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Review

Cytokines and the regulation of hypoxia-inducible factor (HIF)-1α

John J. Haddad[a,b,c,*,1], Hisham L. Harb[b,c]

[a]Department of Biology, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon
[b]Departments of Biology and Biomedical Sciences, Faculty of Arts and Sciences, Lebanese International University, Beirut, Lebanon
[c]Department of Pharmacology, Faculty of Pharmacy, Lebanese International University, Beirut, Lebanon

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Abstract

Hypoxia-inducible factor (HIF)—an oxygen sensor? The HIF–oxygen sensing association type of dogma is, unequivocally, well anchored. But this is only one face of, at least, a double-sided coin. Current concepts charge HIF of taking sides with a yet not well-founded identity—an immunologic sensor and/or regulator. Or, is it really a sensor, put it more correctly, a key player in sensing mechanisms? The evolving association between HIF and immunity emanates from an established linkage that bonds oxidative stress and inflammation—notably the 'biologic response modifiers', or cytokines. HIF is a redox(y)-sensitive transcription factor, and so are cytokines. Recently, cytokines emerged as major regulators of HIF, under physiologic conditions extending the realm of hypoxia. Alternatively, can HIF, like the so infamous inflammatory transcription factor NF-κB, prove itself as a key player in the regulation of cytokines and, subsequently, the inflammatory process. The targeting of HIF would be, at least theoretically, of therapeutic value, but does it make sense given its intricate role in hypoxia signaling? It is the theme of HIF being an immunologic sensor that will be explored therein—with special emphasis on the regulatory role of cytokines.

Keywords: Cytokines; Gene regulation; HIF; Hypoxia; Kinase; MAPK; Sensor; Transcription factors

Abbreviations: NAC, *N*-acetyl-L-cysteine; AP, activating protein; ARDS, acute respiratory distress syndrome; AD, Alzheimer's disease; ARNT, aryl-hydrocarbon receptor nuclear translocator; bHLH-PAS, basic-helix-loop-helix-PAS; CREB, cyclic AMP-response element binding protein; COX, cyclooxygenase; CD, cluster of designation/differentiation; EGF, epidermal growth factor; EPO, erythropoietin; ERK, extracellular signal-regulated kinase; HBX, hepatitis B virus X; HGF, hepatocyte growth factor; hydrogen peroxide, H_2O_2; OH, hydroxyl radical; HIF, hypoxia-inducible factor; HRE, hypoxia response element; HPC, hypoxic preconditioning; iNOS, inducible-nitric oxide synthase; IFN, interferon; IL, interleukin; Jun, c-Jun-N-terminal kinase; LPS, lipopolysaccharide; luc, luciferase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NF-IL-6, nuclear factor-interleukin-6; NO, nitric oxide; PI 3K, phosphatidylinositol 3-kinase; PPT, PAI, plasminogen activator inhibitor; preprotachykinin; PKC, protein kinase C; ROS, reactive oxygen species; Redox, reduction–oxidation; Ref, redox factor; RCC, renal cell carcinoma; SP, substance P; $O_2^{-\cdot}$, superoxide anion; TCR, T cell antigen receptor; TGF, transforming growth factor; TNF, tumor necrosis factor; TNFR, TNF receptor; UPJ, ureteropelvic junction; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von Hippel-Lindau.

* Corresponding author. In affiliation with Prof. Bared Safieh-Garabedian, Department of Biology, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon. Tel.: +961 1350000.

E-mail address: johnjhaddad@yahoo.co.uk (J.J. Haddad).

[1] Previous address: Severenghaus-Radiometer Research Laboratories, University of California, San Francisco, CA, USA.

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Contents

1. Introduction

1.1. Hypoxia-inducible factor (HIF)—an oxygen sensor and master regulator

Unicellular and multicellular organisms have mechanisms for sensing oxygen concentrations [1–5], and for responding to low oxygen levels (hypoxia), with changes in gene expression [6–11]. The transcription factor hypoxia-inducible factor 1 (HIF-1) is one of the master regulators of oxygen homeostasis [12–18]. HIF-1 is required for the development of key physiological systems, such as vasculogenesis and pneumogenesis, during fetal and postnatal life [19–22]. HIF-1 also regulates the physiological responses to hypoxia [23–27] and the pathophysiology of heart attack, cancer, stroke, rheumatoid arthritis, chronic lung disease and other syndromes [28–35].

1.1.1. Basic biochemistry of HIF—an overview

HIF-1α is a basic-helix-loop-helix-PAS (bHLH-PAS) protein [36–40]. It is an obligatory component of HIF-1, which exists as a heterodimer of HIF-1α (an 826 amino acid protein) and another bHLH-PAS protein, the aryl-hydrocarbon receptor nuclear translocator (HIF-1β, ARNT) [36,37,41,42]. ARNT promotes oxygen-independent stabilization of HIF-1α [41–45]. HIF-1α and HIF-1β belong to a larger family of transcription factors that contain bHLH and PER-ARNT-SIM homology domains.

The bHLH and PAS domains comprise the N-terminal halves of both HIF-1α and ARNT, which are required for dimerization and DNA binding [17]. The C-terminal half of both proteins is required for transactivation. In the case of HIF-1α, its transactivation domains are localized to two amino acid residues 531–575 (N-terminal TAD) and 786–826 (C-

terminal TAD), which are separated by an inhibitory domain [15–18]. Two nuclear localization signals (NLSs) are localized to the N-terminal (amino acids 17–74) and the C-terminal parts (amino acids 718–721). The C-terminal NLS motif of HIF-1α plays a crucial role in mediating hypoxia-inducible nuclear import of the protein, whereas the N-terminal NLS motif may be less important [17]. In addition, HIF-1α contains an oxygen-dependent degradation (ODD) domain, which is localized to amino acid residues 401–603 [37–40]. The ODD domain is suggested to control HIF-1α degradation by the ubiquitin-proteasome pathway because its deletion makes HIF-1α stable even under normoxic conditions.

1.1.2. Survey of HIF subunits and isoforms

In addition to the ubiquitously expressed HIF-1α, two other members of this family, HIF-2α and HIF-3α, were identified that show a more restricted tissue expression pattern (Ref. [6] and references therein). Functional comparison between HIF-1α and HIF-2α in vitro revealed similarities concerning genomic organization, modular protein structure, hypoxic protein stabilization, heterodimerization with ARNT, DNA recognition, DNA binding, and *trans*-activation of reporter genes [6]. The three HIFα subunits show partially overlapping expression patterns in vitro and in vivo. Thus, HIF-2 and HIF-3 potentially might interact with the DNA binding site of HIF-1 target genes.

Class I members of this family, such as HIF-1α, HIF-2α and HIF-3α [6], heterodimerize with one of the class II sub-family such as ARNT1, ARNT2 and ARNT3, resulting in different DNA-binding and transcriptional properties depending on the dimer formation [46–49]. HIF mRNA is expressed in human and rodent tissues [50–52]. HIF-2α, HIF-3α, ARNT2 and ARNT3 are restricted to certain tissues, and therefore have a more specialized role in oxygen homeostasis [53–60].

Schematic representation of HIF-1 isoforms and ARNT is depicted in Fig. 1.

1.1.3. HIF-ARNT subunit interactions and modifications

Whereas HIF-1β is constitutively expressed, the expression of HIF-1α is induced by hypoxia [61–65]. Under non-hypoxic conditions, HIF-1α is hydroxylated by a prolyl hydroxylase enzyme [66–68]. This modification is required for the binding of the von Hippel-Lindau (VHL) protein to HIF-1α and its subsequent ubiquitination and degradation in the proteasome [69–82]. Iron chelators and cobalt chloride prevent HIF-1α ubiquitination besides inducing its expression [83–86].

HIF heterodimers bind to the hypoxia response element (HRE), a 5′-RCGTG-3′ consensus sequence [87,88]. Several HIF-1-regulated genes have been identified, including genes coding for proteins involved in angiogenesis, energy metabolism, erythropoiesis, cell proliferation and viability, vascular remodeling and vasomotor responses, oxidative stress and inflammation [89–94].

