HIF-1α in Epidermis: Oxygen Sensing, Cutaneous Angiogenesis, Cancer, and Non-Cancer Disorders

Hamid R. Rezvani[1,2], Nsrein Ali[1,2], Lars J. Nissen[1,2], Ghida Harfouche[1,2], Hubert de Verneuil[1,2], Alain Taïeb[1,2,3] and Frédéric Mazurier[1,2]

Besides lung, postnatal human epidermis is the only epithelium in direct contact with atmospheric oxygen. Skin epidermal oxygenation occurs mostly through atmospheric oxygen rather than tissue vasculature, resulting in a mildly hypoxic microenvironment that favors increased expression of hypoxia-inducible factor-1α (HIF-1α). Considering the wide spectrum of biological processes, such as angiogenesis, inflammation, bioenergetics, proliferation, motility, and apoptosis, that are regulated by this transcription factor, its high expression level in the epidermis might be important to HIF-1α in skin physiology and pathophysiology. Here, we review the role of HIF-1α in cutaneous angiogenesis, skin tumorigenesis, and several skin disorders.

Journal of Investigative Dermatology (2011) **131,** 1793–1805; doi:10.1038/jid.2011.141; published online 2 June 2011

INTRODUCTION

Since the mid-nineteenth century, skin atmospheric oxygen uptake has been documented in vertebrates. Whereas amphibians use skin as a major respiratory surface and fish take up 60% of their oxygen through the skin, transcutaneous oxygen uptake in human adult skin, accounting for 0.4% of the lung epithelium uptake, covers most epidermal needs (Stucker *et al.*, 2002). The importance of oxygen sensing by keratinocytes is already known in premature babies in whom oxygenation through skin has been used as a surrogate to the respiratory route (Cartlidge and Rutter, 1988). Moreover, it has been recently shown that oxygen sensing by keratinocytes in a mouse model affects systemic oxygen delivery to other organs (Boutin *et al.*, 2008). These data among others suggest that epidermis has had a leading role in the adaptation of the organism to environmental oxygen pressure during evolution through its oxygen-sensing capacity.

Metazoan species have evolved a highly conserved key protein, hypoxia-inducible factor-1α (HIF-1α), to regulate oxygen delivery to tissue. Originally discovered as the regulator of oxygen homeostasis through the control of erythropoietin, HIF-1α was then found to drive the expression of hundreds of genes (Wenger *et al.*, 2005; Semenza, 2007) involved in many biological processes, including neovascularization, angiogenesis, cytoskeletal structure, survival/apoptosis, adhesion, migration, invasion, metastasis, glycolysis, and metabolic bioenergetics (review in Semenza, 2003; Pouyssegur *et al.*, 2006).

Quantitative evaluation of tissue oxygenation has shown that physiological oxygen pressure in epidermis is low compared with other tissues (Table 1; Evans and Naylor, 1967; Stewart *et al.*, 1982; Distler *et al.*, 2004; Bedogni *et al.*, 2005; Evans *et al.*, 2006). Although dermal oxygen partial pressure is 10% (corresponding to 76 mm Hg), the pressure corresponding to the epidermis ranges between 0.2 and 8% (Evans *et al.*, 2006). Indeed, epidermal oxygenation, which occurs mostly through atmospheric oxygen (Stucker *et al.*, 2002), results in a mildly hypoxic microenvironment. Consistent with this constitutive low epidermal oxygenation, an accumulation of the hypoxia-detection agent, nitroimidazole/EF5, as well as high levels of nuclear HIF-1α have been detected in both human and mouse epidermis, especially in the basal layer (Figure 1; Distler *et al.*, 2004; Bedogni *et al.*, 2005; Boutin *et al.*, 2008). Considering the broad spectrum of HIF-1α effects, its high level of expression in epidermis could reflect an important role in local and systemic adaptation to environmental stresses. In this review, we highlight the role of HIF-1α in cutaneous angiogenesis, skin tumorigenesis, and other skin disorders.

HIF-1α: STRUCTURE, REGULATION, AND TARGET GENES

Structure of the HIF-1α protein

HIF-1 is related to the family of basic-helix-loop-helix transcription factors. It comprises two subunits, HIF-1α, which is tightly regulated, and the

[1]*INSERM U1035, Bordeaux, France;* [2]*Université Bordeaux Segalen, Bordeaux, France and* [3]*Département de Dermatologie & Dermatologie Pédiatrique, CHU de Bordeaux, Centre de Référence des Maladies Rares de la Peau, Hôpital St André, Bordeaux, France*

Correspondence: Hamid R. Rezvani, INSERM U1035, Université Bordeaux Segalen, Bordeaux, 146, rue Léo Saignat, F-33076, France. E-mail: hamidreza.rezvani@u-bordeaux2.fr

Abbreviations: AKT, protein kinase B (PKB); ECM, extracellular matrix; HIF-1α, hypoxia-inducible factor; ROS, reactive oxygen species; SCC, squamous cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; XP, xeroderma pigmentosum

Received 11 October 2010; revised 22 February 2011; accepted 6 March 2011; published online 2 June 2011

Table 1. Oxygen level in different human tissues

Tissue	Oxygen (%)	Reference
Skin		Evans *et al.* 2006
Dermis	>7	
Epidermis	0.2–8	
Hair follicles	0.1–0.8	
Sebaceous gland	0.1–1.3	
Vessels	4–14	Saltzman *et al.* 2003
Heart	5–10	Roy *et al.* 2003
Brain	0.5–7	Hemphill *et al.* 2005; Nwaigwe *et al.* 2000
Kidney	4–6	Welch and Wilcox, 2001

Atmospheric air contains about 20.9% O_2, which represents a partial atmospheric pressure of 160 mm Hg. The qualitative terms physiological, modest hypoxia, moderate hypoxia, severe hypoxia, and anoxia are used to designate 10–14, 2.5, 0.5, 0.1, and 0% O_2, respectively. These percentages are assigned to partial oxygen pressures of 75–100, 19, 3.8, 0.76, and 0.0 mm Hg, respectively (Evans *et al.*, 2006).

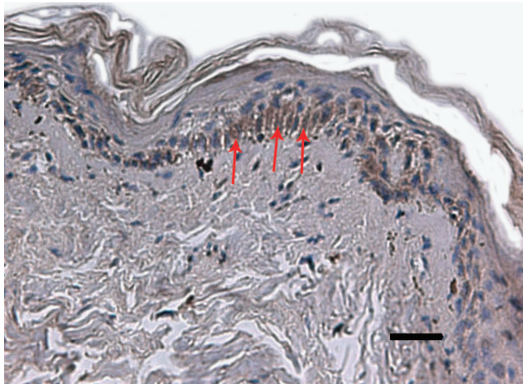

Figure 1. Hypoxia-inducible factor-1α (HIF-1α) expression in skin. Human skin immunolabeled using a specific anti-HIF-1α antibody, followed by envision + horseradish peroxidase reagent, revealed with diaminobenzidine and counterstained with hemalun. HIF-1α-positive cells appear brown. Bar = 100 μm.

constitutively expressed aryl hydrocarbon nuclear translocator ARNT also called HIF-1β (Figure 2a; reviewed by Maxwell, 2004; Metzen and Ratcliffe, 2004). Three isoforms of the α-subunit, named HIF-1α, HIF-2α (also referred to as EPAS-1, MOP2, HLF, and HRF), and HIF-3α, have so far been identified in the human genome (Maynard *et al.*, 2003).

Two transactivation domains, N-terminal and C-terminal, have been identified in HIF-1α. They interact with histone acetyltransferases, such as CBP, p300, and SRC-1, to activate the transcription of target genes. This association is regulated by both oxygen concentration and redox status. The basic-helix-loop-helix and Per-Arnt-Sim (PAS) domains are required for dimerization of HIF-1α with HIF-1β as well as for DNA binding. In addition to the binding to DNA and coactivators, HIF-1α interacts with factors regulating its stability such as heat shock protein-90 (Figure 2a; Brahimi-Horn *et al.*, 2005; Fandrey *et al.*, 2006).

Regulation of HIF-1α

Under atmospheric oxygen pressure (termed normoxia), HIF-1α is rapidly targeted for ubiquitination and proteasomal degradation after binding to the von Hippel–Lindau E3 ligase. The hydroxylation of HIF-1α mediated by prolyl hydroxylases is a prerequisite for the association of HIF-1α with von Hippel–Lindau (Maxwell *et al.*, 1999; Cockman *et al.*, 2000; Kamura *et al.*, 2000; Ohh *et al.*, 2000). Hydroxylation by prolyl hydroxylase occurs on two specific prolines (P402 and P564 in human) present in the oxygen-dependent degradation domain of HIF-1α in the presence of iron, oxygen, and 2-oxoglutarate (Ivan *et al.*, 2001; Jaakkola *et al.*, 2001; Masson *et al.*, 2001). Concurrently, hydroxylation of the asparagine residue 803 by an asparaginyl hydroxylase (also named FIH-1) prohibits binding of p300/CBP to the HIF-1α subunit, which consequently abolishes transactivation of HIF-1α (Mahon *et al.*, 2001). Reduction in prolyl hydroxylase activity under hypoxia results in stabilization and accumulation of HIF-1α. Hypoxia-mediated reactive oxygen species (ROS) modulation and post-transcriptional modifications (e.g., phosphorylation, sumoylation, *S*-nitrosylation, and acetylation) of HIF-1α have also been shown to be crucial in its stabilization and/or transcriptional activation process (Brahimi-Horn *et al.*, 2005; Fandrey *et al.*, 2006). When stabilized, HIF-1α translocates to the nucleus, dimerizes with HIF-1β, and binds to the hypoxia-response element (with an (A/G)CGTG core sequence) of target genes (Figure 2b and Table 2; Wenger *et al.*, 2005).

