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Review article

Hypoxia-inducible factor 1 in autoimmune diseases

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ABSTRACT

Autoimmune disorders are a complicated and varied group of diseases arising from inappropriate immune responses. Recent studies have demonstrated that ongoing inflammatory and immune responses are associated with increased oxygen consumption, a process resulting in localized tissue hypoxia within inflammatory lesions (“inflammatory hypoxia”), in which hypoxia-inducible factor 1 (HIF-1), an oxygen-sensitive transcription factor that allows adaptation to hypoxia environments, has been shown to play an important function. HIF-1 is a regulator of angiogenesis and immune system. Besides, HIF-1-mediated metabolic shift and fibrosis may also play crucial roles in some autoimmune disorders. Firstly, we briefly summarize the role of HIF-1 in angiogenesis, immune responses and fibrosis. Secondly, we will show the major recent findings demonstrating a role for HIF-1 signaling in autoimmune disorders, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic sclerosis and multiple sclerosis. The growing evidences may prompt HIF-1 to be a new target for treatment of autoimmune diseases.

Contents

1. Introduction

Hypoxia-inducible factor 1 (HIF-1), the oxygen-sensitive transcription factor that allows adaptation to hypoxia environments, is a heterodimer of one oxygen-regulated α- and one constitutively expressed β-subunit [1]. Each subunit contains basic helix-loop-helix-PAS (bHLH-PAS) domains that mediate heterodimerization and DNA hypoxia response elements (HREs) binding [2,3]. Because HIF-1β is excessive in vivo, HIF-1 transcriptional activity is mainly determined by HIF-1α protein levels [4]. Besides HIF-1, the family of hypoxia-inducible factors has two other isotypes, HIF-2 and HIF-3, which also play roles in transcriptional responses to hypoxia, immune systems, neovascularization et al. [5–7]. However, HIF-1

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is one of the most important hypoxia-inducible factors involved in cellular metabolism, tissue repair, and inflammatory [8–13].

In normoxia, HIF-1α is rapidly hydroxylated and degraded in Von Hippel-Lindau tumor suppressor protein (VHL)-mediated proteasomal pattern by the prolyl hydroxylase domain-containing protein (PHD). PHD takes O_2 as a substrate, therefore, under hypoxic conditions its activity is declined. Factor inhibiting HIF-1 (FIH-1) could also suppress HIF-1α transcriptional activity under normoxia. By using O_2 and α-ketoglutarate as substrates, it hydroxylates an asparaginyl residue on HIF-1α and then prevents the association of HIF-1α with the p300 coactivator protein [14]. Under hypoxic environment, both PHD and FIH-1 activities are inhibited. Consequently, the α-subunit heterodimerises with the β-subunit to formulate HIF-1 and promote the transcriptional activities of target genes by binding to the HREs [13,15–17].

Studies have demonstrated that ongoing inflammatory and immune responses are associated with increased oxygen consumption, a process resulting in localized tissue hypoxia within inflammatory lesions (“inflammatory hypoxia”) [18,19]. Conditional knockout of HIF-1 in specific types of cells has indicated vital roles of this factor in B lymphocyte development (using lymphocytes specific-HIF-1α-knockout mice) [20], T lymphocyte differentiation (in HIF-1α-knockout T cells) [8,21], and innate immune response (in both HIF-1α-deficient macrophages and dendritic cells) [22]. Recently it has been reported that HIF-1 contributes to the pathogenesis of several autoimmune diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis, systemic sclerosis (SSc) and multiple sclerosis (MS) [23–27]. In this review we update the recent findings on the role of HIF-1 in the autoimmune diseases.

2. Cellular consequences of high-level HIF-1

2.1. HIF-1 and angiogenesis

In both physiological and pathological states, neovascularization is usually connected with hypoxia or “inflammatory hypoxia” [28,29]. HIF-1, as one of the most important product of hypoxia, is believed to orchestrate the process of angiogenesis. Current studies have shown that HIF-1 may contribute to angiogenesis from 3 aspects: 1) activating several angiogenic genes and their receptors (*VEGF*, vascular endothelial growth factor; *PlGF*, placental growth factor; *PDGFB*, platelet-derived growth factor-β et al.); 2) regulating proangiogenic chemokines and receptors (*SDF-1α*, stromal cell derived factor 1α, and *S1P*, sphingosine-1-phosphate, and receptors *CXCR4*, C-X-C chemokine receptor type 4, and *S1PRs*, sphingosine-1-phosphate receptors) to recruit endothelial progenitor cells; 3) enhancing endothelial cells proliferation and division (regulating cyclins, Wnt signaling, et al.) [29,30]. Among them, VEGF is a master of HIF-1-mediated angiogenesis. It has been reported that benzo[α]pyrene opposes angiogenesis because of the inhibitory effect of the metabolite benzo[α]pyrene-3,6-dione on VEGF expression through HIF-1-binding site [31] (Fig. 1).