1.1.4. Oxidant-mediated regulation of HIF

1.1.4.1. Oxygen physiology. The heterogeneous partial pressure of oxygen (pO_2) distribution in tissue

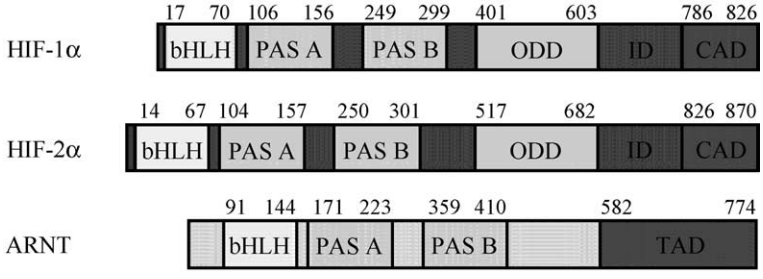

Fig. 1. Schematic representation of human HIF-1α, HIF-2α, and ARNT. HIF-1α, HIF-2α, and ARNT are basic-Helix-Loop-Helix-Per-ARNT-Sim (bHLH-PAS) proteins that contain an N-terminal bHLH domain and two PAS domains. HIF-1 and HIF-2 also contain an oxygen-dependent degradation domain (ODD) that mediates oxygen-regulated stability, and a C-terminal transactivation domain (CAD) whose transcriptional repression in normoxia is controlled by the inhibitory domain (ID). ARNT has a transactivation domain (TAD) that serves no function in the context of HIF-α activity. Amino acid numbers for each domain are indicated. Adapted, with the courtesy of Dr. Anthony Fedele [192].

ranging from about 0 to 90 Torr at a constant arterial pO_2 of about 100 Torr (1 Torr=1 mm Hg at 0 °C) requires an oxygen-sensing system to optimize specific organ functions [2,3,9,35]. Cells located at the arterial inflow have other metabolic properties or electrical activities than cells located at the venous end. To meet the needs for such different functions, an oxygen sensor has to control short- and long-term adaptation of cellular functions via regulation of ion channel conductivity and gene expression [2,4,6,35].

Oxygen is the final acceptor of electrons in the synthesis of ATP by the mitochondrial respiratory chain and is, therefore, an obligatory substrate for energy transformations in most biological systems [6,35,64,65]. A reduction in the level of oxygen in the extracellular milieu severely limits the ability of cells to perform energy-dependent functions and, if hypoxia is severe enough, it can lead to cell death [9,11]. It is, therefore, not surprising that elaborate mechanisms have evolved which allow cells to detect changes in oxygen tension and protect them against hypoxia [9].

The long-range goal of biomedical research is to identify the molecular and cellular mechanisms by which cells detect changes in oxygen tension and how this signal is transduced into the nuclear events responsible for altered gene expression during hypoxia [5–11]. Altered gene expression is essential for development of a hypoxia-tolerant phenotype, which is more resistant to cell damage or death.

1.1.4.2. Hypoxia and gene expression. Although numerous stimuli have been identified which regulate gene expression, perhaps none is more intriguing than hypoxia [6,9]. Hypoxia-induced gene expression has been implicated in a number of physiological processes, including erythropoiesis, carotid body chemoreceptor function, and angiogenesis, all of which enhance the delivery of oxygen to tissue [5–10]. Genes involved in mediating each of these important processes are normally activated by long-term (hours to days) rather than acute (seconds to minutes) episodes of hypoxia [11].

An important transcription factor that is a crucial regulatory element in sensing hypoxic conditions and integrating an adaptive response via gene expression of oxygen-sensitive enzymes and cofactors is HIF-1 (Fig. 2). The signal transduction components which link the availability of oxygen to the activation of these transcription factors are poorly defined, but are broadly believed to hinge on the free abundance of oxidants (i.e., reactive oxygen species [ROS]) in the cytosol [35]. In the case of HIF-1α, post-translational stability, nuclear translocation by ARNT and consensus DNA binding are coupled with oxygen-associated changes in both conformation and activity of a ferroheme containing protein, believed to express peroxide generation via a NADPH oxidase-type activity [14,36,44]. Hypoxic cessation of peroxide production, for instance, mediates HIF-1α stabilization, nuclear translocation and gene expression [6,35].

Adaptive responses to hypoxia, therefore, involve the regulation of gene expression by HIF-1α, whose expression, stability and transcriptional activity are reported to increase exponentially on lowering pO_2 [11,61,62,64,65]. During hypoxia, multiple systemic responses are induced, including angiogenesis, erythropoiesis and glycolysis. HIF-1α is a crucial mediator for increasing the efficiency of oxygen delivery through EPO and VEGF [6,35]. A well-controlled process of adaptation parallels this mechanism with decreased oxygen availability through expression and activation of glucose transporters and glycolytic enzymes. EPO, for example, is responsible for increasing blood oxygen-carrying capacity by stimulating erythropoiesis, VEGF is a transcriptional regulator of vascularization and glycolytic transporters and enzymes increase the efficiency of anaerobic generation of ATP, the vital biological currency. It is expected that any reduction of tissue oxygenation in vivo and in vitro would, therefore, provide a mechanistic stimulus for a graded and adaptive response mediated by HIF-1α [6,9,60–65].

1.2. HIF–an immunologic sensor or an immune-manipulated transcription factor?

The intricate relationship existing between HIF and oxygen sensing indicates a likely potential for the regulation of immunologic responses, such as inflammation, especially in light of the fact that oxidative stress and reduction–oxidation (redox) perturbations are involved with the evolution of inflammatory-related stresses [35,61,62,95–97].

HIF-1α may play an important role not only in regulating the transcription of pO_2-controlled genes