In addition to hypoxia, multiple oncogenic pathways, including growth factor signaling or genetic loss of tumor suppressors, can regulate HIF-1α activity (Figure 2b; Semenza, 2002). Mitogen-activated protein kinases are required for the activation of the transcriptional activity and/or for HIF-1α stabilization (Salceda *et al.*, 1997; Minet *et al.*, 2000; Hur *et al.*, 2001; Rezvani *et al.*, 2007). The loss of the tumor suppressor genes, von Hippel–Lindau or phosphatase and tensin homolog, upregulates HIF-1α activity (Semenza, 2002). HIF-1α stabilization could also be dependent on the phosphatidylinositol 3-kinase, protein kinase B (PKB/AKT), and its effector mammalian target of rapamycin (Paul *et al.*, 2004). Basic fibroblast growth factor, insulin, IL-1, hepatocyte growth factor, and heregulin induce the expression of HIF-1α (Zhong *et al.*, 2000; Sodhi *et al.*, 2001; Tacchini *et al.*, 2001; Stiehl *et al.*, 2002; Kietzmann and Gorlach, 2005). ROS, as second messengers, are other effectors found to

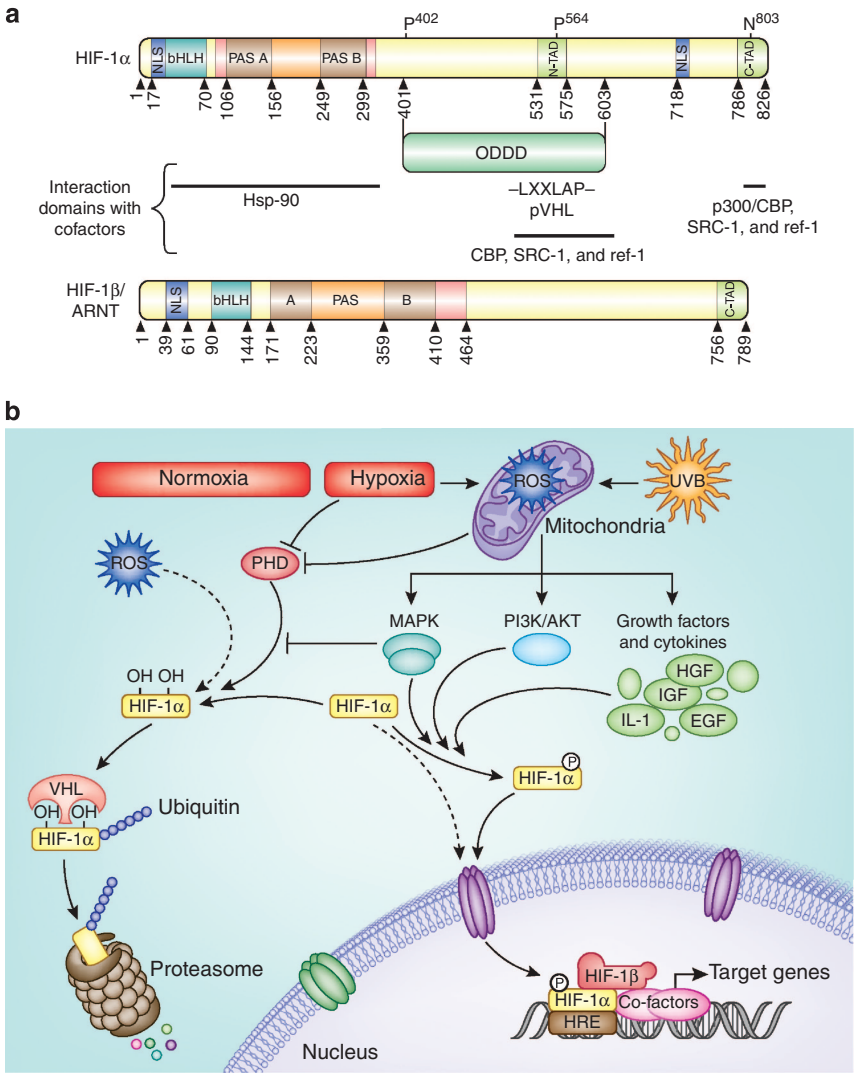

Figure 2. Structure and regulation of hypoxia-inducible factor-1α (HIF-1α) under different stimuli. (**a**) Schematic representation of human HIF-1α and HIF-1β. Both proteins are related to the basic-helix-loop-helix–Per-Arnt-Sim (bHLH–PAS) transcription factor family that contains an N-terminal bHLH domain and two PAS domains. HIF-1α contains an oxygen-dependent degradation domain (ODDD) that mediates oxygen-regulated stability, and a C-terminal transactivation domain (C-TAD) whose transcriptional repression in normoxia is controlled through hydroxylation of the asparagine 803 by the factor-inhibiting HIF-1. Interaction domains with von Hippel–Lindau (VHL) and other cofactors are indicated, as well as amino-acid numbers for each domain. (**b**) Under normoxia, HIF-1α is subjected to oxygen-dependent hydroxylation on proline 402 and 564 in ODDD. Ubiquitination by the VHL targets HIF-1α to proteasomal degradation. Under conditions of hypoxia, UVB irradiation, or upon activation of some growth factor signaling pathways, HIF-1α is stabilized, translocates to the nucleus, interacts with hypoxia-responsive elements (HREs), and finally promotes the activation of target genes. It is important to note that growth factors, cytokines, and AKT activation can also induce HIF-1α protein synthesis or coactivator recruitment. AKT, protein kinase B; HGF, hepatocyte growth factor; Hsp-90, heat shock protein-90; LXXLAP, the motif that is required for interaction with prolyl hydroxylase (PHD) and VHL, and conserved from *Caenorhabditis elegans* to human; MAPK, mitogen-activated protein kinase; NLS, nuclear localization signal; N-TAD, N-terminal transactivation domain; PI3K, phosphatidylinositol 3-kinase; pVHL, protein VHL; ROS, reactive oxygen species.

modulate HIF-1α activation positively or negatively (Gerald *et al.*, 2004; Kietzmann and Gorlach, 2005; Rezvani *et al.*, 2007; Galanis *et al.*, 2008).

HIF-1α targets

Many HIF-1α target genes are important in skin physiology (Table 2). These include genes that encode proteins involved in cell growth and/or apoptosis (e.g., transforming growth factor-β3, connective tissue growth factor, and Noxa), cell adhesion and migration (e.g., integrin-β1 and laminin-332), DNA repair (e.g., xeroderma pigmentosum C (XPC) and XPD), melanogenesis (e.g., stem cell factor), angiogenesis and wound healing (e.g., vascular endothelial growth factor (VEGF), placental growth factor, and platelet-derived growth factor), extracellular matrix (ECM) formation and turnover (e.g., plasminogen activator inhibitor-1), chemotaxis (stromal cell-derived factor-1), and chemokine receptors (C-X-C chemokine receptor type 4; Liu *et al.*, 1995; Forsythe *et al.*, 1996; Takahashi *et al.*, 2000; Fink *et al.*, 2002; Kelly *et al.*, 2003; Pennacchietti *et al.*, 2003; Staller *et al.*, 2003; Ceradini *et al.*, 2004; Choi *et al.*, 2004; Higgins *et al.*, 2004; Kim *et al.*, 2004; Nishi *et al.*, 2004a; Patel *et al.*, 2005; Erler *et al.*, 2006; Bosch-Marce *et al.*, 2007; Fitsialos *et al.*, 2008; Keely *et al.*, 2009; Rezvani *et al.*, 2010a). HIF-1α also mediates glucose uptake and metabolism by binding to promoter of genes encoding several glucose transporters and glycolytic enzymes (such as glucose transporter-1, hexose kinase-1, and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphate-3; Semenza *et al.*, 1994; Ebert *et al.*, 1995; Okino *et al.*, 1998; Fukasawa *et al.*, 2004; Obach *et al.*, 2004; Roth *et al.*, 2004), which are important in metabolic reprogramming from oxidative to glycolytic metabolism (i.e., the Warburg effect) during carcinogenesis (Rezvani *et al.*, 2011a, b).

HIF-1α EXPRESSION IN CUTANEOUS ANGIOGENESIS

A fine-tuned balance between angiogenic and antiangiogenic factors drives the angiogenic process. Once the balance is disrupted, the vasculature rapidly responds by triggering an angiogenic response, the angiogenic switch (Hanahan and Folkman, 1996). The process occurs universally in both physiological and pathological contexts. Physiological examples of cutaneous angiogenesis include cutaneous blood flow, wound healing, and the hair follicle cycle. Cutaneous

Table 2. HIF-1α target genes with an important function in skin physiology

Major effects	Genes	Reference
Cutaneous angiogenesis		
Re-epithelialization, granulation tissue formation, and ECM synthesis and remodeling	*VEGF*	Forsythe *et al.* 1996; Liu *et al.* 1995
	PLGL	Kelly *et al.* 2003; Patel *et al.* 2005
	PDGF	Kelly *et al.* 2003; Patel *et al.* 2005
	TGF-β3	Nishi *et al.* 2004a
	CTGF	Higgins *et al.* 2004
	IGFBP-1	Tazuke *et al.* 1998
	SDF-1	Ceradini *et al.* 2004
Vascular tone	*iNOS*	Melillo *et al.* 1995
	HO	Lee *et al.* 1997
	ET1	Hu *et al.* 1998
ECM metabolism	*PAI-1*	Fink *et al.* 2002
	Lysyl oxidase	Erler *et al.* 2006
	Collagen prolyl-4 hydroxylase	Takahashi *et al.* 2000
Cell proliferation, motility, and migration	*Integrin-β1*	Keely *et al.* 2009
	Laminin-332	Fitsialos *et al.* 2008
Skin tumorigenesis		
DNA repair	*XPC*	Rezvani *et al.* 2010a
	XPD	Rezvani *et al.* 2010a
	CSB	Filippi *et al.* 2008; Rezvani *et al.* 2010a
	MSH-2	Koshiji *et al.* 2005
Cell growth/apoptosis	*BNIP3*	Bruick, 2000; Kothari *et al.* 2003
	Noxa	Kim *et al.* 2004
	MCL-1	Piret *et al.* 2005
	Tert	Nishi *et al.* 2004b; Yatabe *et al.* 2004
Metabolism	*GLUT1*	Ebert *et al.* 1995; Okino *et al.* 1998
	HK1	Roth *et al.* 2004
	PFKFB3	Fukasawa *et al.* 2004; Obach *et al.* 2004
	Phosphoglycerate kinase-1	Semenza *et al.* 1994
	Lactate dehydrogenase A	Firth *et al.* 1995
	ENO1	Semenza *et al.* 1996
	GAPDH	Graven *et al.* 1999; Lu *et al.* 2002
Xenobiotic transporter	*MDR1*	Comerford *et al.* 2002
Others		
Hematopoiesis and melanogenesis	*SCF*	Bosch-Marce *et al.* 2007
Protooncogene, re-epithelialization, and melanogenesis	*C-MET (HGFR)*	Choi *et al.* 2004; Pennacchietti *et al.* 2003

