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Review

The interaction between HIF-1 and AP-1 transcription factors in response to low oxygen

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Abstract

Hypoxia-inducible factor-1 (HIF-1) is a critical regulator of the transcriptional response to low oxygen conditions (hypoxia/anoxia) experienced by mammalian cells in both physiological and pathophysiological circumstances. As our understanding of the biology and biochemistry of HIF-1 has grown, it has become apparent that cells adapt to signals generated by low oxygen through a network of stress responsive transcription factors or complexes, which are influenced by HIF-1 activity. This review summarizes our current understanding of the interaction of HIF-1 with AP-1, a classic example of a family of pleiotropic transcription factors that impact on diverse cellular processes and phenotypes, including the adaptation to low oxygen stress. The review focuses on experimental studies involving cultured cells exposed to hypoxia/anoxia, and describes both established and possible interactions between HIF-1 and AP-1 at different levels of cellular organization.

Keywords: AP-1; HIF-1; Hypoxia/anoxia

Contents

Abbreviations: AEC, aortic endothelial cell; bFGF, basic fibroblast growth factor; cAMP, cyclic adenosine 3′,5′-monophosphate; CKI, cyclin-dependent kinase inhibitor; CRY1, cryptochrome 1; CYP3A6, cytochrome p450 oxidase 3A6; DEC1, deleted in esophageal cancer 1; 4E-BP, eIF4E binding protein; eIF4E, eukaryotic translation initiation factor 4E; ECM, extracellular matrix; EGF, epidermal growth factor; EMSA, electrophoretic mobility shift; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK1/2, extracellular signal regulated protein kinase 1/2; ET-1, endothelin-1; GRP78, glucose-regulated protein 78; HO-1, heme oxygenase-1; HUVEC, human umbilical vein endothelial cell; IGF, insulin-like growth factor; IL-1, IL-8, interleukin-1, -8; Jab1, Jun activation-domain binding protein 1; JNK/SAPK, Jun N-terminal kinase/stress-activated protein kinase; mTOR, mammalian target-of-rapamycin; MAPK, mitogen-activated protein kinase; MT-IIA, metallothionein-IIA; MTF-1, metal-regulatory transcription factor-1; MMP-2, matrix metalloproteinase-2; MNK, MAP-kinase signal integrating kinase; MOP, members of the PAS superfamily; NDRG, N-myc downstream-regulated gene; PER2, period 2; PI-3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; REDD, regulated in development and DNA damage responses; Ref-1/Ape, Redox effector factor-1/apurinic/apyrimidinic endonuclease; RNS, reactive nitrogen species; ROS, reactive oxygen species; S6K, ribosomal protein S6 kinase; SCN, suprachiasmatic nucleus; SILAC, stable isotopic labeling by amino acids in cell culture; TNF-α, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VEGF, vascular endothelial growth factor

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1. Introduction

A fundamental concept of modern systems biology is that the molecular components of cells are embedded within extensive networks, which ultimately determine cellular behavior at multiple levels of organization [1]. Applying this concept to the biology of hypoxia, the homeostatic response of a mammalian cell to oxygen deprivation can be modeled as the adaptation of biochemical networks that coordinate more general processes—for example, those regulating energy metabolism, cell cycle progression, cell mass, and survival. Although our knowledge of the networks active in hypoxic cells is at an early stage, research by several groups has revealed a nexus of transcriptional interactions involving hypoxia-inducible factor-1 (HIF-1), the key genetic regulator of the hypoxic response in mammalian cells (reviewed elsewhere in this issue). This review summarizes current knowledge of the interaction between HIF-1 and another pleiotropic transcription factor, activator protein-1 (AP-1), at different levels of cellular organization.

2. The AP-1 family of transcription factors

AP-1 complexes usually form as heterodimers, which consist of basic-region leucine zipper (bZIP) transcription factors mainly from the Jun, Fos, ATF, MAF, and Nrf protein families (for recent reviews see [2,3]). As a consequence of this variability in subunit composition, AP-1 complexes bind to different response elements (RE's) in genomic regulatory regions, including the TRE, CRE, MRE, and ARE consensus DNA-binding sites [3]. The TRE (5′-TGAC/GTCA-3′) and CRE (5′-TGACGTCA-3′) binding sites are perhaps the most common AP-1 targets. As expected from such diverse combinations of subunits, AP-1 has far-reaching effects on cellular physiology—influencing proliferative, survival, and differentiation responses depending on the cell type and its microenvironment. Each type of AP-1 complex is uniquely regulated, but in general terms AP-1 activity depends on mechanisms that control the abundance and biochemical modifications of its subunits [2]. This regulation is exemplified by AP-1 complexes containing the c-Jun protein, one of the first subunits to be discovered and among the best characterized of the AP-1 transcription factors (reviewed in [4,5]). C-Jun/AP-1 is regulated at multiple levels—from transcription to posttranslational modification—and all these levels can be modulated by low oxygen environments.

c-jun is a member of the immediate-early group of stress and mitogen responsive genes, which are characterized by the rapid and transient induction of transcription in the absence of new protein synthesis [6,7]. The induction of *c-jun* expression by immediate-early signals has been attributed in part to a positive feedback loop in which (c-Jun:ATF2)/AP-1 complexes bind to the *c-jun* proximal promoter region and stimulate transcription [8,4]. At the posttranscriptional level, the lifetime of *c-jun* mRNA is influenced by destabilizing sequences located in the 3′-untranslated region (3′-UTR) [9]. Such sequences are determinants for a specific mechanism that targets the mRNA of various transiently expressed genes for degradation [10]. At the posttranslational level, c-Jun is extensively modified by phosphorylation, oxidation-reduction, ubiquitination, and sumoylation [11–15]. Like other transcription factors, the phosphorylation state of c-Jun primarily determines its transactivational function in an AP-1 complex [15], which may also need to be site-specifically reduced to bind to DNA [12]. Finally, at the genomic level the activity of c-Jun/AP-1 as well as other AP-1 complexes depends on interactions with other transcription factors and transcriptional co-regulators associated with target genes [16,2].

3. AP-1 and changes in the cellular redox environment

AP-1 is exquisitely sensitive to changes in the cellular redox (reduction–oxidation) environment, which is essentially a summation of the thermodynamic redox states of the major electron acceptor-donor couples in the cell (e.g., GSH/GSSG, reduced and oxidized thioredoxin, $NADH/NAD^+$) [17]. Although difficult to measure, this redox environment is normally reducing relative to the outside of the cell (e.g., see [18]). Indeed, most if not all cellular processes depend on a net reducing intracellular environment to function normally. Of relevance here, AP-1 complexes such as those consisting of c-Jun and c-Fos subunits must be reduced for optimal transcriptional activity, and HIF-1 dependent gene expression is enhanced by endogenous reductants such as thioredoxin-1 or Ref-1/APE [12,19–21].

While this review is concerned with the biology of hypoxic/anoxic stress, which may be considered an antioxidant condition, paradoxically there is evidence of a role for oxidative stress (a pro-oxidant condition) in the response of mammalian cells to low oxygen. For example, it has been reported that mitochondrial electron transport is necessary for the stabilization of HIF-1α protein, and thus HIF-1 activity, in hypoxic A549 and HT1080 human carcinoma cell lines [22] (oxygen partial pressure or pO_2 1.5%; relative to air at pO_2