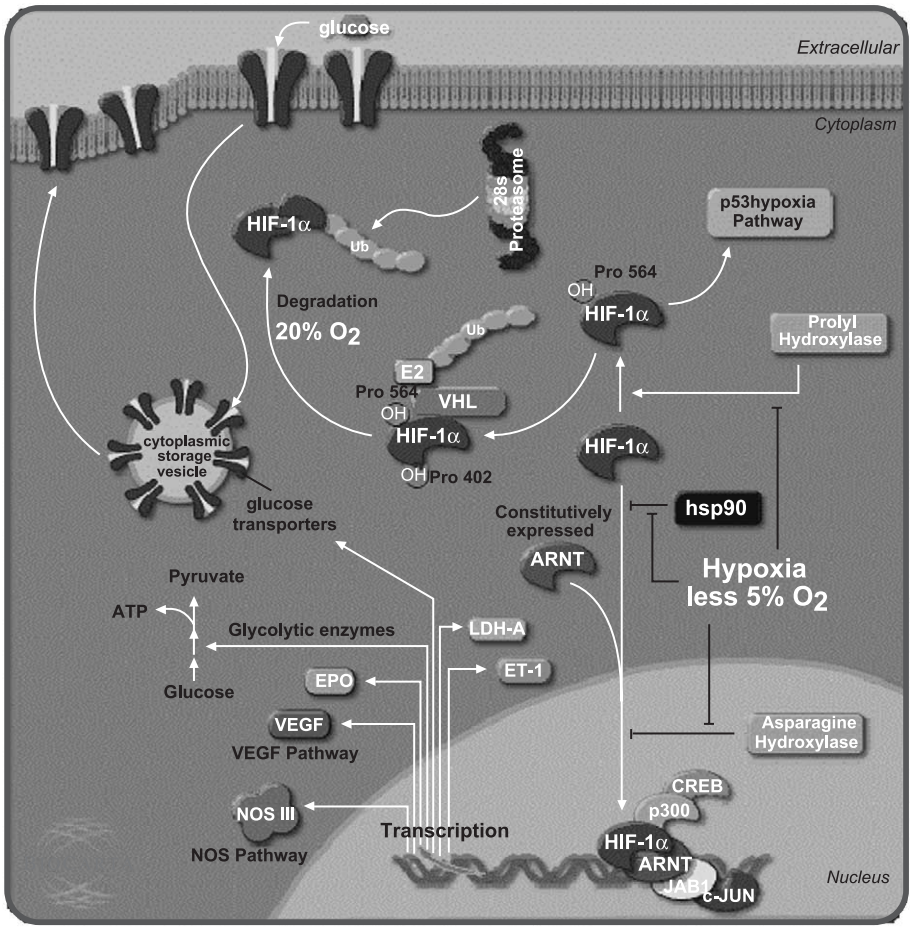

Fig. 2. HIF signaling pathways. The primary molecular mechanism of gene activation during hypoxia is through HIF-1. Several genes involved in cellular differentiation are directly or indirectly regulated by hypoxia. These include EPO, LDH-A, ET-1, transferrin, transferrin receptor, VEGF, Flk-1, Flt-1, platelet-derived growth factor-β (PDGF-β), basic fibroblast growth factor (bFGF), and others genes affecting glycolysis. HIF-1 is a member of the basic helix-loop-helix (bHLH)-PAS family of transcription factors known to induce gene expression by binding to a ~50-bp HRE containing a core 5′-ACGTG-3′ sequence. bHLH-PAS proteins heterodimerize to form transcription complexes that regulate O_2 homeostasis, circadian rhythms, neurogenesis, and toxin metabolism. Three bHLH-PAS proteins in vertebrates respond to hypoxia: HIF-1, EPAS (HIF-2), and HIF-3. These dimerize with aryl hydrocarbon receptor nuclear translocator protein (ARNT), ARNT-2, or ARNT-3. HIF-1 is ubiquitinated and subsequently degraded in less than 5 min under normoxic conditions. Although several candidate O_2-sensing molecules have emerged in the literature, the molecular basis of how cells sense O_2 levels is poorly characterized. pVHL, the protein product of a tumor-suppressor gene responsible for von Hippel Lindau disease, is implicated in this O_2-sensing system by its association with HIF-1, targeting it for ubiquitin-mediated degradation. Similarly, F-box-containing proteins recognize substrates of the ubiquitin ligases, targeting them for phosphorylation-dependent ubiquitination and proteosomal degradation. In addition to F-boxes, most of these proteins also contain a WD40 or a leucine-rich repeat (LLR) domain that presumably functions as a Ser/Thr binding module. A second family of proteins assisting the ubiquitin ligases share a region designated SOCS-box (originally from the suppressor of cytokine signaling proteins SOCS). Under low O_2, HIF-1 is stabilized leading to the formation of a functional transcription factor complex with ARNT. This complex is the master regulator of O_2 homeostasis and induces a network of genes involved in angiogenesis, erythropoiesis and glucose metabolism. Adapted, with the courtesy of Dr. Kosi Gramatikoff, Abgent, San Diego, CA, USA.

and energy homeostasis, but also in influencing immune responses [89–98]. However, the mechanism of cytokine-dependent regulation of the translocation and activation of HIF-1α is being explored. The question is: 'Is cytokine-dependent regulation of HIF oxidant-sensitive or oxidant-mediated?'

Cytokines act as major participants in mediating molecular responses in physiology and pathophysiology. There is accumulating evidence suggesting that the conventionally known 'pro-inflammatory' cytokines can act as oxygen-sensitive mediators, indicating the potential to integrate oxygen-linked pathways mediated by cytokines via ROS-dependent mechanisms [64,65].

ROS, for instance, can induce pro-inflammatory cytokine biosynthesis and this response can be abrogated by selective antioxidants, suggesting an integral role of endogenous ROS [6,35,98]. As such, cytokines could form a pivotal link in ROS-dependent pathways leading to the activation of redox-sensitive transcription factors, such as HIF-1α, whose upregulation determines the specificity of cellular responses to oxidative stress.

Recent investigations have revealed a novel role for ROS signaling in mediating a non-hypoxic effect of cytokines on HIF-1α stabilization, nuclear translocation and activation during normoxia (see discussion below). Despite the fact that HIF-1α was recognized as a transcriptional activator prevailing under hypoxic conditions, ROS signaling pathways that mediate the regulation of HIF-1α have only recently emerged. Consistent with this notion, it was reported that a non-hypoxic pathway mediating the effect of cytokines in regulating the stabilization, translocation and activation of HIF-1α in a ROS-sensitive mechanism [35]. These results suggest that hypoxia may not be the only major player in HIF-1α regulation and that this pathway mediated by inflammatory cytokines may play a major role in controlling HIF-1α regulation in a non-hypoxic environment.

The concept, therefore, has been put forward that ROS and phosphorylation/dephosphorylation events are master regulators of HIF-1α induction and activation; however, the underlying pathways and potential signaling mediators likely to be implicated have yet to be unravelled. Regarding the mechanism of non-hypoxic, ROS-dependent regulation of HIF-1α, a major role for mitochondrial ROS generated at complex III site was reported, thereby causing the accumulation of HIF-1α protein, ostensibly responsible for the initiation of gene expression (reviewed in Ref. [35]).

Furthermore, depletion of the mitochondrial genome has been shown to reverse ROS-mediated induction of HIF-1α (reviewed in Ref. [1]). In addition, it has been reported that HIF-1α-dependent transcriptional activity in the induction of VEGF expression has defined a novel hypoxia-independent mechanism regulating vascular remodeling. Further a field, recent evidence suggested that the reactive nitrogen species (RNS) pathway regulates the stability and activity of HIF-1α. For instance, it was shown that the expression of nitric oxide (NO) synthase could cause HIF-1α accumulation, thus underscoring the role of NO as an intracellular activator of this transcription factor [35].

During inflammation, cytokines, including TNF-α and IL-1β, transiently activate neutrophils and macrophages, thereby causing enhanced production of $O_2^{-\cdot}$ possibly via the activation of NADPH oxidase. This oxidative burst involves a rapid but transient release of ROS as a crucial part of the defense mechanisms against invading microbial pathogens and tumor cell metastasis [35,98–113].

Accumulating evidence indicated that cytokines can increase mitochondrial ROS generation, suggesting that their effect could be mediated through a ROS-sensitive mechanism [105,108]. The results reported by Haddad et al. [35,108] indicate a potential role for cytokines in inducing the accumulation of intracellular ROS, thereby reinforcing the notion that these mediators exert their effect on transcription factors including HIF-1α through a ROS-dependent mechanism.

Regarding the likely source of ROS production engendered by cytokines, at least two sources may be involved: (i) the membrane-bound NADPH oxidase and (ii) the mitochondrial respiratory chain. Although ROS, in general, may be involved in mediating the effect of cytokines on HIF-1α induction, the latter mechanism probably predominates because blockade of mitochondrial respiration abrogates cytokine-dependent activation of HIF-1α. Furthermore, evidence is provided that different ROS species ($O_2^{-\cdot}$, $^{\cdot}OH$ and H_2O_2) may mediate the effect of cytokines on HIF-1α stabilization, localization and activation [6,9,35].

The observation that a non-hypoxic pathway mediates the effect on HIF-1α involves ROS generated within the mitochondrial complex is supported by unequivocal evidence since diphenylene iodonium (DPI), an inhibitor of complex I nicotinamide adenine dinucleotide phosphate-dependent oxidase (which blockades the conversion of ubiquinone→ubiquinol),

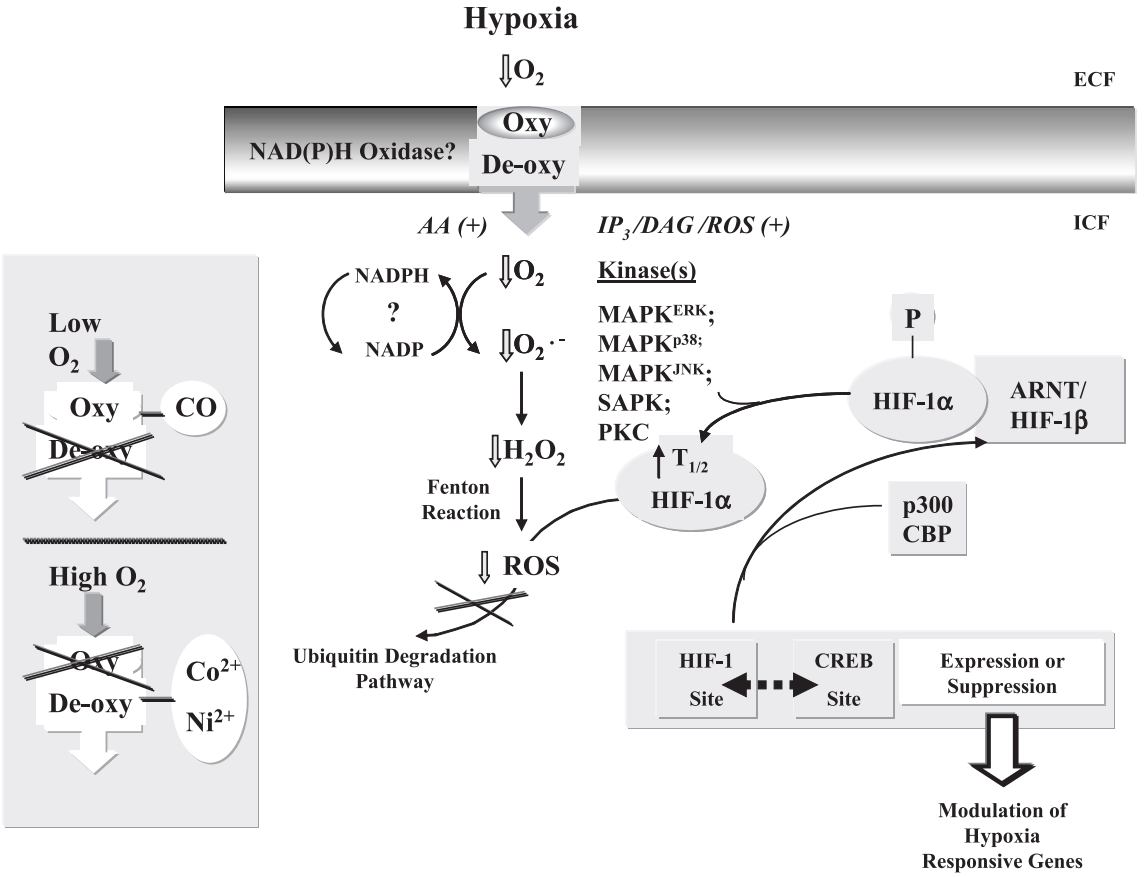

Fig. 3. The role of hypoxia signaling pathways in the regulation of HIF-1 and HIF-1-dependent gene transcription (see text for further discussion) (see Ref. [35]).