Abbreviations: BNIP3, BCL2/adenovirus E1B 19-kDa-interacting protein; CSB, Cockayne syndrome B; CTGF, connective tissue growth factor; ECM, extracellular matrix; ENO1, enolase-1; ET1, endothelin-1; GAPDH, glyceraldehyde phosphate dehydrogenase; GLUT1, glucose transporter-1; HGFR, hepatocyte growth factor receptor; HIF, hypoxia-inducible factor; HK1, hexose kinase-1; HO, heme oxygenase; IGFBP-1, IGF-binding protein-1; iNOS, inducible nitric oxide synthase; MCL-1, myeloid cell leukemia sequence-1; MDR1, multidrug resistance-1; MSH, melanocyte-stimulating hormone; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphate-3; PLGL, placental growth factor; SCF, stem cell factor; SDF-1, stromal cell-derived factor-1; Tert, telomerase reverse transcriptase; TGF-β3, transforming growth factor-β3; VEGF, vascular endothelial growth factor; XPC, xeroderma pigmentosum C; XPD, xeroderma pigmentosum D.
Only those genes were included in which binding of HIF-1α to the target DNA sequence in a DNA-binding assay or functional transactivation of reporter gene expression have been reported.

angiogenesis is also involved in inflammation and cancer. A myriad of angiogenic factors are involved in the angiogenic response of various tissues (Bouis *et al.*, 2006; Laquer *et al.*, 2009; Nguyen *et al.*, 2009). Among these factors, HIF-1α has a critical role by regulating angiogenesis through the modulation of several key factors, such as VEGF-A, fibroblast growth factor-2 (Calvani *et al.*, 2006; Black *et al.*, 2008), or the VEGF receptors (VEGFR1, 2, and 3; Gerber *et al.*, 1997). Moreover, inducible nitric oxide synthase, an enzyme producing nitric oxide (NO) that induces cutaneous vasodilatation in response to local heat, injury, or hypoxia (Harbrecht, 2006; Houghton *et al.*, 2006), is a target of HIF-1α (Melillo *et al.*, 1995).

HIF-1α in cutaneous vascular blood flow

Cutaneous blood flow is regulated by vasodilation and vasoconstriction of blood vessels close to the skin surface, and it controls physiological parameters such as body heat (Minson, 2003; Charkoudian, 2010), as well as ions, water, and gas exchange across the skin (Christensen, 1975; Mahany and Parsons, 1978; Malvin and Hlastala, 1989; Gniadecka *et al.*, 1998). Both neuronal and hormonal regulations of cutaneous vasculature are involved in cutaneous blood flow (Langley, 1911; Krogh *et al.*, 1922; Smith, 1976). Overproduction of the HIF-1α target gene *VEGF* in keratinocytes induces the formation of leaky blood vessels and skin ulcerations (Larcher *et al.*, 1998; Thurston *et al.*, 1999), whereas overexpression of stabilized HIF-1α itself in keratinocytes expands skin dermal vasculature without any vascular leakage, edema, or inflammation phenotype (Elson *et al.*, 2001; Kim *et al.*, 2006). Furthermore, an increased number of dilated blood vessels have been observed in these mice (Elson *et al.*, 2001). These data indicate an important regulatory effect of HIF-1α expression in keratinocytes upon cutaneous blood vessel growth and dilation.

HIF-1α in wound healing

Wound healing, a well-defined cascade of events activated following

cutaneous injury to seal the skin defect, is an interactive process involving soluble mediators, blood cells, ECM, and parenchymal cells (Singer and Clark, 1999; Barrientos *et al.*, 2008).

Following acute injury, the microenvironment of the skin wound becomes more hypoxic due to vascular disruption and high oxygen consumption by cells at the edge of the wound (Hunt *et al.*, 1972; Niinikoski *et al.*, 1972; Varghese *et al.*, 1986). This acute hypoxia, which has a positive role in early skin wound healing, is gradually normalized following neovascularization and completion of wound healing (Tandara and Mustoe, 2004). One of the mechanisms underlying the beneficial effects of acute hypoxia on improvement of the wound healing process could be increased HIF-1α expression (Elson *et al.*, 2000; Albina *et al.*, 2001). In support of the positive role of HIF-1α in wound healing improvement, Loh *et al.* (2009) demonstrated impaired wound healing concomitant to decreased HIF-1α in ageing mice. Moreover, using an epidermal HIF-1α-deficient mice model, we have recently found that loss of HIF-1α in keratinocytes results in a significant delay in wound healing in aged mice (Figure 3a; unpublished data). In fact, HIF-1α could affect the wound healing process in many ways (Figure 3b):

(i) HIF-1α is known to activate many angiogenic factors (growth factors, chemokines, and cytokines) at the transcriptional level, including VEGF, placental growth factor, angiopoietins 1 and 2, platelet-derived growth factor-B, stromal cell-derived factor-1, transforming growth factor-β, and stem cell factor within various cells involved in wound healing (Forsythe *et al.*, 1996; Kelly *et al.*, 2003; Ceradini *et al.*, 2004; Tandara and Mustoe, 2004; Tang *et al.*, 2004; Patel *et al.*, 2005; Bosch-Marce *et al.*, 2007; Simon *et al.*, 2008). These angiogenic factors bind to cognate receptors (e.g., VEGFR1/VEGFR2/VEGFR3, platelet-derived growth factor receptor-α/β, C-X-C chemokine receptor type 4, and C-KIT), which are expressed on the surface of vascular endothelial cells and vascular pericytes/smooth muscle cells. Receptor–ligand interaction activates these cells and promotes the formation of new capillaries from existing vessels. In agreement, gene therapy by overexpression of HIF-1α has recently been found to improve wound healing in diabetic mice (Mace *et al.*, 2007; Botusan *et al.*, 2008; Liu *et al.*, 2008).

(ii) Besides activation of cells in existing vessels, HIF-1α could promote angiogenesis and vascular remodeling in wound healing by mobilizing angiogenic cells from distant sites (including bone marrow and pericytes and endothelial cells from other tissues) to home to the wound (Ceradini *et al.*, 2004; Bosch-Marce *et al.*, 2007; Chang *et al.*, 2007; Sarkar *et al.*, 2009). Expression of a constitutively active form of HIF-1α in mouse skin is sufficient to mobilize circulating angiogenic cells and to improve healing of wounds in diabetic mice (Liu *et al.*, 2008). By contrast, decreased expression of HIF-1α in HIF-1α heterozygous-null mice is associated with impaired recruitment of circulating angiogenic cells to the wound and deficiency of wound vascularization and healing (Zhang et al., 2010).

(iii) HIF-1α could improve wound healing by affecting skin cell motility and proliferation, which are essential factors in the re-epithelialization phase. HIF-1α was found to promote human dermal fibroblast and keratinocyte migration, both *in vitro* and *in vivo,* through addressing the intracellular heat shock protein-90α into the extracellular environment (Li *et al.*, 2007; Woodley *et al.*, 2009). HIF-1α has been shown to modulate cell motility and migration by regulating the expression of ECM proteins and their receptors. Laminin-332, one of the major keratinocyte-secreted ECM protein involved in cell migration during wound healing (Ryan *et al.*, 1994; Nguyen *et al.*, 2000), has been found to be regulated by HIF-1α (Fitsialos *et al.*, 2008). Interaction of laminin-332 with its receptors (integrins-α3β1 and -α6β4), activates signaling pathways that subsequently promote proliferation, survival, and migration of keratinocytes (Rousselle and Aumailley, 1994; Murgia *et al.*, 1998; Nguyen *et al.*, 2000; Nikolopoulos *et al.*, 2005). The effect of HIF-1α on epithelial cell adhesion and migration could go beyond its effect on laminin-332 expression. HIF-1α has also been shown to regulate the expression of integrin-β1 (Keely *et al.*, 2009) as well as that of various metalloproteinases (Semenza, 2003; Shyu *et al.*, 2007; Lee et al., 2010). Finally, HIF-1α functions as an upstream player in the p21-mediated growth arrest of keratinocytes (Cho *et al.*, 2008), suggesting a role in the regulation of keratinocyte proliferation.

ROLE OF HIF-1α IN UV RESPONSE AND SKIN TUMORIGENESIS

HIF-1α and keratinocyte responses to UV irradiation

Solar UVB radiation is the primary environmental risk factor responsible for the induction of skin cancers, including basal cell carcinoma, squamous cell carcinoma (SCC), and melanoma. A major deleterious effect of UVB is the induction of well-defined structural alterations in DNA (Ravanat *et al.*, 2001). UVB-induced DNA damage sets in motion a highly complex well-coordinated series of responses whereby DNA damage and stalled replication forks can be detected. This, in turn, can trigger DNA repair, cell cycle delay, or apoptosis (Latonen and Laiho, 2005). The ultimate fate of cells with damaged DNA is dependent on the type and extent of damage, DNA repair capacity, and UVB-induced apoptotic signaling pathways (Kulms and Schwarz, 2002; Assefa *et al.*, 2005).

