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Review

Uncovering the role of hypoxia inducible factor-1α in skin carcinogenesis

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ABSTRACT

The hypoxia inducible factor-1α (HIF-1α) is a pleiotropic transcription factor typically activated in response to low oxygen tension as well as other stress factors in normoxic conditions. Upon activation HIF-1α mediates the transcriptional activation of target genes involved in a variety of processes comprising stress adaptation, metabolism, growth and invasion, but also apoptotic cell death. The molecular mechanisms, signaling pathways and downstream targets evoked by the activation of HIF-1α in epidermal cells are becoming increasingly understood and underscore the participation of HIF-1α in crucial processes including malignant transformation and cancer progression. Recent studies have implicated HIF-1α as an integral part of the multifaceted signal transduction initiated by the exposure of keratinocytes to ultraviolet radiation B (UVB), which represents the most ubiquitous hazard for human skin and the principal risk factor for skin cancer. HIF-1α activation by UVB exposure contributes to either repair or the removal of UVB-damaged keratinocytes by inducing apoptosis, thus revealing a tumor suppressor role for HIF-1α in these cells. On the other hand, the constitutive expression of HIF-1α evoked by the mild hypoxic state of the skin has been implicated as a positive factor in the transformation of normal melanocytes into malignant melanoma, one of the most aggressive types of human cancers. Here we review the uncovered and complex role of HIF-1α in skin carcinogenesis.

Contents

Abbreviations: Bax, Bcl-2-associated X protein; BCC, Basal cell carcinoma; Bcl-2, B cell lymphoma; Bcl-x_L, B-cell lymphoma-extra large; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CMM, Cutaneous malignant melanoma; CBP, cyclic-AMP response element binding protein (CREB) binding protein; CPDs, Cyclobutane pyrimidine dimers; HIF-1, Hypoxia inducible factor 1; HRE, Hypoxia response element; MAPK, Mitogen activated protein kinase; MEF, Mouse embryonal fibroblast; MITF, Microphthalmia-associated transcription factor; mTOR, Mammalian target of rapamycin; NDRG1, N-myc downstream regulated gene-1; PHD, Prolyl hydroxylase; PI3K, Phosphatidyl inositol-3 kinase; ROS, Reactive oxygen species; SBC, Sunburn cell; SCC, Squamous cell carcinoma; Selenbp1, Selenium binding protein-1; Siah2, Seven of absentia homologue 2; Spry2, Sprouty 2; UV, UltraViolet; VEGF, Vascular endothelial growth factor

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1. HIF-1α is under your skin

1.1. The skin in a nutshell

The skin is the largest organ of the adult human body, constituting about 12–14% of our total body weight. It provides a physical barrier at the interface with the external environment, thereby protecting against dehydration and defending internal tissues against a large variety of chemical and environmental insults. Moreover, the skin plays a role in thermoregulation and as a sensory organ.

The skin consists of an outer squamous epithelium, the epidermis, and an inner connective tissue, the dermis. The epidermis fulfils the crucial barrier function of the skin and undergoes continuous self-renewal due to mitotic activity of the stem cells in the basal layer that provide new keratinocytes. The keratinocytes (the major cellular skin component constituting about 90–95% of the epidermis) complete a differentiation-induced cell death program while moving upward through the different epidermal layers to become the corneocytes in the outer layers of the epidermis, before they are shed from the skin (for an extensive review [1]) (Fig. 1). Imbalances in the delicate physiological turn-over of proliferating or differentiating keratinocytes can result in the disturbance of the skin barrier function and are reflected in many skin disorders [1]. In the epidermal layer, the keratinocytes reside in close contact and interact through homotypic E-cadherin binding with the melanocytes, specialized pigment-producing cells derived through the neural crest, forming the so-called epidermal melanin unit, whereby a constant ratio of keratinocytes to melanocytes is maintained (approximately 35:1). These interactions are of fundamental relevance for skin homeostasis and defense function against major environmental insults, such as Ultraviolet (UV) radiation. From one hand, the keratinocytes appear to be capable of regulating the genetic and phenotypic profiles of the melanocytes as well as their proliferation and melanogenesis (reviewed in Refs. [2,3]). On the other hand the melanocytes, through the production of melanin and stimulation of the tanning response further protect the skin from the adverse genotoxic effects of UV light (discussed further in Section 2). Though far less in number, Langerhans cells (epidermal antigen presenting cells), Merkel cells (thought to be the mechanoreceptors) and lymphocytes are also components of the epidermis.

