene were also reported to be associated with development of psoriatic symptoms (Rogers and D’Amato, 2006), further supporting the role of VEGF in the etiology of psoriasis.

**Phototoxicity**

UV irradiation is a major physical stimulus to skin, causing cutaneous phototoxicity such as photo-irritation, photo-sensitization, photo-aging, and photo-carcinogenesis (Syed et al., 2012). UV exposure induces generation of reactive oxygen species (ROS) affecting cellular macromolecules and DNA, and also activates multiple signaling pathways responsible for cell growth and proliferation. Different signaling pathways are known to be activated by UVA (320-400 nm) and UVB (280-320 nm) (Mildner et al., 1999; Syed et al., 2012). VEGF expression in cultured keratinocytes was induced by UVB irradiation (Brauchle et al., 1996; Yano et al., 2005), both indirectly by releasing soluble factors such as IL-1 and TNF-α or directly by activating transcription factors such as NFκB, AP-1 or AP-2 (Blaudschun et al., 2000; Gille et al., 2000; Brenneisen et al., 2003). While UVB induced VEGF up-regulation in primary human keratinocytes and in immortalized keratinocytes (HaCaT) (Longuet-Perret et al., 1998; Brenneisen et al., 2003), UVA increased VEGF level only in HaCaT cells (Longuet-Perret et al., 1998; Gille et al., 2000) suggesting specific regulation of cutaneous VEGF signaling in the immortalized keratinocytes which may favor tumorigenic transformation. UV irradiation induces skin alteration such as erythema, hyper-permeability, edema, and epidermal hyperplasia, which are closely associated with VEGF. Hirakawa et al. (2005) demonstrated that VEGF promotes sensitivity to UVB-induced cutaneous photodamage in VEGF-transgenic mice, suggesting that VEGF may serve as a target for the prevention of photo-damage.

**Skin carcinogenesis**

It is well-established that tumor cells show increased metabolic demands and initiate angiogenic response. Consistently, VEGF up-regulation was frequently observed in skin cancers and it has been considered to act as an endothelial-specific mitogen (Detmar et al., 1995, Hicklin and Ellis, 2005). It is well known that VEGF regulates endothelial cells in tumor angiogenesis and vascular permeability, but it has been recently found that VEGF also plays an integral role in tumor cell signaling in autocrine manner, such as promoting dedifferentiation and an epithelial-mesenchymal transition (Senger, 2010; Cao et al., 2012; Goel and Mercurio, 2013). Other cells in tumor microenvironment including immune cells and fibroblasts can also be regulated by VEGF, enhancing tumorigenesis (Quail and Joyce, 2013). In skin cancer including squamous cell carcinomas, VEGF-VEGFR signaling was found to be critical for invasion, and selective VEGF over-expression was sufficient for tumor invasiveness in vivo (Detmar, 2000). Angiogenesis and lymphangiogenesis were required for tumor growth, metastasis, and further infiltration of inflammatory cells (Mantovani et al., 2008; Ailtalo et al., 2013). Blockade of VEGF-C and D signaling resulted in suppressed inflammatory tumor microenvironment, leading to significant inhibition of early skin cancer progression (Ailtalo et al., 2013). Interestingly, UVA specifically induced VEGF in HaCaT cells (Gille et al., 2000), suggesting that VEGF signaling may differ in pre-malignant phenotype.

**VEGF INDUCTION BY XENOBIOTICS**

Besides pathological skin conditions, keratinocyte-derived VEGF can be induced by several xenobiotics supporting its potential as a novel biomarker in chemical-induced skin problem. VEGF over-expression in keratinocytes was observed by the treatment with phorbol esters, such as 12-O-tetradecanoylphorbol-13-acetate (TPA) (Diaz et al., 2000). It is also known that oxidants such as H2O2 can enhance VEGF expression in keratinocyte (Brauchle et al., 1996; Sen et al., 2002), suggesting that cutaneous VEGF can be regulated by redox control. Peroxisome proliferator-activated receptor-gamma (PPARγ) agonist troglitazone significantly induced VEGF expression in keratinocytes mediated by p38 MAPK activation (Schiefelbein et al., 2008). Of note, there is an initial study to suggest VEGF as a potential soluble mediator for hyper-permeability and inflammation, where several contact allergens, metals and an irritant induced VEGF in keratinocytes (Palacio et al., 1997). Still, the mechanisms and the roles of chemically induced VEGF in keratinocytes are largely unknown, which warrant future researches.