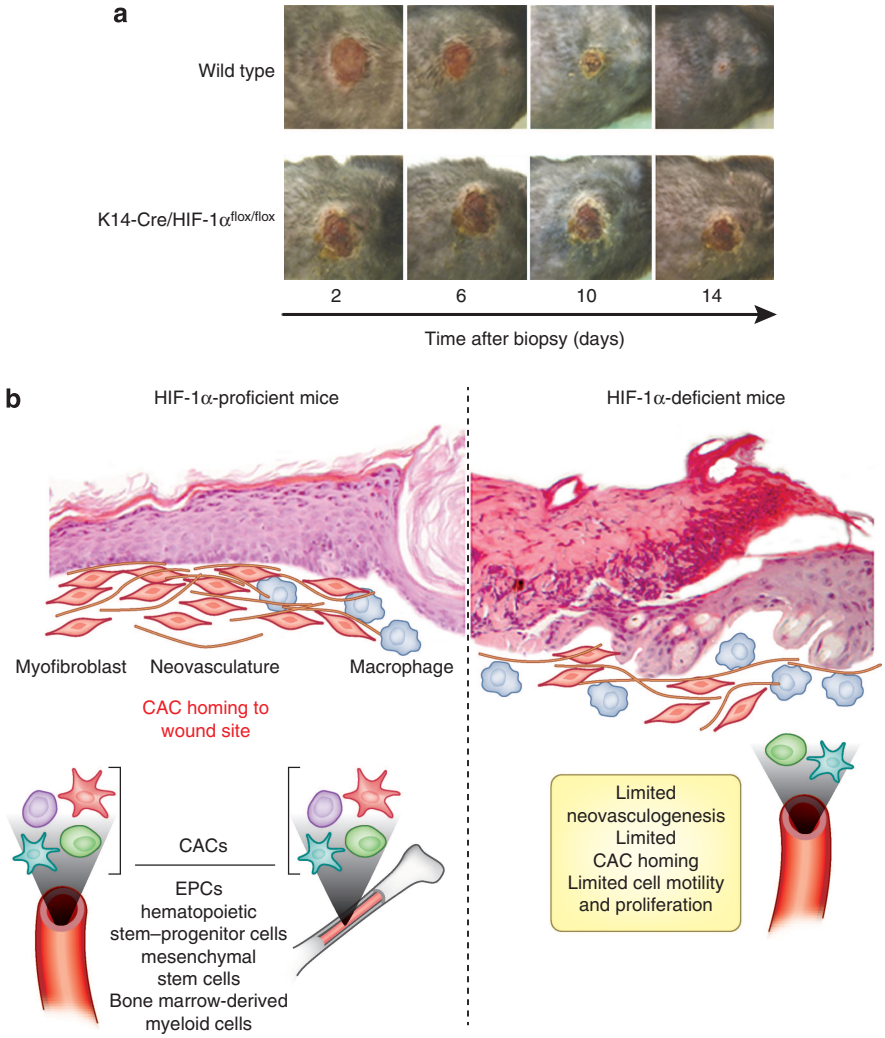

Figure 3. Role of hypoxia-inducible factor-1α (HIF-1α) in wound healing. (**a**) Wound healing is delayed in K14-Cre/HIF-1α$^{flox/flox}$-aged mice. Wound healing assay was performed using standardized 8-mm biopsies on the back of the mice. As compared with control wild-type mice, there was a significant impairment of wound healing in K14-Cre/HIF-1α$^{flox/flox}$ mice. The time course of wound healing in two representative wild-type and HIF-1α-deficient mice shows dramatic impairment of skin regeneration in the absence of HIF-1α expression in keratinocytes. (**b**) A model outlining the effects of HIF-1α in wound healing. The acute wound healing process is derived through interaction among keratinocytes, fibroblasts, endothelial cells, and macrophages. During wound healing, in HIF-1α-proficient mice (left), numerous chemokines released from keratinocytes, such as vascular endothelial growth factor and stromal cell-derived factor-1, trigger the mobilization of circulating angiogenic cells (CACs) at the wound site. In mice with depletion of HIF-1α in keratinocytes (right), the mobilization of CACs and consequently neovascularization are impaired, resulting in limited wound healing. For more explanations, see the text. EPC, endothelial progenitor cell.

We and others have shown that HIF-1α expression is modulated after UVB exposure and that HIF-1α has an important role in the regulation of cellular responses to this type of genotoxic stress (Rezvani *et al.*, 2007; Turchi *et al.*, 2008; Wunderlich *et al.*, 2008). UVB induces ROS, which in turn have a biphasic effect on HIF-1α expression. Whereas rapidly produced cytoplasmic ROS downregulate HIF-1α expression, delayed mitochondrial ROS production results in its upregulation (Rezvani *et al.*, 2007). It is likely that spatiotemporal repression and activation of HIF-1α has a substantial influence on the regulation of keratinocyte responses to UVB irradiation. In fact, downregulation of HIF-1α protein expression immediately after UVB irradiation has been found to be regulated at the translational level and to be important to release keratinocytes from UVB-induced cell cycle arrest (Cho *et al.*, 2009). Late HIF-1α upregulation, which is regulated by mitogen-activated protein kinase (Rezvani *et al.*, 2007; Nys *et al.*, 2010), phosphatidylinositol 3-kinase/AKT (Wunderlich *et al.*, 2008), and/or ATF3 (Turchi *et al.*, 2008), has a proapoptotic effect in UVB-irradiated keratinocytes (Rezvani *et al.*, 2007; Turchi *et al.*, 2008; Nys *et al.*, 2010) through upregulation of proapoptotic genes (such as *Noxa*, *BCL2*/adenovirus E1B 19-kDa-interacting protein (*BNIP3*), or tumor necrosis factor-related apoptosis-inducing ligand (Turchi *et al.*, 2008; Nys *et al.*, 2010) and interaction with p53 (Rezvani *et al.*, 2007). Affecting DNA repair efficiency is the other means by which HIF-1α can modulate keratinocyte responses to UVB (Rezvani *et al.*,

2010a). Biphasic variation of HIF-1α upon exposure of keratinocytes to UVB was also found to regulate the removal rate of 6–4 photoproducts and cyclobutane pyrimidine dimers, the most frequent types of UVB-induced lesions primarily removed by nuclear excision repair. This study showed that the effect of HIF-1α on the nuclear excision repair machinery relies on the transcriptional regulation of XPC, XPD, XPB, XPG, and Cockayne syndrome A and B expression by direct HIF-1α binding to the hypoxia-response elements of these genes in their promoter region (Rezvani *et al.*, 2010a).

HIF-1α in skin cancer

The effects of HIF-1α in cancer are not straightforward. On one hand, HIF-1α can contribute to solid tumor progression via multiple mechanisms, including promotion of angiogenesis, modulation of metabolism through regulation of glycolysis flux and oxidative phosphorylation, and inhibition of apoptosis (Maxwell *et al.*, 1997; Ryan *et al.*, 2000; Hockel and Vaupel, 2001). Elevated levels of HIF-1α protein are often associated with a poor prognosis in several human cancers (Birner *et al.*, 2000; Talks *et al.*, 2000; Zhong *et al.*, 2000; Beasley *et al.*, 2002; Koukourakis *et al.*, 2002).

On the other hand, in certain cancer cells, such as renal or lung cancers, HIF-1α directly and indirectly inhibits *c*-Myc function, resulting in either p21-mediated cell cycle arrest or apoptosis (Savai *et al.*, 2005; Gordan *et al.*, 2007). Direct or indirect interaction of HIF-1α and p53 also contributes to the regulation of tumor development (Hammond and Giaccia, 2006). Induction of the proapoptotic target genes such as *BINP3* may also explain the tumor suppressor capability of HIF-1α (Sowter *et al.*, 2001). Considering the many functions and effects of HIF-1α (Semenza, 2003), it is likely that its contribution in tumor progression is complex and dependent on the cell origin and status of other activated or inactivated genes.

HIF-1α expression in non-melanoma skin cancer

HIF-1α expression has not yet been studied in basal cell carcinoma, and little is known about the role of HIF-1α in skin SCC. HIF-1α gain of function in keratinocytes results in an increased number of papillomas, a benign neoplasm that sometimes converts to a premalignant lesion, after chemical carcinogenesis induction (Scortegagna *et al.*, 2009). This observation can partially be explained by HIF-1α overexpression-mediated increased angiogenesis, which was documented to be an early event in papilloma development (Bolontrade *et al.*, 1998; Elson *et al.*, 2001; Scortegagna *et al.*, 2009). Although these papillomas appear earlier, their proliferation is lower and their cells are more differentiated, suggesting suppression of epithelial–mesenchymal transition. Furthermore, conversion of these papillomas to SCCs is largely inhibited compared with those formed in control mice (Scortegagna *et al.*, 2009). The effect of HIF-1α upregulation on SCC differentiation may be related to HIF-1α-mediated upregulation of p21, which has a key role in the onset of keratinocyte growth arrest and differentiation upon different stimuli (Missero *et al.*, 1995; Todd and Reynolds, 1998). Consistently, the intradermal injection of HIF-1α small interfering RNA was recently found to diminish p21 expression in rat epidermis and to induce skin hyperplasia (Cho *et al.*, 2008, 2010).

In addition to the role of HIF-1α in SCC formation, it may have another role in tumoral invasion for the following reasons: (1) several angiogenic factors, namely, VEGF, fibroblast growth factor-2, platelet-derived growth factor, and angiopoietin are expressed in SCCs (Czubayko *et al.*, 1997; Strieth *et al.*, 2000; Hawighorst *et al.*, 2002; Bran *et al.*, 2009); (2) HIF-1α regulates the expression of numerous angiogenic factors and metalloproteinases; and (3) VEGF can increase HIF-1α mRNA translation into protein via phosphoinositol-3 kinase and AKT (Semenza, 2000; Kilic *et al.*, 2006). Consistently, overexpression of VEGF-A in immortalized keratinocytes leads to invasive and malignant SCCs following xenografting into immune-deficient mice (Lederle *et al.*, 2010), whereas the metastatic ability of transformed VEGF-null keratinocytes is completely abolished (Mirones *et al.*, 2009). Although the incidence and angiogenic status of chemically induced SCCs in mice overexpressing the angiogenesis inhibitor endostatin in keratinocytes is comparable to the incidence in control mice, both lymph vessels and lymphatic metastases are highly reduced in tumors carrying these keratinocytes, indicating an inhibitory role for endostatin in the aggressiveness of the tumor (Brideau *et al.*, 2007).

HIF-1α and melanoma

This cancer has a high propensity to metastasize early, which results in high mortality. Alteration of several signaling pathways, such as NRAS, BRAF, phosphatase and tensin homolog/phosphatidylinositol 3-kinase/AKT, and p16/ARF, occurs in melanoma and leads to acquisition of growth advantages, resistance to apoptosis, and invasive/metastatic behavior (Cannon-Albright *et al.*, 1996; Demunter *et al.*, 2001; Davies *et al.*, 2002; Stahl *et al.*, 2004).

Constitutive activation of AKT characterizes a high percentage of human melanomas and is associated with a poor prognosis. AKT has been shown to transform melanocytes only when cells are grown in a hypoxic environment in an HIF-1α-dependent manner (Bedogni *et al.*, 2005, 2008). Melanomas harboring the BRAF mutation, $BRAF^{V600E}$, have higher expression of HIF-1α (Kumar *et al.*, 2007). Enhanced HIF-1α expression in these melanoma cells results in a higher cell survival in hypoxic conditions, suggesting that the effects of the oncogenic $BRAF^{V600E}$ mutation may be partially mediated by the HIF-1α pathway (Kumar *et al.*, 2007). However, melanocytic nevi, the pigmented lesions that are usually quiescent/senescent and rarely progress to melanoma, also comprise cells with the $BRAF^{V600E}$ mutation (Garraway *et al.*, 2005), suggesting that these melanocytes have to acquire additional alterations to escape senescence and become cancerous. Amplification of microphthalmia-associated transcription factor might be one of these modifications. In fact, microphthalmia-associated transcription factor has been shown to be amplified in a large number of melanomas containing the

BRAF mutation (Garraway *et al.*, 2005). It has been found that microphthalmia-associated transcription factor can regulate HIF-1α expression by binding directly to the HIF-1α promoter, and that overexpression of HIF-1α has prosurvival effects on melanoma cells (Busca *et al.*, 2005).

Besides BRAF and AKT, increased ROS level, NFκB activation (Kuphal et al., 2010), and overexpression of endothelin B receptor (Spinella *et al.*, 2007) could all result in increased HIF-1α expression and activity in melanomas. An endothelin-mediated increase in HIF-1α expression can promote VEGF secretion and matrix metalloproteinase activation in melanoma cells, which in turn affects their invasion capacity (Spinella *et al.*, 2007). Altogether, these studies suggest a tumor-promoting effect of HIF-1α in melanoma.

