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Hypoxia-Inducible Factor-1: A Critical Player in the Survival Strategy of Stressed Cells

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ABSTRACT

HIF-1 activation has been well known as an adaptive strategy to hypoxia. Recently it became clear that hypoxia was often accompanied by insufficient supply of glucose or amino acids as a common result of poor circulation that frequently occurs in solid tumors and ischemic lesions, creating a mixed nutrient insufficiency. In response to nutrient insufficiency, stressed cells elicit survival strategies including activation of AMPK and HIF-1 to cope with the stress. Particularly, in solid tumors, HIF-1 promotes cell survival and migration, stimulates angiogenesis, and induces resistance to radiation and chemotherapy. Interestingly, radiation and some chemotherapeutics are reported to trigger the activation of AMPK. Here we discuss the recent advances that may potentially link the stress responsive mechanisms including AMPK activation, ATF4 activation and the enhancement of Hsp70/Hsp90 function to HIF-1 activation. Potential implication and application of the stress-facilitated HIF-1 activation in solid tumors and ischemic disorders will be discussed. A better understanding of HIF-1 activation in cells exposed to stresses is expected to facilitate the design of therapeutic approaches that specifically modulate cell survival strategy. J. Cell. Biochem. 117: 267–278, 2016.

KEY WORDS: AMPK; HDAC4; HDAC5; HIF-1; Hsp70; Hsp90; STRESS RESPONSE; HYPOXIA

Hypoxia-inducible factor -1 (HIF-1) was first discovered in the studies of hypoxia-triggered elevation of human erythropoietin (EPO), a glycoprotein hormone made in renal cells and fetal hepatocytes which stimulates bone marrow hematopoietic cell proliferation to produce red blood cells [Semenza and Wang, 1992]. Early purification work using DNA affinity chromatography and subsequent biochemical characterization revealed that HIF-1 is a heterodimer consisting of HIF-1α and HIF-1β [Wang and Semenza, 1995]. HIF-1α protein levels increase dramatically when oxygen concentration decreases [Wang et al., 1995]. As a transcription factor, activated HIF-1 enters the nucleus, recruits coactivator p300/CBP, and reprograms gene expression to alter cellular processes, facilitating cell survival under transient hypoxic condition. Since the identification of HIF-1, more than 1,000 HIF-1 targets have been identified by a variety of approaches [Manalo et al., 2005; Xia et al., 2009; Schodel et al., 2011]. Metabolically, activation of HIF-1 switches the ATP producing mode from aerobic respiration to the oxygen-independent fermentation, a more rapid, but less efficient way of glucose utilization. Consequently, HIF-1 drives the overexpression of glucose transporter 1 (GLUT1), which increases glucose uptake to compensate the low efficiency. Increased lactate dehydrogenase (LDH) accelerates the conversion of pyruvate and NADH to lactate and NAD+, respectively, ensuring an undisrupted glycolytic process and maintaining an intracellular redox balance. HIF-1 also stimulates the expression of carbonic anhydrase 9 (CA-IX), which maintains intracellular pH by exporting protons to the extracellular matrix.

In this review, we will briefly summarize the activation of HIF-1 by hypoxia to set the platform for the subsequent discussion of the control of HIF-1α translation and posttranslational processing as a survival strategy of stressed cells (Fig. 1). Integrating knowledge in literature and recent findings, we propose a crucial role of HIF-1 as a facilitator of adaptation to a variety of cellular stresses such as proliferative biosynthesis, nutrient insufficiency and radiation therapy.