**IN VolvE of VEGFR**

Although VEGFRs are predominantly expressed in ECs supporting the paracrine signaling of keratinocyte-derived VEGF, all types of identified VEGFRs are also expressed in keratinocytes in normal epidermis (Man et al., 2006). The VEGFR signaling in keratinocytes involves in the proliferation and migration of normal keratinocytes (Man et al., 2006). Using VEGFR-1 specific neutralizing antibody, it was demonstrated that VEGFR-1 in keratinocytes promoted re-epithelialization through a novel autocrine pathway (Wilgus et al., 2005). Besides the constitutive expression in normal keratinocytes, VEGFRs are found to be functionally over-expressed in pathological condition including psoriatic epidermis (Man et al., 2006; 2008; Zhu et al., 2013), and can be up-regulated by UV irradiation (Zhu et al., 2012).
FUTURE DIRECTIONS

Identification of a biomarker for skin damage is an emerging issue for safety assessment of cosmetics or topically-administered medicinal compounds. Traditional skin toxicity test methods have been mostly performed in animal models. However, especially in cosmetic industries, the use of experimental animal is prohibited by the implementation of the 7th Amendment of the Cosmetic Directives in Europe (Directive 2003/15/EC), based on a growing attention on animal welfare. There have been intensive efforts to develop non-animal alternative tests for skin toxicity. The identification of reliable biomarkers for skin damage is prerequisite for development of new alternative methods. Also, a biomarker that can represent an integrated in vivo alteration would be useful to predict the potential biological effect and toxicity. Here we discussed the possibility of VEGF as a novel biomarker for keratinocytic damage in skin toxicity testing, based on the clear evidences on a significant role of VEGF in pathological alteration of keratinocytes under skin disorders.

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REFERENCES

Alitalo, A. K., Proulx, S. T., Karaman, S., Aebischer, D., Martino, S., Jost, M., Schneider, N., Bly, M. and Detmar, M. (2013) VEGF-C and VEGF-D blockade inhibits inflammatory skin carcinogenesis. Cancer Res. 73, 4212-4221.

Bernard, F. X., Morel, F., Camus, M., Pedretti, N., Barrault, C., Garnier, J. and Lecron, J. C. (2012) Keratinocytes under fire of proinflammatory cytokines: Bona fide innate immune cells involved in the physiopathology of chronic atopic dermatitis and psoriasis. J. Allergy (Cairo) 2012, 718725.

Ballau, C., Wegner, W., Uthman, A., Weich, H. and Tscharck, E. (1995) Human keratinocytes express the three major splice forms of vascular endothelial growth factor. J. Invest. Dermatol. 104, 7-10.

Bhushan, M., McLaughlin, B., Weiss, J. B. and Griffiths, C. E. (1999) Levels of endothelial cell stimulating angiogenesis factor and vascular endothelial growth factor are elevated in psoriasis. Br. J. Dermatol. 141, 1054-1060.

Blauschudn, R., Brenneisen, P., Wlaschek, M., Meeves, C. and Schaffetter-Kochanek, K. (2000) The first peak of the UVB irradiation-dependent biphasic induction of vascular endothelial growth factor (VEGF) is due to phosphorylation of the epidural growth factor receptor and independent of autocrine transforming growth factor alpha. FEBS Lett. 474, 195-200.

Brauchle, M., Funk, J. O., Kind, P. and Werner, S. (1996) Ultraviolet B and H2O2 are potent inducers of vascular endothelial growth factor expression in cultured keratinocytes. J. Biol. Chem. 271, 21793-21797.

Brenneisen, P., Blauschudn, R., Gille, J., Schneider, L., Hinrichs, R., Wlaschek, M., Eming, S. and Schaffetter-Kochanek, K. (2003) Essential role of an activator protein-2 (AP-2)/specificity protein 1 (Sp1) cluster in the UVB-mediated induction of the human vascular endothelial growth factor in HaCaT keratinocytes. Biochem. J. 369, 341-349.