HIF-1α IN NON-CANCER SKIN DISORDERS

HIF-1α in microbial infection

In addition to serving as the body's outermost protective covering, the skin protects the body against infectious diseases by its innate immune responses, especially the production of antimicrobial peptides capable of inactivating many microorganisms (Boukamp *et al.*, 1988; Ganz, 2002; Braff and Gallo, 2006). It has been reported that HIF-1α is upregulated in the skin upon infection with various bacterial, viral, fungal, or parasitic infections both *in vitro* or *in vivo* (Werth et al., 2010). Using a keratinocyte-targeted deletion of HIF-1α, it has been shown that HIF-1α provides protection against necrotic skin lesions induced by bacteria via upregulation of cathelicidin, an antimicrobial peptide coded by the human *LL-37* gene (Peyssonnaux *et al.*, 2008). Interestingly, cathelicidin production is decreased in some inflammatory skin disorders such as atopic dermatitis (Ong *et al.*, 2002).

HIF-1α in psoriasis

Several lines of evidence suggest that HIF-1α could have an important role in psoriasis, a chronic skin disease characterized by keratinocyte hyperproliferation, epidermal inflammation, and angiogenesis. In fact, pivotal angiogenic genes such as *VEGF* and its receptors are upregulated in psoriasis (Detmar *et al.*, 1994). Transgenic mice with VEGF upregulation in keratinocytes show inflammation and all the hallmarks of psoriasis, suggesting a causative role of VEGF in this disease (Xia *et al.*, 2003). On the other hand, transgenic delivery to the skin of inflammatory mediators, such as tumor necrosis factor-α or keratinocyte growth factors like transforming growth factor-α, did not completely reproduce the psoriatic phenotype (Vassar and Fuchs, 1991; Cheng *et al.*, 1992; Guo *et al.*, 1993; Carroll *et al.*, 1997; Schon, 1999), suggesting that VEGF upregulation is an early step in the pathophysiology of this disease (Detmar, 2004). HIF-1α has been found to be upregulated in psoriatic epidermis, in an expression pattern similar to VEGF mRNA expression (Rosenberger *et al.*, 2007; Tovar-Castillo *et al.*, 2007; Ioannou *et al.*, 2009), thereby suggesting a possible application of HIF-1α inhibitors in the therapy of psoriasis.

HIF-1α in systemic sclerosis and keloids

Apart from infection and psoriasis, upregulation of HIF-1α has been reported in systemic sclerosis and keloids. Systemic sclerosis is characterized by microvascular alterations and excessive fibrosis of the skin and the internal organs. Activation of HIF-1α in dermal fibroblasts of systemic sclerosis patients might contribute to the progression of skin fibrosis (Hong *et al.*, 2006; Distler *et al.*, 2007) via upregulation of connective tissue growth factor, a cytokine expressed by the endothelium and fibroblasts (Hong *et al.*, 2006). Keloids are skin fibrotic conditions characterized by an excessive accumulation of ECM components in response to cutaneous injury. Upregulation of plasminogen activator inhibitor-1 in an HIF-1α-dependent manner contributes to keloid pathogenesis (Zhang *et al.*, 2004). Metabolic analysis of keloid fibroblasts indicated a bioenergetics similar to that of most cancer cells, i.e., increased glycolysis and decreased oxidative phosphorylation, which might be related to increased HIF-1α expression (Vincent *et al.*, 2008).

In summary, growing evidence strongly supports an important role of HIF-1α signaling in non-cancer skin pathophysiology, although the detailed mechanistic aspects and therapeutic applications remain relatively unexplored.

CONCLUSION AND PERSPECTIVES

Although fetal skin develops in a liquid milieu, adult epidermis is in contact with the atmospheric oxygen and its oxygenation depends heavily on atmospheric oxygen (Stucker *et al.*, 2002). Thus, the skin faces dramatically different environments between the fetal and neonatal periods. It is well known that skin barrier maturation is important immediately after birth in humans and that premature babies can be oxygenated through the skin (Fluhr et al., 2010). Considering the functions of HIF-1α, its role could be crucial in the context of neonatal adaptation to atmospheric conditions to increase the maturation of the epidermal barrier as well as to adapt neonatal dermal vascularization. Some of the HIF-1α-regulated genes such as *XPD* (Rezvani *et al.*, 2010a) are involved in the transcriptional machinery, and their mutation can affect epidermal differentiation, which manifests at birth with a collodion membrane engaging the skin, as noted in the disease trichothiodystrophy (Morice-Picard *et al.*, 2009; Rezvani *et al.*, 2010b).

Besides the neonatal period, it is likely that HIF-1α has an important role in the regulation of physiological skin responses to different stressors. By affecting the expression of various key cutaneous genes, HIF-1α regulates cutaneous angiogenesis, controls inflammatory and innate immune responses, modulates skin responses to sunlight by affecting the DNA repair machinery, apoptosis, and lastly the tumorigenic processes. Thus, its importance in dermatology deserves closer attention.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Albina JE, Mastrofrancesco B, Vessella JA *et al.* (2001) HIF-1 expression in healing wounds: HIF-1alpha induction in primary inflammatory cells by TNF-alpha. *Am J Physiol Cell Physiol* 281:C1971–7

Assefa Z, Van Laethem A, Garmyn M *et al.* (2005) Ultraviolet radiation-induced apoptosis in keratinocytes: on the role of cytosolic factors. *Biochim Biophys Acta* 1755: 90–106

Barrientos S, Stojadinovic O, Golinko MS *et al.* (2008) Growth factors and cytokines in wound healing. *Wound Repair Regen* 16:585–601

Beasley NJ, Leek R, Alam M *et al.* (2002) Hypoxia-inducible factors HIF-1alpha and HIF-2alpha in head and neck cancer: relationship to tumor biology and treatment outcome in surgically resected patients. *Cancer Res* 62:2493–7

Bedogni B, Warneke JA, Nickoloff BJ *et al.* (2008) Notch1 is an effector of Akt and hypoxia in melanoma development. *J Clin Invest* 118:3660–70

Bedogni B, Welford SM, Cassarino DS *et al.* (2005) The hypoxic microenvironment of the skin contributes to Akt-mediated melanocyte transformation. *Cancer Cell* 8:443–54

Birner P, Schindl M, Obermair A *et al.* (2000) Overexpression of hypoxia-inducible factor 1alpha is a marker for an unfavorable prognosis in early-stage invasive cervical cancer. *Cancer Res* 60:4693–6

Black SM, DeVol JM, Wedgwood S (2008) Regulation of fibroblast growth factor-2 expression in pulmonary arterial smooth muscle cells involves increased reactive oxygen species generation. *Am J Physiol Cell Physiol* 294:C345–54

Bolontrade MF, Stern MC, Binder RL *et al.* (1998) Angiogenesis is an early event in the development of chemically induced skin tumors. *Carcinogenesis* 19:2107–13

Bosch-Marce M, Okuyama H, Wesley JB *et al.* (2007) Effects of aging and hypoxia-inducible factor-1 activity on angiogenic cell mobilization and recovery of perfusion after limb ischemia. *Circ Res* 101:1310–8

Botusan IR, Sunkari VG, Savu O *et al.* (2008) Stabilization of HIF-1alpha is critical to improve wound healing in diabetic mice. *Proc Natl Acad Sci USA* 105:19426–31

Bouis D, Kusumanto Y, Meijer C *et al.* (2006) A review on pro- and anti-angiogenic factors as targets of clinical intervention. *Pharmacol Res* 53:89–103

Boukamp P, Petrussevska RT, Breitkreutz D *et al.* (1988) Normal keratinization in a spontaneously immortalized aneuploid human keratinocyte cell line. *J Cell Biol* 106:761–71

Boutin AT, Weidemann A, Fu Z *et al.* (2008) Epidermal sensing of oxygen is essential for systemic hypoxic response. *Cell* 133:223–34

Braff MH, Gallo RL (2006) Antimicrobial peptides: an essential component of the skin defensive barrier. *Curr Top Microbiol Immunol* 306:91–110

Bran B, Bran G, Hormann K *et al.* (2009) The platelet-derived growth factor receptor as a target for vascular endothelial growth factor-mediated anti-angiogenetic therapy in head and neck cancer. *Int J Oncol* 34:255–61

Brahimi-Horn C, Mazure N, Pouyssegur J (2005) Signalling via the hypoxia-inducible factor-1alpha requires multiple posttranslational modifications. *Cell Signal* 17:1–9

Brideau G, Makinen MJ, Elamaa H *et al.* (2007) Endostatin overexpression inhibits lymphangiogenesis and lymph node metastasis in mice. *Cancer Res* 67:11528–35

Bruick RK (2000) Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. *Proc Natl Acad Sci USA* 97:9082–7

Busca R, Berra E, Gaggioli C *et al.* (2005) Hypoxia-inducible factor 1{alpha} is a new target of microphthalmia-associated transcription factor (MITF) in melanoma cells. *J Cell Biol* 170:49–59

Calvani M, Rapisarda A, Uranchimeg B *et al.* (2006) Hypoxic induction of an HIF-1alpha-dependent bFGF autocrine loop drives angiogenesis in human endothelial cells. *Blood* 107:2705–12

Cannon-Albright LA, Kamb A, Skolnick M (1996) A review of inherited predisposition to melanoma. *Semin Oncol* 23:667–72

Carroll JM, Crompton T, Seery JP *et al.* (1997) Transgenic mice expressing IFN-gamma in the epidermis have eczema, hair hypopigmentation, and hair loss. *J Invest Dermatol* 108:412–22

Cartlidge PH, Rutter N (1988) Percutaneous oxygen delivery to the preterm infant. *Lancet* 1:315–7

Ceradini DJ, Kulkarni AR, Callaghan MJ *et al.* (2004) Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. *Nat Med* 10:858–64

Chang EI, Loh SA, Ceradini DJ *et al.* (2007) Age decreases endothelial progenitor cell recruitment through decreases in hypoxia-inducible factor 1alpha stabilization during ischemia. *Circulation* 116:2818–29

Charkoudian N (2010) Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J Appl Physiol* 109:1221–8

Cheng J, Turksen K, Yu QC *et al.* (1992) Cachexia and graft-vs.-host-disease-type skin changes in keratin promoter-driven TNF alpha transgenic mice. *Genes Dev* 6:1444–56

Cho YS, Bae JM, Chun YS *et al.* (2008) HIF-1alpha controls keratinocyte proliferation by up-regulating p21(WAF1/Cip1). *Biochim Biophys Acta* 1783:323–33