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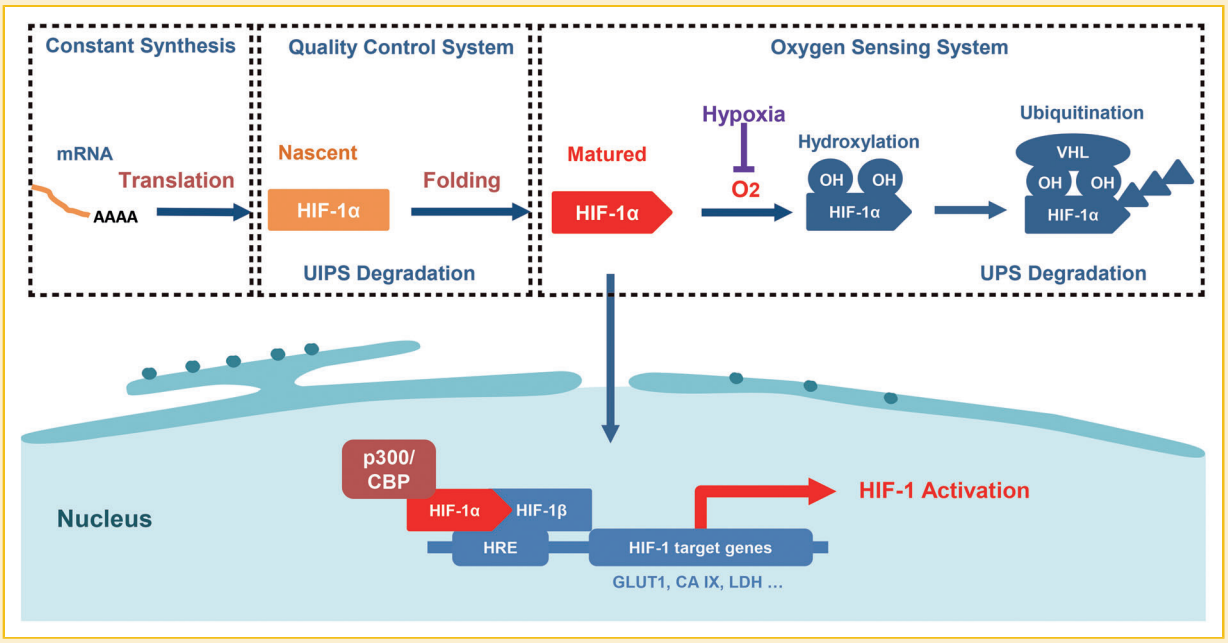

Fig. 1. Summary of the synthesis, posttranslational processing and hypoxia-controlled degradation of HIF-1α. After translation, nascent HIF-1α interacts with the molecule chaperone Hsp70/Hsp90 system for processing and maturation. Proteins that fail the posttranslational folding processes will be degraded by a quality control system using an ubiquitination-independent proteasome degradation pathway (UIP). The protein levels of correctly folded functional HIF-1α will be regulated by the oxygen-dependent hydroxylation-ubiquitination mechanism.

OXYGEN SENSING PATHWAYS ACTIVATE HIF-1 BY HYPOXIC STABILIZATION OF MATURE HIF-1α

As a general final electron acceptor in oxidative phosphorylation and other redox reactions, molecular oxygen is essential for mammalian cell survival, energy homeostasis and other cellular processes. A constant supply of oxygen is indispensable for maintaining normal tissue functions, particularly in cardiac and brain function. Hypoxia, a state in which oxygen supply is insufficient, has been involved in the pathogenesis of multiple diseases with top leading mortality rates, including heart diseases, chronic respiration disease, stroke, anemia and bleeding [Kochanek et al., 2014]. Hypoxia also contributes to tumor progression, metastasis and resistance to radiation and chemotherapy [Semenza, 2003, 2012; Kaelin and Ratcliffe, 2008]. The identification of HIF-1 as a major regulator of adaptation to hypoxia gave us a better understanding of the molecular mechanisms underlying oxygen sensing pathways, oxygen homeostasis, energy homeostasis and disease pathology [Keith and Simon, 2007; Takubo et al., 2010; Zhang et al., 2011; Doedens et al., 2013; Semenza, 2014].