Brown, L. F., Yeo, K. T., Berse, B., Yeo, T. K., Senger, D. R., Dvorak, H. F. and van de Water, L. (1992) Expression of vascular permeability factor (vascular endothelial growth factor) by epidermal keratinocytes during wound healing. J. Exp. Med. 176, 1375-1379.

Canavese, M., Altruda, F., Ruzicka, T. and Schaubner, J. (2010) Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis—a possible target for novel therapies? J. Dermatol. Sci. 58, 173-176.

Cao, Y. E. G., Wang, E. P., Pal, K., Dutta, S. K., Bar-Sagi, D. and Mukhopadhyay, D. (2012) VEGF exerts an angiogenesis-independent function in cancer cells to promote their malignant progression. Cancer Res. 72, 3912-3918.

Carmeliet, P. (2000) Mechanisms of angiogenesis and arteriogenesis. Nat. Med. 6, 389-395.

Christensen, T. E., Callis, K. P., Papenfuss, J., Hoffman, M. S., Hansen, C. B., Wong, B., Panko, J. M. and Krueger, G. G. (2006) Observations of psoriasis in the absence of therapeutic intervention identifies two unappreciated morphologic variants, thin-plateau and thick-plateau psoriasis, and their associated phenotypes. J. Invest. Dermatol. 126, 2397-2403.

Cohen, T., Nahari, D., Cerem, L. W., Neufeld, G. and Levi, B. Z. (1996) Interleukin 6 induces the expression of vascular endothelial growth factor. J. Biol. Chem. 271, 736-741.

de Vries, C., Escobedo, J. A., Ueno, H., Houck, K., Ferrara, N. and Williams, L. T. (1992) The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. Science 255, 989-991.

Detmar, M. (1996) Molecular regulation of angiogenesis in the skin, J. Invest. Dermatol. 106, 207-208.

Detmar, M. (2000) The role of VEGF and thrombospondins in skin angiogenesis. J. Dermatol. Sci. 24 Suppl 1, S78-84.

Detmar, M., Brown, L. F., Berse, B., Jackman, R. W., Elicker, B. M., Dvorak, H. F. and Claffey, K. P. (1997) Hypoxia regulates the expression of vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) and its receptors in human skin. J. Invest. Dermatol. 108, 263-268.

Detmar, M., Brown, L. F., Claffey, K. P., Yeo, K. T., Kocher, O., Jackman, R. W., Berse, B. and Dvorak, H. F. (1994) Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J. Exp. Med. 180, 1141-1146.

Detmar, M., Brown, L. F., Schno, M. P., Elicker, B. M., Velasco, P., Richard, L., Fukumura, D., Monsky, W., Claffey, K. P. and Jain, R. K. (1998) Increased microvascular density and enhanced leukocyte rolling and adhesion in the skin of VEGF transgenic mice. J. Invest. Dermatol. 111, 1-6.

Detmar, M., Yeo, K. T., Nagy, J. A., Van de Water, L., Brown, L. F., Berse, B., Elicker, B. M., Ledbetter, S. and Dvorak, H. F. (1995) Keratinocyte-derived vascular permeability factor (vascular endothelial growth factor) is a potent mitogen for dermal microvascular endothelial cells. J. Invest. Dermatol. 105, 44-50.

Diaz, B. V., Lenoir, M. C., Ladoix, A., Frelin, C., Demarchez, M. and Michel, S. (2000) Regulation of vascular endothelial growth factor expression in human keratinocytes by retinoids. J. Biol. Chem. 275, 642-650.

Elis, P. M., Arbiser, J., Brown, B. E., Rossiter, H., Man, M. Q., Cerimele, F., Crumrine, D., Gunathilake, R., Choi, E. H., Uchida, Y., Tscharck, E. and Feingold, K. R. (2008) Epidermal vascular endothelial growth factor production is required for permeability barrier homeostasis, dermal angiogenesis, and the development of epidermal hyperplasia: implications for the pathogenesis of psoriasis. Am. J. Pathol. 173, 689-699.