abrogates cytokine-mediated activation of HIF-1α, indicating a crucial role for mitochondria-derived ROS in HIF-1α signalling [108].

Although it has been suggested that ROS mediate their signaling by affecting kinases and/or phosphatase activities, the downstream pathway(s) affected by ROS, which govern HIF-1α translocation/activation, have yet to be precisely identified. It is concluded, therefore, that the production of ROS is clearly involved in cytokine-mediated normoxic regulation of HIF-1α stabilization, translocation and activation [35,108].

The underlying mechanisms are being explored, but essentially hinge around the ability of HIF to mediate transcriptional control over many genes closely related to the regulation of the inflammatory milieu [95–98]. Whether HIF may well act as an immunologic sensor or is indirectly regulated by mediators of the immune response will likely shape the identity of this transcription factor not only as an oxygen sensor but also a mediator of immunity and inflammatory responses.

Schematic representation of the role of various cofactors in mediating the regulation of HIF is depicted in Fig. 3.

2. Cytokines, immunity and HIF regulation

2.1. HIF and inflammation–role for NF-κB and other inflammatory mediators

The role of HIF in oxidant-induced inflammation is less clear than that of other transcription factors, such

as the nuclear factor-κB (NF-κB) [99–104]. However, direct and indirect, yet unprecedented and unequivocal, evidence was recently established to implicate HIF as a possible regulator of the evolution and propagation of the inflammatory process [90,95,105–111].

This bears particular relevance in knockouts. Granulocytes and monocytes/macrophages of the myeloid lineage are the chief cellular agents of innate immunity. For instance, Cramer et al. [112] have examined the inflammatory response in mice with conditional knockouts of HIF-1α, its negative regulator VHL, and a known downstream target, VEGF. The activation of HIF-1α is essential for myeloid cell infiltration and activation in vivo through a mechanism independent of VEGF. In addition, loss of VHL leads to a large increase in acute inflammatory responses. These results show that HIF-1α is essential for the regulation of glycolytic capacity in myeloid cells: when HIF-1α is absent, the cellular ATP pool is drastically reduced. The metabolic defect results in profound impairment of myeloid cell aggregation, motility, invasiveness, and bacterial killing [112]. This role for HIF-1α demonstrates its direct regulation of survival and function in the inflammatory microenvironment [112,113].

The original report (discussed below) to relate HIF with inflammation and inflammatory mediators emerged with the role reported for interleukin (IL)-1β and tumor necrosis factor (TNF)-α in stimulating the DNA binding of HIF-1 [105]. Moreover, a role for HIF-1 in mediating the transcriptional activation of ceruloplasmin by iron deficiency, suggested its involvement in hemorrhage, renal failure, sickle cell disease, pregnancy and inflammation [114].

Consistent with the observations reported on HIF relation with inflammation, IL-1 induced HIF-1 in human gingival and synovial fibroblasts, suggesting that this transcription factor might have a role in inflammation, possibly in attempting to re-establish homoeostasis [106]. In addition, NO-evoked HIF-1 induction as a heretofore inflammatory response in association with NO formation was confirmed with the observation that the induction of HIF-1 by NO is mediated via the phosphatidylinositol 3-kinase (PI 3K) pathway [115,116].

On the molecular mechanisms implicated, it has been noted that the early immediate response genes inducible-nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)-2 promote the inflammatory response by the rapid and excessive production of NO and prostaglandins (PGs). HIF-1 may regulate the induction of iNOS during the ischemic phase of hemorrhagic shock, a condition which involves the downstream activation of NF-κB and the release of inflammatory mediators [117].

This was corroborated with the regulation of HIF-1α by the NO [107] and TNF-α [101,107,108] under normoxic conditions. In concert, it has been reported that NO and TNF-α released from activated macrophages can stabilize HIF-1α [101–108]. Additionally, HIF induction by TNF-α in normoxic cells was reported to require receptor-interacting protein-dependent NF-κB activation [101]. Of note, it was observed that IL-1β-mediated upregulation of HIF-1α via an NF-κB/COX-2 pathway identified HIF-1 as a critical link between inflammation and oncogenesis [102].

In transgenic mice expressing constitutively active HIF-1α, it has been reported that the induction of hypervascularity occurred without leakage, edema or inflammation, despite the increase in vascular endothelial growth factor (VEGF) expression [109]. Furthermore, the induction of HIF-1α and activation of caspase-3 in hypoxia-reoxygenated bone marrow stroma was negatively regulated by the delayed production of substance P (SP), the major peptide encoded by the immune/hemopoietic modulator gene, preprotachykinin-1 (PPT-I) [118].

Differential regulation of two alternatively spliced isoforms of HIF-1α was reported in activated T lymphocytes. For example, the T cell antigen receptor (TCR)-triggered activation of normal ex vivo T cells and differentiated T cells resulted in the upregulation of expression of I.1 isoform of HIF-1α mRNA without an effect on constitutive I.2 HIF-1α mRNA expression [119]. In addition, the accumulation of I.1 HIF-1α mRNA isoform in T lymphocytes was also demonstrated during cytokine-mediated inflammation in vivo, suggesting a physiological role of short HIF-1α isoform in activated lymphocytes.

Of interest, the TCR-triggered, protein kinase C and Ca^{2+}/calcineurin-mediated HIF-1α I.1 mRNA induction was protein synthesis-independent, suggesting that the HIF-1α I.1 gene might be expressed as an immediate early response gene [119]. Similarly, HIF was reported to regulate the survival of antigen

receptor-driven T cells, suggesting a mode of action involving peripheral immunity [120]. Of interest, the cluster of designation/differentiation (CD)40-mediated immune/non-immune cell interactions induced mucosal fibroblast chemokines leading to T-cell transmigration in an HIF-dependent manner, suggesting a role in chronic inflammation [121,122].

The expression of the HIF-1 during acute inflammation was also investigated in experimental wounds. HIF-1α induction in primary inflammatory cells was reported to be TNF-α-dependent, the expression of which in early wounds may contribute to the regulation of iNOS and VEGF, two HIF-1-responsive genes intimately related to the process of repair [110]. In addition, COX-2 and presenilin-1 gene expression induced by IL-1β and amyloid β42 peptide was potentiated by hypoxia in primary human neural cells, with HIF-1 contributing episodically to amyloidogenesis, inflammation and Alzheimer's disease (AD) pathophysiology [123]. Interestingly, HIF-1α and inflammatory mediators were observed to co-localize in the hypoxic synovium of inflamed joints in adjuvant-induced arthritis [124]. A role of hypoxia in the pathogenesis of alcoholic liver disease was also observed [125].

Neutrophil apoptosis represents a major mechanism involved in the resolution of acute inflammation [126,127]. In contrast to the effect of hypoxia observed in many other cell types, oxygen deprivation, can cause a profound but reversible delay in the rate of constitutive apoptosis in human neutrophils when aged in vitro. In this regard, it has been observed that the neutrophil has a ferroprotein oxygen-sensing mechanism identical to that for erythropoietin (EPO) regulation which results in HIF-1α upregulation with profound but reversible inhibition of neutrophil apoptosis [111]. This finding may have important implications for the resolution of granulocytic inflammation at sites of low-oxygen tension.