Structurally, HIF-1 is a basic helix-loop-helix (bHLH) transcription factor of the PER-ARNT-SIM (PAS) subfamily. HIF-1α and HIF-1β are structurally similar, each containing a bHLH domain for DNA binding, a PAS domain for hetero-dimerization and transactivation domain for transcriptional activity regulation [Semenza, 2003] (Fig. 2). HIF-1β, also known as aryl hydrocarbon nuclear translocator (ARNT), is a stable protein, serving as a common dimerization partner for multiple transcription factors, while the protein level and functionality of HIF-1α determine the transactivation activity of HIF-1. Like HIF-1β, HIF-1α is also constitutively translated; unlike HIF-1β, HIF-1α protein is subject to degradation through an oxygen-dependent mechanism (Fig. 2). In the presence of adequate molecular oxygen, HIF-1α protein will be recognized by three prolyl hydroxylases (PHDs), which hydroxylate HIF-1α at two prolyl residues (P402 and P564) [Bruick and McKnight, 2001; Epstein et al., 2001]. The hydroxylated HIF-1α is recognized by the von Hippel Lindau protein (VHL), a ubiquitin ligase, leading to HIF-1α polyubiquitination. The ubiquitinated HIF-1α will be finally degraded by the 26S proteasome [Salceda and Caro, 1997; Huang et al., 1998].

The PHDs that determine the stability of mature HIF-1α belong to a dioxygenase family [Schofield and Ratcliffe, 2004]. These enzymes require molecular oxygen and α-ketoglutarate as co-substrates, as well as Fe^{2+} and ascorbate (vitamin C) as co-factors for enzymatic activity (Fig. 2) [Hirsilä et al., 2003]. Mutations of succinate dehydrogenase (SDH) and fumarate hydratase (FH), two enzymes of the tricarboxylic acid cycle, were found to block PHDs activity and increase HIF-1α protein levels by increasing the concentration of succinate and fumarate respectively, which act as PHD inhibitors [Isaacs et al., 2005; Pollard et al., 2005; Selak et al., 2005]. Moreover, reports showed that mutations in the cytosolic isocitrate dehydrogenase (IDH1,2) may result in a decrease of α-ketoglutarate, thus stabilizing HIF-1α protein [Zhao et al., 2009]. More recent reports demonstrate that mutations in IDH1 or IDH2 result in the formation of abnormal metabolite (R)-2-hydroxyl-glutarate, which stimulates PHD activity, thus decreasing HIF-1α protein levels in gliomas [Koivunen et al., 2012]. However, clinical

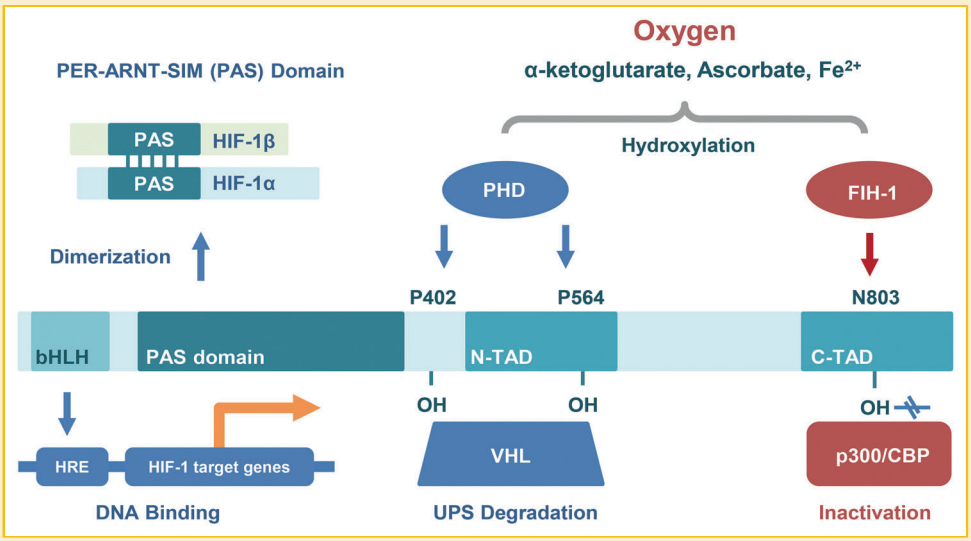

Fig. 2. Schematic structure of HIF-1α and the conventional oxygen-dependent inhibition of HIF-1.