Cho YS, Kim CH, Park JW (2009) Involvement of HIF-1alpha in UVB-induced epidermal hyperplasia. *Mol Cells* 28:537–43

Cho YS, Lee KH, Park JW (2010) Pyrithione-zinc Prevents UVB-induced Epidermal Hyperplasia by Inducing HIF-1alpha. *Korean J Physiol Pharmacol* 14:91–7

Choi JW, Park SC, Kang GH *et al.* (2004) Nur77 activated by hypoxia-inducible factor-1alpha overproduces proopiomelanocortin in von Hippel-Lindau-mutated renal cell carcinoma. *Cancer Res* 64:35–9

Christensen CU (1975) Effects of dehydration, vasotocin and hypertonicity on net water flux through the isolated, perfused pelvic skin of *Bufo bufo bufo* (L.). *Comp Biochem Physiol A Comp Physiol* 51:7–10

Cockman ME, Masson N, Mole DR *et al.* (2000) Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppressor protein. *J Biol Chem* 275:25733–41

Comerford KM, Wallace TJ, Karhausen J *et al.* (2002) Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (*MDR1*) gene. *Cancer Res* 62:3387–94

Czubayko F, Liaudet-Coopman ED, Aigner A *et al.* (1997) A secreted FGF-binding protein can serve as the angiogenic switch in human cancer. *Nat Med* 3:1137–40

Davies H, Bignell GR, Cox C *et al.* (2002) Mutations of the *BRAF* gene in human cancer. *Nature* 417:949–54

Demunter A, Ahmadian MR, Libbrecht L *et al.* (2001) A novel N-ras mutation in malignant melanoma is associated with excellent prognosis. *Cancer Res* 61:4916–22

Detmar M (2004) Evidence for vascular endothelial growth factor (*VEGF*) as a modifier gene in psoriasis. *J Invest Dermatol* 122:xiv–xv

Detmar M, Brown LF, Claffey KP *et al.* (1994) Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. *J Exp Med* 180:1141–6

Distler JH, Jungel A, Pileckyte M *et al.* (2007) Hypoxia-induced increase in the production of extracellular matrix proteins in systemic sclerosis. *Arthritis Rheum* 56:4203–15

Distler O, Distler JH, Scheid A *et al.* (2004) Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. *Circ Res* 95:109–16

Ebert BL, Firth JD, Ratcliffe PJ (1995) Hypoxia and mitochondrial inhibitors regulate expression of glucose transporter-1 via distinct Cis-acting sequences. *J Biol Chem* 270:29083–9

Elson DA, Ryan HE, Snow JW *et al.* (2000) Coordinate up-regulation of hypoxia inducible factor (HIF)-1alpha and HIF-1 target genes during multi-stage epidermal carcinogenesis and wound healing. *Cancer Res* 60:6189–95

Elson DA, Thurston G, Huang LE *et al.* (2001) Induction of hypervascularity without leakage or inflammation in transgenic mice overexpressing hypoxia-inducible factor-1alpha. *Genes Dev* 15:2520–32

Erler JT, Bennewith KL, Nicolau M *et al.* (2006) Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature* 440:1222–6

Evans NT, Naylor PF (1967) The oxygen tension gradient across human epidermis. *Respir Physiol* 3:38–42

Evans SM, Schrlau AE, Chalian AA *et al.* (2006) Oxygen levels in normal and previously

irradiated human skin as assessed by EF5 binding. *J Invest Dermatol* 126:2596–606

Fandrey J, Gorr TA, Gassmann M (2006) Regulating cellular oxygen sensing by hydroxylation. *Cardiovasc Res* 71:642–51

Filippi S, Latini P, Frontini M *et al.* (2008) CSB protein is (a direct target of HIF-1 and) a critical mediator of the hypoxic response. *EMBO J* 27:2545–56

Fink T, Kazlauskas A, Poellinger L *et al.* (2002) Identification of a tightly regulated hypoxia-response element in the promoter of human plasminogen activator inhibitor-1. *Blood* 99:2077–83

Firth JD, Ebert BL, Ratcliffe PJ (1995) Hypoxic regulation of lactate dehydrogenase A. Interaction between hypoxia-inducible factor 1 and cAMP response elements. *J Biol Chem* 270:21021–7

Fitsialos G, Bourget I, Augier S *et al.* (2008) HIF1 transcription factor regulates laminin-332 expression and keratinocyte migration. *J Cell Sci* 121:2992–3001

Fluhr JW, Darlenski R, Taieb A *et al.* (2010) Functional skin adaptation in infancy—almost complete but not fully competent. *Exp Dermatol* 19:483–92

Forsythe JA, Jiang BH, Iyer NV *et al.* (1996) Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 16:4604–13

Fukasawa M, Tsuchiya T, Takayama E *et al.* (2004) Identification and characterization of the hypoxia-responsive element of the human placental 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase gene. *J Biochem* 136:273–7

Galanis A, Pappa A, Giannakakis A *et al.* (2008) Reactive oxygen species and HIF-1 signalling in cancer. *Cancer Lett* 266:12–20

Ganz T (2002) Epithelia: not just physical barriers. *Proc Natl Acad Sci USA* 99:3357–8

Garraway LA, Widlund HR, Rubin MA *et al.* (2005) Integrative genomic analyses identify MITF as a lineage survival oncogene amplified in malignant melanoma. *Nature* 436:117–22

Gerald D, Berra E, Frapart YM *et al.* (2004) JunD reduces tumor angiogenesis by protecting cells from oxidative stress. *Cell* 118: 781–94

Gerber HP, Condorelli F, Park J *et al.* (1997) Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes. Flt-1, but not Flk-1/KDR, is up-regulated by hypoxia. *J Biol Chem* 272:23659–67

Gniadecka M, Nielsen OF, Wessel S *et al.* (1998) Water and protein structure in photoaged and chronically aged skin. *J Invest Dermatol* 111:1129–33

Gordan JD, Thompson CB, Simon MC (2007) HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer cell* 12:108–13

Graven KK, Yu Q, Pan D *et al.* (1999) Identification of an oxygen responsive enhancer element in the glyceraldehyde-3-phosphate dehydrogenase gene. *Biochim Biophys Acta* 1447:208–18

Guo L, Yu QC, Fuchs E (1993) Targeting expression of keratinocyte growth factor to keratinocytes elicits striking changes in epithelial differentiation in transgenic mice. *EMBO J* 12:973–86

Hammond EM, Giaccia AJ (2006) Hypoxia-inducible factor-1 and p53: friends, acquaintances, or strangers? *Clin Cancer Res* 12:5007–9

Hanahan D, Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 86:353–64

Harbrecht BG (2006) Therapeutic use of nitric oxide scavengers in shock and sepsis. *Curr Pharm Des* 12:3543–9

Hawighorst T, Skobe M, Streit M *et al.* (2002) Activation of the tie2 receptor by angiopoietin-1 enhances tumor vessel maturation and impairs squamous cell carcinoma growth. *Am J Pathol* 160:1381–92

Hemphill JC, Smith WS, Sonne DC *et al.* (2005) Relationship between brain tissue oxygen tension and CT perfusion: feasibility and initial results. *AJNR Am J Neuroradiol* 26:1095–100

Higgins DF, Biju MP, Akai Y *et al.* (2004) Hypoxic induction of Ctgf is directly mediated by Hif-1. *Am J Renal Physiol* 287:F1223–32

Hockel M, Vaupel P (2001) Biological consequences of tumor hypoxia. *Semin Oncol* 28:36–41

Hong KH, Yoo SA, Kang SS *et al.* (2006) Hypoxia induces expression of connective tissue growth factor in scleroderma skin fibroblasts. *Clin Exp Immunol* 146:362–70

Houghton BL, Meendering JR, Wong BJ *et al.* (2006) Nitric oxide and noradrenaline contribute to the temperature threshold of the axon reflex response to gradual local heating in human skin. *J Physiol* 572:811–20

Hu J, Discher DJ, Bishopric NH *et al.* (1998) Hypoxia regulates expression of the endothelin-1 gene through a proximal hypoxia-inducible factor-1 binding site on the antisense strand. *Biochem Biophys Res Commun* 245:894–9

Hunt TK, Niinikoski J, Zederfeldt B (1972) Role of oxygen in repair processes. *Acta Chir Scand* 138:109–10

Hur E, Chang KY, Lee E *et al.* (2001) Mitogen-activated protein kinase kinase inhibitor PD98059 blocks the trans-activation but not the stabilization or DNA binding ability of hypoxia-inducible factor-1alpha. *Mol Pharmacol* 59:1216–24

Ioannou M, Sourli F, Mylonis I *et al.* (2009) Increased HIF-1 alpha immunostaining in psoriasis compared to psoriasiform dermatitides. *J Cutan Pathol* 36:1255–61

Ivan M, Kondo K, Yang H *et al.* (2001) HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science* 292:464–8

Jaakkola P, Mole DR, Tian YM *et al.* (2001) Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science* 292:468–72

Kamura T, Sato S, Iwai K *et al.* (2000) Activation of HIF1alpha ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proc Natl Acad Sci USA* 97:10430–5

Keely S, Glover LE, MacManus CF *et al.* (2009) Selective induction of integrin beta1 by hypoxia-inducible factor: implications for wound healing. *FASEB J* 23:1338–46

Kelly BD, Hackett SF, Hirota K *et al.* (2003) Cell type-specific regulation of angiogenic growth factor gene expression and induction of angiogenesis in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1. *Circ Res* 93:1074–81

Kietzmann T, Gorlach A (2005) Reactive oxygen species in the control of hypoxia-inducible factor-mediated gene expression. *Semin Cell Dev Biol* 16:474–86

Kilic E, Kilic U, Wang Y *et al.* (2006) The phosphatidylinositol-3 kinase/Akt pathway mediates VEGF's neuroprotective activity and induces blood brain barrier permeability after focal cerebral ischemia. *FASEB J* 20:1185–7

Kim JY, Ahn HJ, Ryu JH *et al.* (2004) BH3-only protein Noxa is a mediator of hypoxic cell death induced by hypoxia-inducible factor 1alpha. *J Exp Med* 199:113–24

Kim WY, Safran M, Buckley MR *et al.* (2006) Failure to prolyl hydroxylate hypoxia-inducible factor alpha phenocopies VHL inactivation *in vivo*. *EMBO J* 25:4650–62

Koshiji M, To KK, Hammer S *et al.* (2005) HIF-1alpha induces genetic instability by transcriptionally downregulating MutSalpha expression. *Mol Cell* 17:793–803