Additionally, alveolar hypoxia, with the involvement of HIF-1 and NF-κB, was observed to induce macrophage recruitment, an increase in albumin leakage and enhanced expression of inflammatory mediators, which were mainly macrophage dependent, thereby implicating alveolar macrophages to have a prominent role in the inflammatory response in hypoxia-induced lung injury and the related upregulation of inflammatory mediators [35,98,99]. This mechanism has also been confirmed with HIF-1α being essential for myeloid cell-mediated inflammation [112,128]. Similarly, it has been observed that the hypoxic gene activation by lipopolysaccharide (LPS) in macrophages implicated HIF-1α [113,122].

2.2. HIF and cytokines—role for interleukins and related mediators

As mentioned previously, cytokines are emanating as critical regulators of HIF. This section will further elaborate on the molecular mechanisms mediating cytokine-dependent HIF regulation.

2.2.1. Role for IL-1

IL-1β was reported to stimulate the DNA binding activity of HIF-1. IL-1-induced inhibition of EPO production, for example, was not mediated by the impairment of HIF-1 function, indicating that HIF-1 may well be involved in modulating gene expression during inflammation [105]. In addition, hypoxia and IL-1β were reported to stimulate VEGF production in human proximal tubular cells, ostensibly due to increased DNA binding of HIF-1 to hypoxia-responsive elements in the VEGF gene promoter, thereby contributing to microvascular leakage and monocyte extravasation [129]. This in agreement with another report which indicated that IL-1 induced HIF-1 in human gingival and synovial fibroblasts, as indicated above [106].

The observation that cytokines, such as IL-1, have the ability to induce the expression and stability of HIF-1 under normoxic conditions remains of particular interest. For instance, it has been reported that the normoxic induction of HIF-1α by insulin and IL-1β involved the PI 3-kinase pathway, followed by the downregulation of EPO production [130]. Recently, Haddad reported that recombinant human IL-1 β-mediated regulation of HIF-1α stabilization, nuclear translocation and activation required an antioxidant/reactive oxygen species (ROS)-sensitive mechanism, indicating that a non-hypoxic pathway is mediating cytokine-dependent regulation of HIF-1α [131].

Similarly, as noted earlier, IL-1β-mediated upregulation of HIF-1α required an NF-κB/COX-2 pathway that identified HIF-1 as a critical link between inflammation and oncogenesis [102], knowing that

NF-κB is a major player in the regulation of genes encoding cytokines. Further elaborating on the essential mechanisms, it has been observed that the normoxic induction of HIF-1α by IL-1β involved the extracellular signal-regulated kinase (ERK)1/2 pathway (mitogen-activated protein kinase (MAPK)$^{ERK1/2}$) in normal human cytotrophoblast cells [132].

It has also been reported that IL-1β upregulates the expression of epidermal growth factor (EGF) and VEGF receptor (VEGFR), raising the possibility that IL-1β might play an important role in VEGF-mediated neo-vascularization [133]. The aforementioned study demonstrated that IL-1β played a key role in ischemia-induced neo-vascularization essentially by mobilizing $CD34^-/B220^-CD3^-Flk\text{-}1^+$ endothelial precursor cells in a VEGF-dependent manner as well as by upregulating expressions of VEGF, VEGFR and adhesion molecules on endothelial cells [133].

2.2.2. Role for IL-2

In an interesting study, hypoxic exposure and TCR-mediated activation were reported to be additive in enhancing levels of hypoxia response element-containing gene products in lymphocyte supernatants [134]. In contrast, hypoxia inhibited the accumulation of non-hypoxia response element-containing gene products (e.g., IL-2 and interferon (IFN)-γ), suggesting that T cell activation in hypoxic conditions may lead to different patterns of lymphokine secretion and accumulation of cytokines (e.g., VEGF) affecting endothelial cells and vascular permeabilization [134]. Moreover, targeting of the VHL-HIF-hypoxia-induced gene pathway for renal cell carcinoma therapy was reported to implicate IL-2 and other cytokines, suggesting therapeutic synergism [135].

2.2.3. Role for IL-6

It has been reported that NF-κB factor was upregulated and pro-inflammatory cytokines, including IL-6, were activated in patients with ureteropelvic junction (UPJ) obstruction who failed endopyelotomy [136]. Those patients with increased expression of NF-κB demonstrated increases in IL-6 expression as well. In addition, HIF was identified in all the tissue samples tested and the stimulation of the human urothelial cells by hypoxia, known to activate NF-κB, resulted in an increase in the levels of IL-1 and IL-6 transcripts compared with hypoxia-exposed cells in the presence of NF-κB inhibitors. This suggested that pro-inflammatory cytokines upregulated by this nuclear factor can result in fibrosis and affect healing after endopyelotomy [136]. Of interest, hypoxia, and apparently HIF, appeared to participate in the activation of this transcription factor. Furthermore, the expression of pro-inflammatory cytokines via HIF-1α and NF-κB activation on desferrioxamine-stimulated mast cells revealed that cytokines seem to be under transcriptional regulation in hypoxic conditions [137].

2.2.4. Role for IL-8

The regulation of IL-8, a chemokine, by hypoxia in human macrophages revealed a potential role in the pathogenesis of many diseases, such as the acute respiratory distress syndrome (ARDS) of the lung [138]. Rapidly raised intrapulmonary IL-8 levels were associated with ARDS progression in patients with major trauma. In addition, acute hypoxia, a clinically relevant stimulus, rapidly and selectively upregulated IL-8 associated with a novel pattern of transcription factor activation (HIF). It was suggested that acute hypoxia may represent one of potentially several pro-inflammatory stimuli responsible for rapid intrapulmonary IL-8 generation in patients at-risk of ARDS [138].

In another setting, it was reported that increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia involved the secretion of IL-8 and other mediators, suggesting that hypoxia might be a key factor contributing to prostate pathophysiology [139].

2.2.5. Role for IL-12

Metastatic renal cell cancer remains a disease which is difficult to treat medically. Prognosis often depends more on intrinsic disease features than on treatment choices. The central role of VHL in clear cell renal cell carcinoma (RCC) pathogenesis is conspicuous. Some clinically applied agents whose clinical results were highlighted included 5-FU, retinoids, thalidomide, razoxane and IL-12 [140].

Features of the pathophysiology of VHL were described, with attention to potential novel therapies targeting HIF-1α, VEGF, transforming growth factor (TGF)-β1 and TGF-α pathways. Of interest, most

basic are cytokine therapies incorporating new IL-2 and IFN-α schedules. Newer cytokine-based drugs include pegylated forms and IL-12 [140]. In addition, allogeneic mini-transplantation has generated much interest. For example, tumor-associated antigens are being used to direct therapy using both identified and non-identified epitopes. A variety of tumor-cell vaccine and dendritic-cell vaccine clinical approaches are discussed. Finally, nephrectomy for known metastatic disease has been demonstrated to be helpful in retrospective and now prospective trials [140].

2.2.6. Role for IL-15

Expression of angiogenic factors was reported to have been upregulated in hyperplastic mucosa adjacent to colon cancer, and that this upregulation was closely associated with cancer growth and metastasis [141]. In the hyperplastic mucosa adjacent to KM12SM tumor in the cecum of athymic mice, VEGF upregulation was associated with HIF-1α induction. The hyperplastic mucosa also showed hypoacetylation of histone H4 and reduction of both p53 and VHL proteins [141].

To examine the effects of growth factors and cytokines on histone acetylation and levels of p53, VHL and HIF-1α, the rat intestinal epithelial cell line IEC6 was treated with EGF and IL-15. Notably, acetylated histone H4, p53 protein and ubiquitinated protein levels were reduced, whereas HIF-1α production was upregulated in EGF- and IL-15-treated cells, suggesting that EGF- or IL-15-induced histone H4 hypoacetylation is associated with repression of p53 and VHL genes [141]. The subsequent suppression of protein ubiquitination can lead to upregulation of VEGF production by HIF-1α retention.

2.2.7. Role for TNF

TNF-α was reported to have a stimulatory effect on HIF-1 DNA binding activity in a manner similar to that of IL-1 [105]. In addition, the induction of adhesion molecules, partakers in local inflammation, with hypoxia were reported to have been induced by IL-1 and TNF-α that was caused with anoxia/reperfusion [142]. This was corroborated with the observation that the upregulation of redox factor-1 (Ref-1), a transcription factor, promoted endothelial cell survival in response to hypoxia and TNF through NF-κB-independent and NF-κB-dependent signaling cascades, respectively, indicating that Ref-1 may act as a critical cofactor mediating the TNF-induced NF-κB response in the vascular endothelium [143].