1.2. Skin hypoxia: a physiological HIF-1α mediator

A distinguished characteristic of rodent and human epidermis is the absence of vasculature that results in a constitutive low level of tissue oxygenation. A recent evaluation of the O_2 tension (pO_2) in human skin showed that while the dermis is well oxygenated and vascularized displaying a pO_2 of 10% , in the epidermis the pO_2 gradient ranges from mildly hypoxic (e.g. 5%) to severely hypoxic (e.g. 0.5%) in some skin appendages such as the sebaceous glands and hair follicles [4]. Consistent with this, murine and human skin exhibits an extensive binding of hypoxia-sensitive agents (such as nitroimidazole EF5) particularly in the basal epidermal compartment along with increased levels of the key oxygen sensor hypoxia inducible factor-1α (HIF-1α) [4–6].

HIF-1 is a heterodimeric transcription factor consisting of an O_2-regulated HIF-1α and a constitutively expressed HIF-1β subunit, also called aryl hydrocarbon receptor nuclear translocator (ARNT) [7]. HIF-1β can also heterodimerize with the structurally related HIF-2α isoform, which displays a more restricted tissue expression [8]. Although HIF-2α is also involved in the hypoxia response and is regulated in an O_2-dependent manner an overlapping, yet not completely identical, subset of genes [9], this review addresses primarily the role of the most ubiquitous and better characterized HIF-1α.

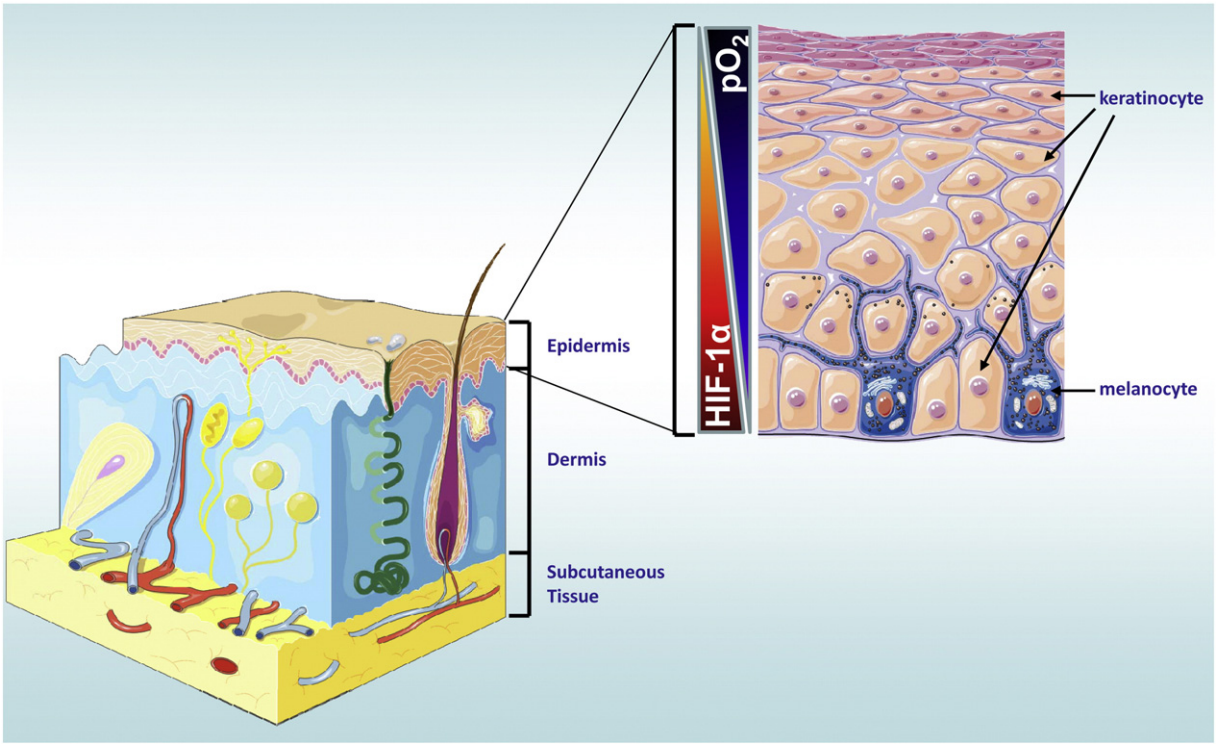

Fig. 1. Constitutive expression of HIF-1α in the epidermis of the human skin. Schematic representation of the skin (epidermis, dermis, supported by the subcutaneous tissue) with a magnification of the epidermis (keratinocytes in layers of increased differentiation toward the external environment with melanocytes residing in the basal compartment). From the external environment toward the basal epidermal compartment the pO_2 diminishes while concomitantly the HIF-1α protein level rises.