studies by directly imaging HIF-1 target gene expression in tumors indicate that the relationship between IDH mutations and HIF-1 activity in vivo remains unclear[Metellus et al., 2011]. In addition, HIF-1α transcriptional activity is also regulated by an oxygen-dependent hydroxylation event. Factor inhibiting HIF-1 (FIH) [Mahon et al., 2001], another oxygen-dependent hydroxylase, modifies the asparagine residue (N803) in the carboxyl terminal activation domain and disrupts its interaction with p300/CBP [Lando et al., 2002; Sang et al., 2002]. In summary, the oxygen-dependent hydroxylation of HIF-1α forms the biochemical basis for the conventional oxygen sensing pathway (Fig. 1), representing the initiation of a physiological adaptation to hypoxia.

PROLIFERATIVE SIGNALING PATHWAYS ACTIVATE HIF-1 BY ACCELERATED TRANSLATION

Proliferating cells usually demand more molecular oxygen to support active biosynthesis. Growth factors, which activate the major signaling pathways such as mitogen activated protein kinase (MAPK) and insulin-stimulated PI3K pathways for cell proliferation, also increase HIF-1α protein synthesis to promote glucose utilization and ATP production [Semenza, 2003, 2012; Kaelin and Ratcliffe, 2008]. In solid tumors, activation of oncogenes (Ras, PI3K/AKT) and loss of tumor suppressors (PTEN, LKB1 and TSC2/1) may activate HIF-1 by enhancing HIF-1α protein synthesis (Fig. 3). As in the translation of other proteins, mechanistic target of rapamycin (mTOR, also known as mammalian target of rapamycin), as part of mTOR complex 1 (mTORC1), is the key regulator that transmits growth signals to translational machinery, which is often dysregulated in cancers [Benjamin et al., 2011]. As an integrator of growth singaling pathways and nutrient status, mTOR stimulates protein translation by phosphorylating ribosomal protein S6 kinase (S6K), eukaryotic elongation factor 2 kinase (EEF2K) and eukaryotic translation initiation factor 4E (EIF4E)-binding protein 1 (4EBP1), leading to increased protein translation [Wouters and Koritzinsky, 2008]. Particularly insulin/IGF and EGF, the most important cellular signaling pathways that regulate cell proliferation, stimulate mTORC1 [Harris and Lawrence, 2003]. The mechanism by which these signal pathways activate mTORC1 has been highlighted by the discovery that mTOR is suppressed by the tuberous sclerosis complex (TSC) gene products TSC2/1 [Inoki et al., 2005], and TSC2 is

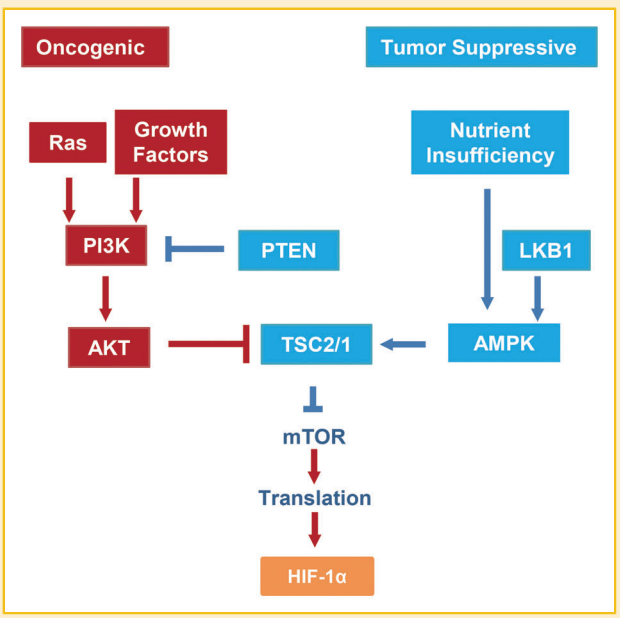

Fig. 3. Signaling pathways that controls the rate of HIF-1α translation. Activation of oncogenes or loss of tumor suppressors promotes HIF-1α translation, which is suppressed by mTOR inhibition.