Recently, Sandau et al. [107] reported that the regulation of the HIF-1α by the inflammatory mediators NO and TNF-α requires diverse agonists under normoxic conditions, which employ different signaling pathways. Similarly, HIF-1 expression in early wounds was reported to possibly contribute to the regulation of iNOS and VEGF, two HIF-1-responsive genes intimately related to the process of repair, in a TNF-α-dependent stream [110].

On the mechanisms implicated with TNF-α-dependent regulation of HIF-1α, Hehlgans et al. [144] reported that the hypoxic upregulation of TNF receptor type 2 expression involved nuclear factor-interleukin-6 (NF-IL-6) and was independent of HIF-1 or HIF-2. TNF is well known to exert its biologic activity via two distinct membrane receptors: TNF receptor type 1 (p55TNFR) and TNF receptor type 2 (p75TNFR). Whereas the p55TNFR gene is rather constitutively expressed, transcription of p75TNFR is strongly modulated by a number of stimulatory agents [145].

Experimental evidence suggested the involvement of p75TNFR in endothelial cell activation. Northern blot analysis revealed that p75TNFR mRNA was upregulated in NIH3T3 cells under hypoxia and reoxygenation. This observation directly originated from transcriptional activation of the p75TNFR gene, as shown by reporter gene analysis [144]. In addition, co-transfection experiments clearly showed that the transcriptional induction of the p75TNFR gene was independent of HIF-1α and HIF-2α. Of particular interest, using deletion mutants of the 5′-flanking region of the p75TNFR gene, the authors were able to identify a putative DNA binding site for NF-IL-6 to be responsible for the transcriptional upregulation of the p75TNFR gene under conditions of hypoxia and reoxygenation.

Furthermore, Haddad et al. [108,131] suggested a non-hypoxic, ROS-sensitive pathway mediating TNF-α-dependent regulation of HIF-α in alveolar epithelial cells. TNF-α activated the translocation of HIF-1α, associated with upregulating its activity

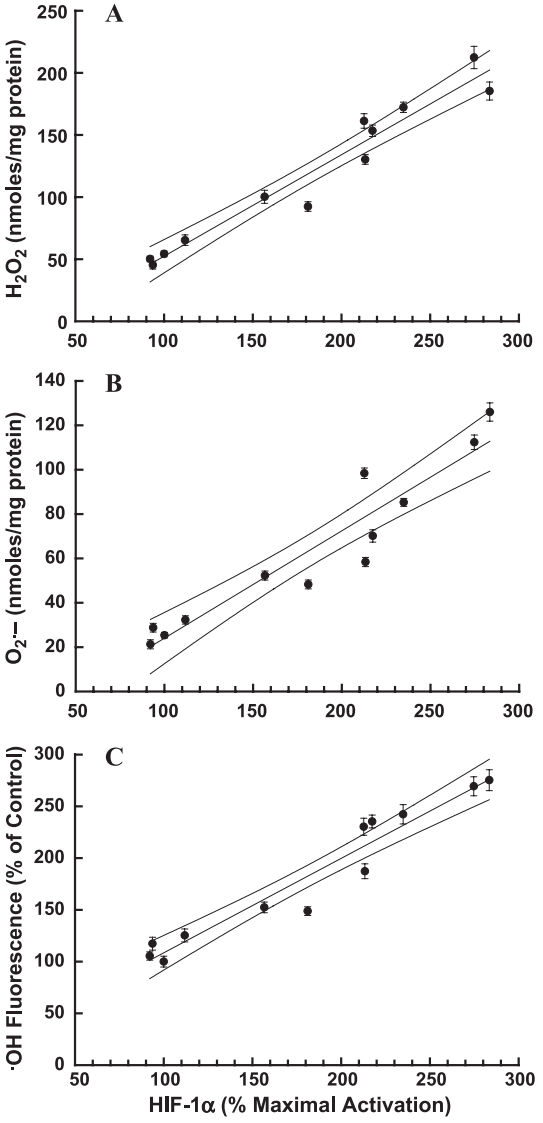

Fig. 4. Subset correlation analysis of ROS-dependent activation of HIF-1α. (A) Correlation with H_2O_2. (B) Correlation with $O_2^{-\bullet}$. (C) Correlation with $^{\bullet}OH$. All forms of ROS tested in vitro show positive correlation with HIF-1α activation. The regression wizard lines represent the degree of confidence at 95% limit. n=3, which represents the number of independent experiments in alveolar epithelial cells (see Refs. [9,64,65,108,131]).

under normoxia. Moreover, analysis of the mode of action of TNF-α revealed the accumulation of hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{-\cdot}$) and the hydroxyl radical ($^{\cdot}OH$) (Fig. 4). The source of those ROS is a matter of discrepancy, however, it swings in the least between NADPH oxidase and the mitochondrion [1,108].

Antioxidants purported as prototypical scavengers of H_2O_2 and $^{\cdot}OH$, attenuated TNF-α-induced HIF-1α activation, and blockading NADPH-oxidase by scavenging $O_2^{-\cdot}$ reduced the activity of HIF-1α (see Fig. 3). Furthermore, inhibition of the mitochondrion complex I abrogated TNF-α-dependent activation of HIF-1α, while interrupting the respiratory chain reversed the excitatory effect of TNF-α on HIF-1α [108].

In another experimental setup, it was reported that capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), a known natural dietary chemo-preventive agent, which inhibits malignant melanoma cell proliferation, has the ability to regulate VEGF expression by modulation of HIF-1α in human malignant melanoma cells independent of IL-1 or TNF-α [146], suggesting that the inhibition of cellular proliferation by capsaicin follows enhanced VEGF production by enhancing HIF-1α expression and binding to HRE.

Furthermore, it has been reported that TNF-α induced the accumulation of a ubiquitinated form of HIF-1α through a NF-κB-dependent pathway, thereby allowing optimum interaction with pVHL [147].

Fig. 5. MAPK signaling pathways and their ramifications. The ever evolving MAPK pathways consist of four major groupings and numerous related proteins which constitute interrelated signal transduction cascades activated by stimuli such as growth factors, stress, cytokines and inflammation. The four major groupings are the ERK, JNK or SAPK, p38 and the Big MAPK or ERK5 cascades. Signals from cell surface receptors such as GPCRs and growth factor receptors are transduced, directly or via small G proteins such as Ras and Rac, to multiple tiers of protein kinases that amplify these signals and/or regulate each other. The diagram is organized to illustrate the cascades by the background colors and also the tiers of kinases as indicated down the left hand side and separated by the horizontal dashed lines. In some cascades the first activation tier involves the MAPKKKKs, MAP kinase kinase kinase kinases or MAP4K proteins. The next tier are the serine/threonine MAPKKKs, MAP kinase kinase kinase or MAP3Ks such as RAF, TAK, ASK, and MEKK1. This level has the greatest amount of cross-communication currently known. The serine/threonine/tyrosine MAPKKs, MAP Kinase kinases or MAP2Ks, such as the MKK and MEK kinases, are one step up from the MAP kinase cascade, phosphorylating and activating these kinases. The focal tier, the MAPKs or MAP kinases includes JNK1, p38, and ERKs, and are the kinases that give each cascade its name. The endpoints of these cascades, shown in the bottom tier, include the MAPK activated protein kinases (MAPKAPK) and some of the numerous transcription factors that regulate genes involved in apoptosis, inflammation, cell growth and differentiation (see Ref. [9]).