Enerbäck, C. (2011) Soluble biomarkers in psoriasis. Eur. J. Dermatol. 21, 844-850.

Ferrara, N., Gerber, H. P. and LeCouter, J. (2003) The biology of VEGF and its receptors. Nat. Med. 9, 669-676.

Finkenzeller, G., Sparacio, A., Technau, A., Marme, D. and Siemens, G. (1997) Sp1 recognition sites in the proximal promoter of the human vascular endothelial growth factor gene are essential for platelet-derived growth factor-induced gene expression. Oncogene 15, 669-676.

Fontaine, J. A., Jiang, B. H., Iyer, N. V., Agani, F., Leung, S. W., Koos, R. D. and Semenza, G. L. (1996) Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Mol. Cell. Biol. 16, 4604-4613.

Frank, S., Hubner, G., Breier, G., Longaker, M. T., Greenhah, D. G. and Werner, S. (1995) Regulation of vascular endothelial growth factor expression in cultured keratinocytes. Implications for normal
and impaired wound healing. J. Biol. Chem. 270, 12607-12613.

Geretti, E., Shimizu, A. and Klagsbrun, M. (2008) Neuropilin structure governs VEGF and semaphorin binding and regulates angiogenesis. Angiogenesis 11, 31-39.

Gille, J., Reisinger, K., Asbe-Vollkopf, A., Hardt-Weinelt, K. and Kaufmann, R. (2000) Ultraviolet-A-induced transactivation of the vascular endothelial growth factor gene in HaCaT keratinocytes is conveyed by activator protein-2 transcription factor. J. Invest. Dermatol. 115, 30-36.

Gille, J., Swerlick, R. A. and Caughman, S. W. (1997) Transforming growth factor-alpha-induced transcriptional activation of the vascular permeability factor (VPF/VEGF) gene requires AP-2-dependent DNA binding and transactivation. EMBO J. 16, 750-759.

Goel, H. L. and Mercurio, A. M. (2013) VEGF targets the tumour cell. Nat. Rev. Cancer 13, 871-882.

Hännel, K. H., Cornelissen, C., Lüscher, B. and Baron, J. M. (2013) Cyclophillin A governs VEGF and semaphorin binding and regulates angiogenesis. Blood 112, 3071-3078.

Goel, H. L. and Mercurio, A. M. (2013) VEGF targets the tumour cell. Nat. Rev. Cancer 13, 871-882.

Huggenberger, R. and Detmar, M. (2011) The cutaneous vascular system in chronic skin inflammation. J. Investig. Dermatol. Symp. Proc. 15, 24-32.

Hirakawa, S., Fujii, S., Kajiya, Y., Yan, Q. and Detmar, M. (2005) Vascular endothelial growth factor promotes sensitivity to ultraviolet B-induced cutaneous photocarcinogenesis. Blood 105, 2392-2399.

Hynes, R. O. (2013) Integrins in cancer biology. Nat. Rev. Cancer 13, 13-26.

Jalanko, H., Kallioniemi, O., Kallioniemi, P., Pajukoski, K., Saarinen, A., Seal, S., Knuutila, S., de Sauvage, F. J. and Komminoth, P. (1999) 26S proteasome-mediated degradation of c-FLIP blocks apoptosis by glucocorticoids in endothelial cells. EMBO J. 18, 1623-1631.

Kariya, M., Demitsu, T., Umemoto, N., Kobayashi, Y., Inoue-Narita, T., Kimura, K., Obika, K., Yano, K. and Detmar, M. (2014) Possible pathogenic role of T helper type 9 cells and interleukin (IL)-9 in atopic dermatitis. Clin. Exp. Immunol. 175, 25-31.

Man, X. Y., Yang, X. H., Cai, S. Q., Bu, Z. Y. and Zheng, M. (2008) Overexpression of vascular endothelial growth factor (VEGF) receptors on keratinocytes in psoriasis: regulated by calcium independent of VEGF. J. Cell. Mol. Med. 12, 649-660.