phosphorylated and inhibited by AKT [Manning et al., 2002; Potter et al., 2002], which is activated by PI3K [Kumar et al., 2005]. Either stimulating any of the Ras, PI3K, AKT and mTOR signaling pathways or inhibiting TSC2 enhances HIF-1α translation [Blancher et al., 2001; Chen et al., 2001; Hudson et al., 2002; Brugarolas et al., 2003, 2004; Majumder et al., 2004; Bernardi et al., 2006]. On the contrary, phosphatase and tensin homolog (PTEN), a suppressor of PI3K [Carracedo and Pandolfi, 2008], was found to be a negative regulator of HIF-1α translation [Zundel et al., 2000].

On the other hand, mTOR signaling is inhibited by activativation of AMPK, which phosphorylates TSC2 [Kimura et al., 2003]. Upstream to the AMPK, the LKB1 tumor suppressor gene encodes a serine/threonine kinase [Hawley et al., 2003], and the LKB1-AMPK pathway inactivates mTOR signaling [Shaw et al., 2004]. Protein levels of HIF-1α and its target GLUT1 are increased in LKB1-deficient and AMPK-deficient fibroblasts, and the epithelia of gastrointestinal hamartomas of Lkb1+/− mice also show increased HIF-1α and GLUT1 compared with the surrounding normal tissue [Shackelford et al., 2009]. It is important to note that as the energy sensor, AMPK is activated by low glucose, low glutamine and hypoxia [Laderoute et al., 2006; Jibb and Richards, 2008; Mungai et al., 2011; Davie et al., 2015]. Therefore, nutrients insufficiency represents another fundamental parameter determining rate of cell growth and proliferation as well as HIF-1α translation [Harris and Lawrence, 2003].

STRESSES FACILITATE HIF-1 ACTIVATION BY ENHANCING POSTTRANSLATIONAL PROCESSING OF HIF-1α

At the cellular level, HIF-1 activation drives the utilization of glucose and rapid production of ATP, a process that is not only critical for proliferating cells, but also facilitates cells to survive stress conditions such as nutrient insufficiency and cell damage caused by a variety of physical, chemical and mechanical factors. How HIF-1 is activated under stress conditions has been revealed by the analysis of a variety of compounds that destabilize HIF-1α and/or inhibit HIF-1 function (Table I). While not fully understood, efforts to dissect the molecular mechanisms underlying the repressive effects of drugs on HIF-1 indicate the involvement of the molecular chaperone heat shock protein 90 kD (Hsp90) [Isaacs et al., 2002] and heat shock protein 70 kD (Hsp70) [Kong et al., 2006; Luo et al., 2010]. They form a quality control (QC) system of HIF-1α and are responsible for the posttranslational processing and stabilization of nascent HIF-1α (Fig. 4). Hsp90 is one of the most abundant cytosolic proteins, counting 1–2% of total amount of proteins inside mammalian cells [Borkovich et al., 1989]. Hsp90 assists varieties of proteins (known as clients), including key regulatory proteins