Kothari S, Cizeau J, McMillan-Ward E *et al.* (2003) BNIP3 plays a role in hypoxic cell death in human epithelial cells that is inhibited by growth factors EGF and IGF. *Oncogene* 22:4734–44

Koukourakis MI, Giatromanolaki A, Sivridis E *et al.* (2002) Hypoxia-inducible factor (HIF1A and HIF2A), angiogenesis, and chemoradiotherapy outcome of squamous cell head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 53:1192–202

Krogh A, Harrop GA, Rehberg PB (1922) Studies on the physiology of capillaries: III. The innervation of the blood vessels in the hind legs of the frog. *J Physiol* 56:179–89

Kulms D, Schwarz T (2002) Independent contribution of three different pathways to ultraviolet-B-induced apoptosis. *Biochem Pharmacol* 64:837–41

Kumar SM, Yu H, Edwards R *et al.* (2007) Mutant V600E BRAF increases hypoxia inducible factor-1alpha expression in melanoma. *Cancer Res* 67:3177–84

Kuphal S, Winklmeier A, Warnecke C *et al.* (2010) Constitutive HIF-1 activity in malignant melanoma. *Eur J Cancer* 46:1159–69

Langley JN (1911) The origin and course of the vaso-motor fibres of the frog's foot. *J Physiol* 41:483–98

Laquer V, Hoang V, Nguyen A *et al.* (2009) Angiogenesis in cutaneous disease: part II. *J Am Acad Dermatol* 61:945–58; quiz 59–60

Larcher F, Murillas R, Bolontrade M *et al.* (1998) VEGF/VPF overexpression in skin of transgenic mice induces angiogenesis, vascular hyperpermeability and accelerated tumor development. *Oncogene* 17:303–11

Latonen L, Laiho M (2005) Cellular UV damage responses—functions of tumor suppressor p53. *Biochim Biophys Acta* 1755:71–89

Lederle W, Linde N, Heusel J *et al.* (2010) Platelet-derived growth factor-B normalizes micromorphology and vessel function in vascular endothelial growth factor-A-induced squamous cell carcinomas. *Am J Pathol* 176:981–94

Lee PJ, Jiang BH, Chin BY *et al.* (1997) Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. *J Biol Chem* 272:5375–81

Lee SH, Lee YJ, Han HJ (2010) Effect of arachidonic acid on hypoxia-induced IL-6 production in mouse ES cells: Involvement of MAPKs, NF-kappaB, and HIF-1alpha. *J Cell Physiol* 222:574–85

Li W, Li Y, Guan S *et al.* (2007) Extracellular heat shock protein-90alpha: linking hypoxia to skin cell motility and wound healing. *EMBO J* 26:1221–33

Liu L, Marti GP, Wei X *et al.* (2008) Age-dependent impairment of HIF-1alpha expression in diabetic mice: correction with electroporation-facilitated gene therapy increases wound healing, angiogenesis, and circulating angiogenic cells. *J Cell Physiol* 217:319–27

Liu Y, Cox SR, Morita T *et al.* (1995) Hypoxia regulates vascular endothelial growth factor gene expression in endothelial cells. Identification of a 5′ enhancer. *Circ Res* 77:638–43

Loh SA, Chang EI, Galvez MG *et al.* (2009) SDF-1 alpha expression during wound healing in the aged is HIF dependent. *Plast Reconstr Surg* 123:65S–75S

Lu S, Gu X, Hoestje S *et al.* (2002) Identification of an additional hypoxia responsive element in the glyceraldehyde-3-phosphate dehydrogenase gene promoter. *Biochim Biophys Acta* 1574:152–6

Mace KA, Yu DH, Paydar KZ *et al.* (2007) Sustained expression of Hif-1alpha in the diabetic environment promotes angiogenesis and cutaneous wound repair. *Wound Repair Regen* 15:636–45

Mahany TM, Parsons RH (1978) Circulatory effects on osmotic water exchange in *Rana pipiens*. *Am J Physiol* 234:R172–7

Mahon PC, Hirota K, Semenza GL (2001) FIH-1: a novel protein that interacts with HIF-1alpha and VHL to mediate repression of HIF-1 transcriptional activity. *Genes Dev* 15: 2675–86

Malvin GM, Hlastala MP (1989) Effects of environmental O2 on blood flow and diffusing capacity in amphibian skin. *Respir Physiol* 76:229–41

Masson N, Willam C, Maxwell PH *et al.* (2001) Independent function of two destruction domains in hypoxia-inducible factor-alpha chains activated by prolyl hydroxylation. *EMBO J* 20:5197–206

Maxwell PH (2004) HIF-1's relationship to oxygen: simple yet sophisticated. *Cell Cycle* 3:156–9

Maxwell PH, Dachs GU, Gleadle JM *et al.* (1997) Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angiogenesis and tumor growth. *Proc Natl Acad Sci USA* 94:8104–9

Maxwell PH, Wiesener MS, Chang GW *et al.* (1999) The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 399:271–5

Maynard MA, Qi H, Chung J *et al.* (2003) Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem* 278:11032–40

Melillo G, Musso T, Sica A *et al.* (1995) A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter. *J Exp Med* 182:1683–93

Metzen E, Ratcliffe PJ (2004) HIF hydroxylation and cellular oxygen sensing. *Biol Chem* 385:223–30

Minet E, Arnould T, Michel G *et al.* (2000) ERK activation upon hypoxia: involvement in HIF-1 activation. *FEBS Lett* 468:53–8

Minson CT (2003) Hypoxic regulation of blood flow in humans. Skin blood flow and temperature regulation. *Adv Exp Med Biol* 543:249–62

Mirones I, Conti CJ, Martinez J *et al.* (2009) Complexity of VEGF responses in skin carcinogenesis revealed through *ex vivo* assays based on a VEGF-A null mouse keratinocyte cell line. *J Invest Dermatol* 129:730–41

Missero C, Calautti E, Eckner R *et al.* (1995) Involvement of the cell-cycle inhibitor Cip1/WAF1 and the E1A-associated p300 protein in terminal differentiation. *Proc Natl Acad Sci USA* 92:5451–5

Morice-Picard F, Cario-Andre M, Rezvani H *et al.* (2009) New clinico-genetic classification of trichothiodystrophy. *Am J Med Genet A* 149A:2020–30

Murgia C, Blaikie P, Kim N *et al.* (1998) Cell cycle and adhesion defects in mice carrying a targeted deletion of the integrin beta4 cytoplasmic domain. *EMBO J* 17:3940–51

Nguyen BP, Ryan MC, Gil SG *et al.* (2000) Deposition of laminin 5 in epidermal wounds regulates integrin signaling and adhesion. *Curr Opin Cell Biol* 12:554–62

Nguyen A, Hoang V, Laquer V *et al.* (2009) Angiogenesis in cutaneous disease: part I. *J Am Acad Dermatol* 61:921–42; quiz 43–4

Niinikoski J, Grislis G, Hunt TK (1972) Respiratory gas tensions and collagen in infected wounds. *Ann Surg* 175:588–93

Nikolopoulos SN, Blaikie P, Yoshioka T *et al.* (2005) Targeted deletion of the integrin beta4 signaling domain suppresses laminin-5-dependent nuclear entry of mitogen-activated protein kinases and NF-kappaB, causing defects in epidermal growth and migration. *Mol Cell Biol* 25:6090–102

Nishi H, Nakada T, Hokamura M *et al.* (2004a) Hypoxia-inducible factor-1 transactivates transforming growth factor-beta3 in trophoblast. *Endocrinology* 145:4113–8

Nishi H, Nakada T, Kyo S *et al.* (2004b) Hypoxia-inducible factor 1 mediates upregulation of telomerase (hTERT). *Mo Cell Biol* 24: 6076–83

Nwaigwe CI, Roche MA, Grinberg O *et al.* (2000) Effect of hyperventilation on brain tissue oxygenation and cerebrovenous PO2 in rats. *Brain Res* 868:150–6

Nys K, Van Laethem A, Michiels C *et al.* (2010) A p38(MAPK)/HIF-1 pathway initiated by UVB irradiation is required to induce Noxa and apoptosis of human keratinocytes. *J Invest Dermatol* 130:2269–76

Obach M, Navarro-Sabate A, Caro J *et al.* (2004) 6-Phosphofructo-2-kinase (*pfkfb3*) gene promoter contains hypoxia-inducible factor-1 binding sites necessary for transactivation in response to hypoxia. *J Biol Chem* 279:53562–70

Ohh M, Park CW, Ivan M *et al.* (2000) Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol* 2:423–7

Okino ST, Chichester CH, Whitlock Jr JP (1998) Hypoxia-inducible mammalian gene expression analyzed *in vivo* at a TATA-driven promoter and at an initiator-driven promoter. *J Biol Chem* 273:23837–43

Ong PY, Ohtake T, Brandt C *et al.* (2002) Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 347:1151–60

Patel TH, Kimura H, Weiss CR, Semenza GL, Hofmann LV (2005) Constitutively active HIF-1alpha improves perfusion and arterial remodeling in an endovascular model of limb ischemia. *Cardiovasc Res* 68:144–54

Paul SA, Simons JW, Mabjeesh NJ (2004) HIF at the crossroads between ischemia and carcinogenesis. *J Cell Physiol* 200:20–30

Pennacchietti S, Michieli P, Galluzzo M *et al.* (2003) Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. *Cancer cell* 3:347–61

Peyssonnaux C, Boutin AT, Zinkernagel AS *et al.* (2008) Critical role of HIF-1alpha in keratinocyte defense against bacterial infection. *J Invest Dermatol* 128:1964–8

Piret JP, Minet E, Cosse JP *et al.* (2005) Hypoxia-inducible factor-1-dependent overexpression of myeloid cell factor-1 protects hypoxic cells against tert-butyl hydroperoxide-induced apoptosis. *J Biol Chem* 280:9336–44

Pouyssegur J, Dayan F, Mazure NM (2006) Hypoxia signalling in cancer and approaches to enforce tumour regression. *Nature* 441:437–43

Ravanat JL, Douki T, Cadet J (2001) Direct and indirect effects of UV radiation on DNA and

its components. *J Photochem Photobiol B* 63:88–102

Rezvani HR, Dedieu S, North S *et al.* (2007) Hypoxia-inducible factor-1alpha, a key factor in the keratinocyte response to UVB exposure. *J Biol Chem* 282:16413–22

Rezvani HR, Kim AL, Rossignol R *et al.* (2011a) XPC silencing in normal human keratinocytes triggers metabolic alterations that drive the formation of squamous cell carcinomas. *J Clin Invest* 121:195–211