Mildner, M., Weninger, W., Trautinger, F., Ban, J. and Tschachler, E. (1999) UVA and UVB radiation differentially regulate vascular endothelial growth factor expression in keratinocyte-derived cell lines and in human keratinocytes. Photochem. Photobiol. 70, 674-679.

Nakai, K., Yoneda, K., Morie, T., Igarashi, J., Kosaka, H. and Kubota, Y. (2009) HB-EGF-induced VEGF production and eNOS activation depend on both PI3 kinase and MAP kinase in HaCaT cells. J. Dermatol. Sci. 55, 170-178.

Nielsen, H. J., Christensen, I. J., Svendsen, M. N., Hansen, U., Werth, V., Brunner, N., Petersen, L. J. and Kristensen, J. K. (2002) Elevated plasma levels of vascular endothelial growth factor and plasminogen activator inhibitor-1 decrease during improvement of psoriasis. Inflamm. Res. 51, 563-567.

Nissen, N. M., Polverini, P. J., Koch, A. E., Volin, M. V., Gamelli, R. L. and DiPietro, L. A. (1998) Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. Am. J. Pathol. 152, 1445-1452.

Olsson, A. K., Dimberg, A., Kreuger, J. and Claesson-Welsh, L. (2006) VEGF receptor signalling - in control of vascular function. Nat. Rev. Mol. Cell. Biol. 7, 359-371.

Palacio, S., Schmitt, D. and Viac, J. (1997) Contact allergens and sodium lauryl sulphate upregulate vascular endothelial growth factor in normal keratinocytes. Br. J. Dermatol. 137, 540-544.

Quail, D. F. and Joyce, J. A. (2013) Microenvironmental regulation of tumor progression and metastasis. Nat. Med. 19, 1423-1437.

Rogers, M. S. and D’Amato, R. J. (2006) The effect of genetic diversity on angiogenesis. Exp. Cell Res. 312, 561-574.

Ruiz de Almodovar, C., Lambrechts, D., Mazzone, M. and Carmeliet, P. (2009) Role and therapeutic potential of VEGF in the nervous system. Physiol. Rev. 89, 607-648.

Senger, D. R. (2010) Vascular endothelial growth factor: much more than an angiogenesis factor. J. Invest. Dermatol. 134, 2126-2128.

Schiefelbein, D., Seitz, O., Goren, I., Diasmann, J. P., Schmidt, H., Bechmann, M., Sader, R., Geisslinger, G., Pfeilschifter, J. and Frank, S. (2008) Keratinocyte-derived vascular endothelial growth factor biosynthesis represents a pleiotropic side effect of peroxisome proliferator-activated receptor-gamma agonist troglitazone but not rosiglitazone and involves activation of p38 mitogen-activated protein kinase: implications for diabetes-impaired skin repair. Mol. Pharmacol. 74, 952-963.

Schonthaler, H. B., Huggenberger, R., Wculek, S., Detmar, M. and Wagner, E. F. (2009) Systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis. Proc. Natl. Acad. Sci. U.S.A. 106, 21264-21269.

Scortegagna, M., Cataisson, C., Martin, R. J., Hicklin, D. J., Schreiber, R. D., Yuspa, S. H. and Arbeit, J. M. (2008) HIF-1alpha regulates epithelial inflammation by cell autonomous NFkappaB activation and paracrine stromal remodeling. Blood 111, 3343-3354.

Sen, C. K., Khanna, S., Babiory, B. M., Hunt, T. K., Ellision, E. C. and Roy, S. (2002) Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. J. Biol. Chem. 277, 33284-33290.

Senger, D. R. (2010) Vascular endothelial growth factor: much more than an angiogenesis factor. Mol. Biol. Cell 21, 377-379.

Senger, D. R., Galli, S. J., Dvorak, A. M., Perruzzi, C. A., Harvey, V. S. and Dvorak, D. H. (1983) Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 219, 983-985.

Shi, V. Y., Bao, L. and Chan, L. S. (2012) Inflammation-driven dermal lymphangiogenesis in atopic dermatitis is associated with CD11b+ macrophage recruitment and VEGF-C up-regulation in the IL-4-transgenic mouse model. Microcirculation 19, 687-679.

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