Extracellular
Growth Factors, UV, Trophic Factors, etc.
Stress: Osmotic Shock, γ radiation, Anisomycin
FASL, Inflammatory Cytokines, UV, etc.
TGFβ
TGFβ R1
TRADD
TRAF2
RIP
DAXX
RAS-GEF
SHC
GRB2
RAS
RAC1
PAK1
PAK2
MAP4K5
KHS
GCKR
MAP4K1
HPK1
MAP3K5
ASK1
MAP3K7
TAK1
MAP3K11
PTK1
MLK3
MAP3K14
NIK
MAP4K2
GCK
BL44
MAP4K3
GLK
MAP4K4
HGK
MAP3K1
MEKK1
MAP3K2
MAP3K3
MAP3K8
MAP3K12
MAP3K4
MTK1
MEKK4
DLK
ZPK
MAP2K4
MEKK5
MAP2K3
MAP2K6
MEK3
MKK3
MEK6
MKK6
MAP3K6
MLK1
MAP3K13
MAP3K10
MAP3K9
LZK
MAP3K13
MAP3K10
MAP3K6
MAP2K1
MEK1
MAPKK1
MAP2K2
MEK2
PRMK2
MAPKK2
RAF1
A-RAF
B-RAF
MAP2K5
MEK5
MAP2K7
MKK7
MKK7
JNKK2
MEK7
MEK4
MKK4
JNKK1
SEK1
SERK1
MAPK8
MAPK9
MAPK10
JNK1
JNK
SAPK1
MAPK9
JNK2
p54aSAPK
MAPK10
JNK3
p54bSAPK
MAPK11
p38beta2
MAPK12
p38gamma
ERK6
MAPK13
p38delta
MAPK14
p38alpha
MAPK7
ERK5
BMK1
MAPK1
ERK2
ERK
p42mapk
ERK1
p44erk1
p44mapk
MAPK3
MAPK6
ERK3
p97Mapk
MAPK4
ERK3
Related
MAPKAPK2
MAPKAPK3
3PK
MAPKAPK5
PRAK
MAPKAPK2
MAPKAPK3
MAPKAPK2
RPS6KA5
MSK1
MSPK1
RLPK
RPS6KA1
RPS6KA2
p90RSK
RSK1
MAPKAPK1A
RPS6KA3
RSK2
RSK2
MAPKAPK1B
RSK3
MAPKAPK1C
RPS6KA5
MSK1
MKNK2
MNK2
RPS6KB1
RPS6KB2
p70s6K
MKNK1
MNK1
RPS6KA4
MSK2
p70S6Kβ
IKKα
IKKβ
NFkB
IkBa
NFkB
IkBa
Elk-1
c-FOS
MEF2
c-JUN
c-MYC
CREB
ATF-2
MAX
SP1
c/EBPα
STAT1
Cytoplasm
MAP4K
MAP3K
MAP2K
MAPK
Targets of MAPK
Kinases
Transcription Factors

Reciprocally, inflammatory cytokines seem to be under HIF-1α or NF-κB transcriptional regulation under hypoxia in mast cells [137].

2.3. HIF and MAPKs–role for cytokines

MAPKs were identified by virtue of their activation in response to growth factor stimulation of cells in culture, hence their well known nomenclature. MAPKs have similar biochemical properties, immuno-cross-reactivities, amino acid sequence and ability to phosphorylate similar substrates. Maximal MAPK activity requires that both tyrosine and threonine residues are phosphorylated. This indicates that MAPKs act as switch kinases that transmit information of increased intracellular tyrosine phosphorylation to that of serine/threonine phosphorylation.

It is beyond the scope of this paper, however, to discuss the entirety of MAPK regulation and their bifurcations. Excellent reviews, in this regard, have been recently released covering this topic [148–157]. Therefore, we will concentrate on the pathways mediating HIF–MAPK interactions, with emphasis on the role of cytokines. For clarity, MAPK signaling pathways and their ramifications have been depicted in Fig. 5.

HIF-1, during hypoxic stress, triggers the expression of genes essentially encoding for glycolytic enzymes and angiogenic factors, as noted earlier. To be active, HIF-1 must be phosphorylated. HIF-1 is a substrate for various kinase pathways including MAPKs. Several transduction pathways have been proposed which act downstream of putative oxygen sensors and lead to the activation of these kinases [158].

2.3.1. HIF and $MAPK^{p38}$

The elucidation of the molecular mechanisms governing the HIF–MAPK interactions was initially revealed in phenotypic changes associated with malignancy. For instance, it has been reported that the Kaposi's sarcoma-associated herpes virus G protein-coupled receptor upregulated VEGF expression and secretion through MAPK and $MAPK^{p38}$ pathways acting on HIF-1α [159].

Moreover, Tacchini et al. [160] showed that *N*-acetyl-L-cysteine (NAC), an antioxidant, reduced the stimulatory effect of hepatocyte growth factor (HGF) on stress kinase activities, while $MAPK^{p42/44}$ was unmodified, suggesting the involvement of c-Jun-N-terminal kinase (JNK; $MAPK^{JNK}$) and $MAPK^{p38}$ in HIF-1 activation. Of note, LY294002 inhibitor blocked the activity of PI 3K, one of the principal transducers of HGF/Met receptor signaling, prevented the enhancement of HIF-1 DNA binding and $MAPK^{JNK}$ activity, but the inhibition of $MAPK^{p42/44}$ phosphorylation with PD98059 was ineffective, suggesting that HGF can trigger a signal transduction cascade involving PI 3K and ultimately can activate HIF-1 [160].

Similarly, the insulin-induced retinal HIF-1α and VEGF increases and the related blood–retinal barrier breakdown were suppressed by inhibitors of $MAPK^{p38}$ and PI 3K, but not inhibitors of $MAPK^{p42/p44}$ or protein kinase C (PKC) [161]. In addition, cell density mediated pericellular hypoxia was shown to lead to the induction of HIF-1α via NO and Ras/MAPK-mediated signaling pathways [162].

In head and neck squamous cell carcinoma lines, hypoxia induced $MAPK^{p38}$ activity [163]. This activation was correlated with the induction of HIF-1α expression and DNA binding activity, which was blocked by the $MAPK^{p38}$ inhibitor, SB203580. Hypoxia also increased VEGF production, which was inhibited by treatment with SB203580. Interestingly, overexpression of $MAPK^{p38}$ was sufficient to induce HIF-1α and VEGF expression [163].

This is corroborated by the observation of $MAPK^{p38}$-mediated HIF-1α and VEGF induction by chromium (VI), a potent inducer of tumors in animals, in DU145 human prostate carcinoma cells [164]. In contrast, evidence was provided for a role of $MAPK^{p38}$ in HIF-1α-independent induction of VEGF expression by sodium arsenate in human ovarian cancer cells [165] and human glioma cells [166].

Regulation of the hypoxia-dependent plasminogen activator inhibitor (PAI) expression by MAPKs has also been reported. Under hypoxic conditions, the expression of PAI-1 (PAI-1) is mainly controlled by HIF-1 [167]. For instance, treatment with SB203580 and Y294002, but not with the MEK1 inhibitor PD98059, abrogated hypoxia-dependent PAI-1 induction in HepG2 cells. Consistently, overexpression of PKB or of the $MAPK^{p38}$ upstream kinases MKK6 and MKK3 and of $MAPK^{JNK}$, but not of $MAPK^{p42/p44}$,

enhanced PAI-1 mRNA levels [167]. In MKK3-, MKK6- and protein kinase B (PKB)-expressing cells luciferase (Luc) activities from a hypoxia-inducible PAI-1-Luc construct or from a HIF-dependent Luc construct and, concomitantly, HIF-1α protein levels were enhanced, indicating that $MAPK^{p38}$- and PKB-dependent signaling pathways contribute to enhanced PAI-1 levels in the hypoxic response. Moreover, it has been shown that suppression of the dual-specificity phosphatase MKP-1 enhanced HIF-1 transactivation and increased the expression of EPO [168].

Leukocyte–endothelial interactions are regulated by a cascade of molecular steps of cytokines, chemokines and adhesion molecules. $MAPK^{p38}$ is one of the essential mediators in cytokine and chemokine expression through the activation of NF-κB and activating protein (AP)-1. Moreover, HIF-1-related gene expression results in protection of ischemia–reperfusion injury, ostensibly via the regulation of inflammatory cytokines [169]. Moreover, activation of the CD40/CD40L (CD40 ligand) system in the gut mucosa triggered a self-sustaining loop of immune–nonimmune cell interactions leading to an antigen-independent influx of T cells that contributed to chronic inflammation in an HIF-1-dependent pathways [170].

2.3.2. HIF and $MAPK^{p42/p44}$

The initial report which described HIF-$MAPK^{p42/p44}$ interactions indicated a correlation between the phosphorylation of HIF-1 and its transcriptional activity [171]. In addition, Pages et al. [172] demonstrated that $MAPK^{p42/p44}$ stoichiometrically phosphorylated HIF-1α in vitro and that HIF-1-dependent VEGF gene expression was strongly enhanced by the exclusive activation of $MAPK^{p42/p44}$ [173,174]. However, $MAPK^{p42/p44}$ did not modulate the degradation/stabilization profile of HIF-1α [175]. Similarly, PD98059 was shown to block the transactivation but not the stabilization or DNA binding ability of this transcription factor [176].

The transactivation domain of HIF-1α was recently dissected in correlation with specific domains of HIF-1α interacting with specific signaling pathways. During long-term stimulation, $MAPK^{p42/p44}$ becomes inactive while accumulating in the nucleus. This inactivation was demonstrated with phospho-specific immunostaining and dephosphorylation of a nuclear $MAPK^{p42/p44}$ substrate, HIF-1α [177], suggesting that the nucleus is a critical site for mitogenic signal termination by: (1) nuclear sequestration of $MAPK^{p42/p44}$ away from MEK, their cytoplasmic activator; and (2) dephosphorylation by specific nuclear phosphatases.