Rezvani HR, Mahfouf W, Ali N *et al.* (2010a) Hypoxia-inducible factor-1alpha regulates the expression of nucleotide excision repair proteins in keratinocytes. *Nucleic Acids Res* 38:797–809

Rezvani HR, Mazurier H, Morice-Picard F *et al.* (2010b) Xeroderma pigmentosum: clues to understanding cancer initiation. *Dermatologica Sinica* 28:93–101

Rezvani HR, Rossignol R, Ali N *et al.* (2011b) XPC silencing in normal human keratinocytes triggers metabolic alterations through NOX-1 activation-mediated reactive oxygen species. *Biochim Biophys Acta* 1807: 609–19

Rosenberger C, Solovan C, Rosenberger AD *et al.* (2007) Upregulation of hypoxia-inducible factors in normal and psoriatic skin. *J Invest Dermatol* 127:2445–52

Roth U, Curth K, Unterman TG *et al.* (2004) The transcription factors HIF-1 and HNF-4 and the coactivator p300 are involved in insulin-regulated glucokinase gene expression via the phosphatidylinositol 3-kinase/protein kinase B pathway. *J Biol Chem* 279: 2623–31

Rousselle P, Aumailley M (1994) Kalinin is more efficient than laminin in promoting adhesion of primary keratinocytes and some other epithelial cells and has a different requirement for integrin receptors. *J Cell Biol* 125:205–14

Roy S, Khanna S, Wallace WA *et al.* (2003) Characterization of perceived hyperoxia in isolated primary cardiac fibroblasts and in the reoxygenated heart. *J Biol Chem* 278:47129–35

Ryan HE, Poloni M, McNulty W *et al.* (2000) Hypoxia-inducible factor-1alpha is a positive factor in solid tumor growth. *Cancer Res* 60:4010–5

Ryan MC, Tizard R, VanDevanter DR *et al.* (1994) Cloning of the *LamA3* gene encoding the alpha 3 chain of the adhesive ligand epiligrin. Expression in wound repair. *J Biol Chem* 269:22779–87

Salceda S, Beck I, Srinivas V *et al.* (1997) Complex role of protein phosphorylation in gene activation by hypoxia. *Kidney Int* 51:556–9

Saltzman DJ, Toth A, Tsai AG *et al.* (2003) Oxygen tension distribution in postcapillary venules in resting skeletal muscle. *Am J Physiol Heart Circ Physiol* 285:H1980–5

Sarkar K, Fox-Talbot K, Steenbergen C *et al.* (2009) Adenoviral transfer of HIF-1alpha enhances vascular responses to critical limb ischemia in diabetic mice. *Proc Natl Acad Sci USA* 106:18769–74

Savai R, Schermuly RT, Voswinckel R *et al.* (2005) HIF-1alpha attenuates tumor growth in spite of augmented vascularization in an A549 adenocarcinoma mouse model. *Int J Oncol* 27:393–400

Schon MP (1999) Animal models of psoriasis - what can we learn from them? *J Invest Dermatol* 112:405–10

Scortegagna M, Martin RJ, Kladney RD *et al.* (2009) Hypoxia-inducible factor-1alpha suppresses squamous carcinogenic progression and epithelial-mesenchymal transition. *Cancer Res* 69:2638–46

Semenza G (2002) Signal transduction to hypoxia-inducible factor 1. *Biochem Pharmacol* 64:993–8

Semenza GL (2000) HIF-1: using two hands to flip the angiogenic switch. *Cancer Metastasis Rev* 19:59–65

Semenza GL (2003) Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* 3:721–32

Semenza GL (2007) Oxygen-dependent regulation of mitochondrial respiration by hypoxia-inducible factor 1. *Biochem J* 405:1–9

Semenza GL, Jiang BH, Leung SW *et al.* (1996) Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1. *J Biol Chem* 271:32529–37

Semenza GL, Roth PH, Fang HM *et al.* (1994) Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. *J Biol Chem* 269:23757–63

Shyu KG, Hsu FL, Wang MJ *et al.* (2007) Hypoxia-inducible factor 1alpha regulates lung adenocarcinoma cell invasion. *Exp Cell Res* 313:1181–91

Simon MP, Tournaire R, Pouyssegur J (2008) The angiopoietin-2 gene of endothelial cells is up-regulated in hypoxia by a HIF binding site located in its first intron and by the central factors GATA-2 and Ets-1. *J Cell Physiol* 217:809–18

Singer AJ, Clark RA (1999) Cutaneous wound healing. *N Engl J Med* 341:738–46

Smith DG (1976) The innervation of the cutaneous artery in the toad *Bufo marinus*. *Gen Pharmacol* 7:405–9

Sodhi A, Montaner S, Miyazaki H *et al.* (2001) MAPK and Akt act cooperatively but independently on hypoxia inducible factor-1alpha in rasV12 upregulation of VEGF. *Biochem Biophys Res Commun* 287:292–300

Sowter HM, Ratcliffe PJ, Watson P *et al.* (2001) HIF-1-dependent regulation of hypoxic induction of the cell death factors BNIP3 and NIX in human tumors. *Cancer Res* 61:6669–73

Spinella F, Rosano L, Di Castro V *et al.* (2007) Endothelin-1 and endothelin-3 promote invasive behavior via hypoxia-inducible factor-1alpha in human melanoma cells. *Cancer Res* 67:1725–34

Stahl JM, Sharma A, Cheung M *et al.* (2004) Deregulated Akt3 activity promotes development of malignant melanoma. *Cancer Res* 64:7002–10

Staller P, Sulitkova J, Lisztwan J *et al.* (2003) Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL. *Nature* 425:307–11

Stewart FA, Denekamp J, Randhawa VS (1982) Skin sensitization by misonidazole: a demonstration of uniform mild hypoxia. *Br J Cancer* 45:869–77

Stiehl DP, Jelkmann W, Wenger RH *et al.* (2002) Normoxic induction of the hypoxia-inducible factor 1alpha by insulin and interleukin-1beta involves the phosphatidylinositol 3-kinase pathway. *FEBS Lett* 512:157–62

Strieth S, Hartschuh W, Pilz L *et al.* (2000) Angiogenic switch occurs late in squamous cell carcinomas of human skin. *Br J Cancer* 82:591–600

Stucker M, Struk A, Altmeyer P *et al.* (2002) The cutaneous uptake of atmospheric oxygen contributes significantly to the oxygen supply of human dermis and epidermis. *J Physiol* 538:985–94

Tacchini L, Dansi P, Matteucci E *et al.* (2001) Hepatocyte growth factor signalling stimulates hypoxia inducible factor-1 (HIF-1) activity in HepG2 hepatoma cells. *Carcinogenesis* 22:1363–71

Takahashi Y, Takahashi S, Shiga Y *et al.* (2000) Hypoxic induction of prolyl 4-hydroxylase alpha (I) in cultured cells. *J Biol Chem* 275:14139–46

Talks KL, Turley H, Gatter KC *et al.* (2000) The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. *Am J Pathol* 157:411–21

Tandara AA, Mustoe TA (2004) Oxygen in wound healing—more than a nutrient. *World J Surg* 28:294–300

Tang N, Wang L, Esko J *et al.* (2004) Loss of HIF-1alpha in endothelial cells disrupts a hypoxia-driven VEGF autocrine loop necessary for tumorigenesis. *Cancer cell* 6:485–95

Tazuke SI, Mazure NM, Sugawara J *et al.* (1998) Hypoxia stimulates insulin-like growth factor binding protein 1 (*IGFBP-1*) gene expression in HepG2 cells: a possible model for IGFBP-1 expression in fetal hypoxia. *Proc Natl Acad Sci USA* 95:10188–93

Thurston G, Suri C, Smith K *et al.* (1999) Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science* 286:2511–4

Todd C, Reynolds NJ (1998) Up-regulation of p21WAF1 by phorbol ester and calcium in human keratinocytes through a protein kinase C-dependent pathway. *Am J Pathol* 153: 39–45

Tovar-Castillo LE, Cancino-Diaz JC, Garcia-Vazquez F *et al.* (2007) Under-expression of VHL and over-expression of HDAC-1, HIF-1alpha, LL-37, and IAP-2 in affected skin biopsies of patients with psoriasis. *Int J Dermatol* 46:239–46

Turchi L, Aberdam E, Mazure N *et al.* (2008) Hif-2alpha mediates UV-induced apoptosis through a novel ATF3-dependent death pathway. *Cell Death Differ* 15:1472–80

Varghese MC, Balin AK, Carter DM *et al.* (1986) Local environment of chronic wounds under synthetic dressings. *Arch Dermatol* 122:52–7

Vassar R, Fuchs E (1991) Transgenic mice provide new insights into the role of TGF-alpha during epidermal development and differentiation. *Genes Dev* 5:714–27

Vincent AS, Phan TT, Mukhopadhyay A *et al.* (2008) Human skin keloid fibroblasts display bioenergetics of cancer cells. *J Invest Dermatol* 128:702–9

Welch WJ, Wilcox CS (2001) AT1 receptor antagonist combats oxidative stress and restores nitric oxide signaling in the SHR. *Kidney Int* 59:1257–63

Wenger RH, Stiehl DP, Camenisch G (2005) Integration of oxygen signaling at the consensus HRE. *Sci STKE* 2005:re12

Werth N, Beerlage C, Rosenberger C *et al.* (2010) Activation of hypoxia inducible factor 1 is a general phenomenon in infections with human pathogens. *PLoS One* 5:e11576

Woodley DT, Fan J, Cheng CF *et al.* (2009) Participation of the lipoprotein receptor LRP1 in hypoxia-HSP90alpha autocrine signaling to promote keratinocyte migration. *J Cell Sci* 122:1495–8

Wunderlich L, Paragh G, Wikonkal NM *et al.* (2008) UVB induces a biphasic response of HIF-1alpha in cultured human keratinocytes. *Exp Dermatol* 17:335–42

Xia YP, Li B, Hylton D *et al.* (2003) Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. *Blood* 102:161–8

Yatabe N, Kyo S, Maida Y *et al.* (2004) HIF-1-mediated activation of telomerase in cervical cancer cells. *Oncogene* 23: 3708–15

Zhang Q, Wu Y, Chau CH *et al.* (2004) Crosstalk of hypoxia-mediated signaling pathways in upregulating plasminogen activator inhibitor-1 expression in keloid fibroblasts. *J Cell Physiol* 199:89–97

Zhang X, Liu L, Wei X *et al.* (2010) Impaired angiogenesis and mobilization of circulating angiogenic cells in HIF-1alpha heterozygous-null mice after burn wounding. *Wound Repair Regen* 18:193–201

Zhong H, Chiles K, Feldser D *et al.* (2000) Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res* 60:1541–5