Hypoxia or “inflammatory hypoxia” usually enhanced in pathological states such as solid tumors or chronic inflammatory disorders [28,32]. Taken the pathological conditions into account, angiogenesis here may be different from that in physiological states. In tumor cells, accumulated HIF-1 promotes TAp73 and DNp73 (two major forms of p73) stabilization. Thus, TAp73 and DNp73 can up-regulate pro-angiogenic genes such as *VEGF-A, PDGFB* et al. to support angiogenesis and tumorigenesis [33,34]. Besides, HIF-1's transcriptional activity can also be increased by other proteins such

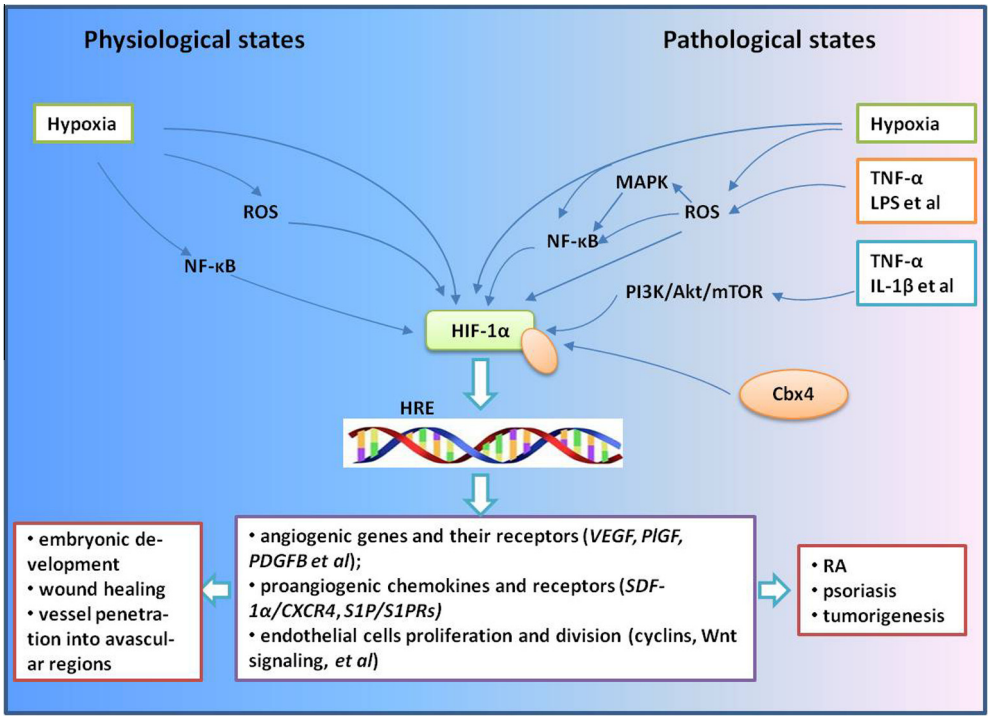

Fig. 1. The model of hypoxia-inducible factor 1-mediated angiogenesis. In physiological states, HIF-1 is usually stimulated by hypoxia directly and indirectly. While in pathological states, HIF-1 can be stimulated by hypoxia, inflammatory cytokines (e.g. TNF-α, IL-1β), LPS et al. through NF-κB, MAPK and PI3K/Akt/mTOR pathways. Besides, HIF-1's transcriptional activity can also be increased by other proteins such as Cbx4 (a SUMO E3 ligase) in tumor cells. Current studies have shown that HIF-1 may contribute to angiogenesis from 3 aspects: 1) activating several angiogenic genes and their receptors; 2) regulating proangiogenic chemokines and receptors to recruit endothelial progenitor cells; 3) enhancing endothelial cells proliferation and division. HIF-1, hypoxia-inducible factor-1; TNF-α, tumor necrosis factor α; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; PDGFB, platelet-derived growth factor-β; SDF-1α, stromal cell derived factor 1α; CXCR4, C-X-C chemokine receptor type 4; S1P, sphingosine-1-phosphate; S1PRs, sphingosine-1-phosphate receptors; RA, rheumatoid arthritis.

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