Furthermore, Lee et al. [178] designed several fusion proteins that contain deletion mutants of HIF-1α linked to the DNA binding domain of the yeast protein Gal4. By using the Gal4-driven reporter system, the transactivation activities of the Gal4/HIF-1αa fusion proteins in Hep3B cells were investigated. The findings suggested that tyrosine kinases, the MEK-1/$MAPK^{p42/p44}$ pathway, but not the PI-3 kinase/Akt pathway, were involved in the hypoxia-induced transactivation of HIF-1α [178].

It was also shown that the functional transactivation activities are located at both 522–649 and 650–822 amino acids of HIF-1α. Treatment of PD98059 blocked the hypoxia-induced transactivation abilities of both the 522–649 and 650–822 amino acids of the C-terminal half of this transcription factor, implying that the MEK-1/$MAPK^{p42/p44}$ signaling pathway cannot distinguish between the two hypoxia-induced transactivation domains [178].

Hepatitis B virus X (HBX) protein was also shown to enhance the transcriptional activity of HIF-1α through activation of MAPK pathway [179]. The stability of HIF-1α protein was increased by HBx in HBx-inducible Chang liver cells as well as in transient HBx expression system of non-hepatic cells. Moreover, immunofluorescence studies revealed that the HBx-induced HIF-1α was partially translocated into the nucleus in majority of cells while additional $CoCl_2$-induced hypoxic condition caused complete nuclear translocation.

HBx induced the phosphorylation of HIF-1α and activation of $MAPK^{p42/p44}$, which were synergistically enhanced in the presence of $CoCl_2$. Furthermore, HBx enhanced transcriptional activity of HIF-1α in the reporter genes encoding hypoxia response element or VEGF promoter. Either treatment of PD98059 or coexpression of dominant-negative MAPK mutants abolished the HBx-induced transcriptional activity and protein stability as well as nuclear translocation of HIF-1α, suggesting that HBx activates HIF-1α through MAPK pathway [179].

The association of HIF-1α with VHL was decreased but the association with cyclic AMP-response element binding protein (CREB)-binding protein was enhanced in the presence of HBx, indicating that the molecular mechanism by which HBx enhances the protein stability and transactivation function of HIF-1α. It was also demonstrated that expression of HIF-1α and VEGF was increased in the liver of HBx-transgenic mice, suggesting that the cross-talk between HIF-1α and HBx may lead to transcriptional activation of HIF-1α target genes, which play a critical role in hepatocarcinogenesis [179].

Concomitantly, hypoxic preconditioning (HPC) was reported to protect neonatal cardiomyocytes against H/R injury by promoting cardiomyocyte survival and membrane integrity [180]. The protective mechanism was attributed to the upregulation of HIF-1α phosphorylation, induced by $MAPK^{p42/p44}$.

2.3.3. HIF and $MAPK^{JNK}$

C-Jun (AP-1), a transcriptional entity regulated by the upstream $MAPK^{JNK}$, and HIF-1 functionally cooperates in hypoxia-induced gene transcription. For instance, a dominant-negative mutant of c-Jun which lacks its transactivation domain partially inhibited HIF-1-mediated transcription [181]. This cooperative effect was not due to an increase in the nuclear amount of the HIF-1α subunit, nor did it require direct binding of c-Jun to DNA. In addition, c-Jun and HIF-1α were able to associate in vivo but not

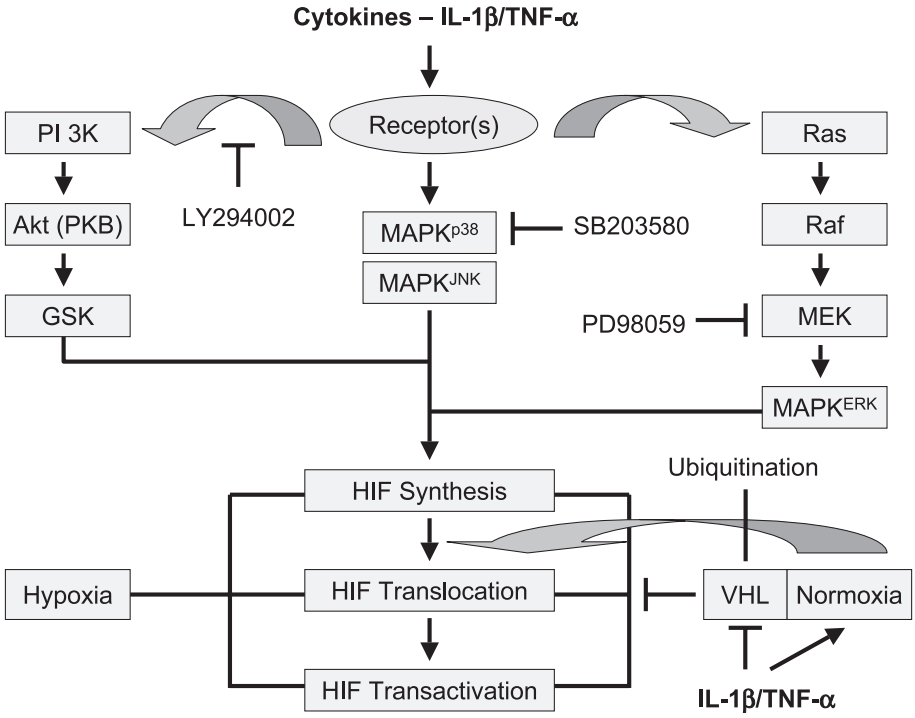

Fig. 6. Signaling transduction pathways mediating cytokine-dependent regulation of HIF, with the involvement of MAPKs. Cytokines, such as IL-1β and TNF-α, initiate a cascade of receptor-mediates mechanisms, which diverge at the level of G-coupled receptors (Ras), upstream kinases involved with the phosphorylation of $MAPK^{p38}$/$MAPK^{JNK}$, and phosphatidylinositol-3 kinase pathway. Subsequent phosphorylation/activation mechanisms upregulate the biosynthesis of the α subunit of HIF, which couples with the constitutively expressed β subunit, thereby allowing nuclear translocation and transactivation of this transcription factor. The activation of HIF-1α requires phosphorylation. This scenario is likely provided with the normoxic induction by cytokines, which stabilize the α subunit, ostensibly via downregulation of VHL and/or upregulation of upstream kinases such as MAPKs. Adapted with modification from Wenger [6] and Lee et al. [14].

in vitro, suggesting that this interaction might involve the participation of additional proteins and/or a posttranslational modification of these factors [181].

In this context, hypoxia induced phosphorylation of c-Jun at Ser^{63} in endothelial cells [182]. This process was involved in its cooperative effect, since specific blockade of the $MAPK^{JNK}$ pathway and mutation of c-Jun at Ser^{63} and Ser^{73} impaired its functional cooperation with HIF-1. Notably, it was demonstrated that HIF-1 and AP-1 can cooperate to increase gene expression in hypoxia with particular role for MAPKs [183–191].

Signaling pathways involving HIF–cytokine interactions and the role of MAPK signaling pathways are illustrated in Fig. 6.

3. Summary, conclusion and prospects

HIF–cytokine interactions research continues apace—ostensibly due to the fact that major unanswered quotations about the role of HIF in cytokine regulation, and inflammation, remain to be addressed. On the immunologic features that characterize HIF, it is conspicuous that HIF can act as a dual sensor: a relatively established player in hypoxia/hyperoxia signaling, an oxygen/redox sensor, and a burgeoning participant in immune functions, a putative immunologic sensor. The latter feature characterizes what perhaps may be the keynote of transduction pathways culminating in a well-defined transcriptional response targeted at alleviating the strains imposed with oxidative stress and inflammation.

The evolving relationship among diverse, yet closely related, mechanisms mediating the regulation of oxidative stress, oxygens, inflammation and HIF, reveals another face for HIF—an immunologically orientated transcription factor with the powers of shaping oxygen sensing and transduction pathways. It remains a particular interest to decipher the molecular codes that define the modes of action of HIF, and as such reveal the possible therapeutic values of knowing the identity of this intriguing factor. In light of the aforementioned, it is imperative that the classic understanding of HIF as an oxygen sensor be revisited to finely tune with current notes being played within the immunology symphony.

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