TABLE I. Summary of Compounds That Repress HIF-1

Mechanism	Drug classification	Dugs	Potential implication in the QC model
Repressing HIF-1α translation	EGFR inhibitor	Erlotinib [Pore et al., 2006]	Translation driven by oncogenic and proliferative signals
		Galbanic acid [Eskandani et al., 2015]	
		Gefitinib [Pore et al., 2006]	
	Her2/ErbB2 inhibitor	Herceptin [Laughner et al., 2001]	
	PI3K inhibitor	Apigenin [Fang et al., 2005]	
		NVP-BEZ235 [Cho et al., 2010]	
	mTOR inhibitor	CCI-779 [Wan et al., 2006]	
		Everolimus [Majumder et al., 2004]	
		Rapamycin [Laughner et al., 2001]	
	?	PX-478[Welsh et al., 2004; Koh et al., 2008]	Stress-related select initiation?
Reduce HIF-1α stability	Hsp90 inhibitors	17-AAG [Isaacs et al., 2002; Kong et al., 2006; Liu et al., 2007]	Hsp70/Hsp90 function is needed for posttranslational stabilization of HIF-1α
		17-DMAG [Lang et al., 2007]	
		Geldanamycin [Mabjeesh et al., 2002; Zagzag et al., 2003]	
		KF58333 [Kurebayashi et al., 2001]	
	HDAC inhibitors	FK228 [Lee et al., 2003]	
		LAQ824 [Qian et al., 2006]	
		LMK235 [Chen et al., 2015]	
		SAHA [Kong et al., 2006]	
		TSA [Kong et al., 2006]	
	Microtubule-disrupting drugs	2ME2 [Mabjeesh et al., 2003; Escuin et al., 2005]	Microtubule dynamics is involved in the posttranslational QC processing?
		Colchicine [Escuin et al., 2005]	
		Discodermolide [Escuin et al., 2005] Epothilone B [Escuin et al., 2005]	
		Taxotere [Escuin et al., 2005]	
		Vincristine [Escuin et al., 2005]	
	Electron transfer chain disrupting	BAY 87-2243 [Berhoerster et al., 2011]	ROS inhibits PHD activity, stabilizing mature HIF-1α
Decrease HIF-1 transactivation	HDAC inhibitors	SAHA [Fath et al., 2006]	Cytosolic deacetylases facilitate Hsp70/Hsp90 function, promoting formation of mature HIF-1α
		TSA [Fath et al., 2006]	
	Proteasome inhibitors	Velcade [Kaluz et al., 2006]	Accumulation of misfold HIF-1α inhibits normal HIF-1α activity
	p300/CBP inhibitors	Chetomin [Staab et al., 2007]	HIF-1/coactivator interaction is crucial

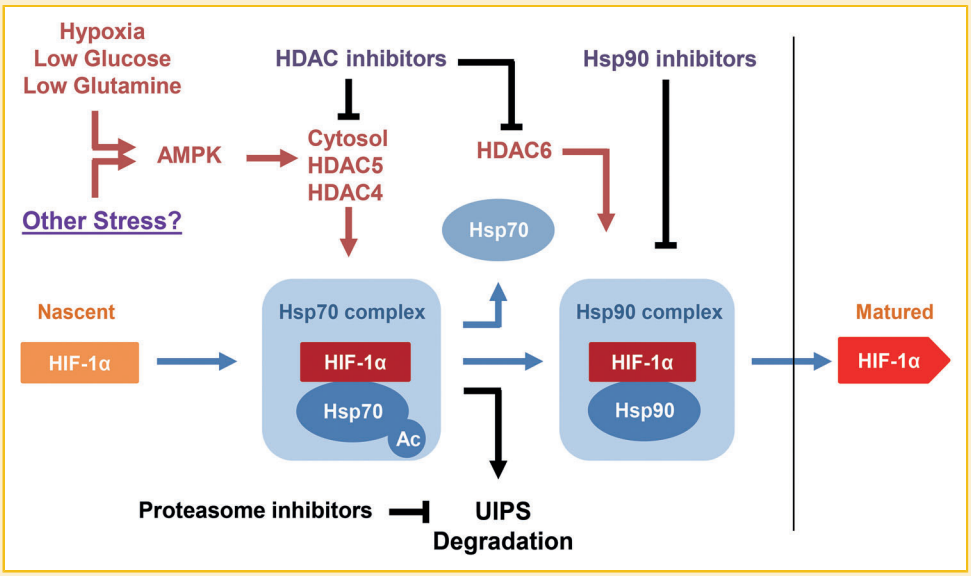

Fig. 4. Proposed model of AMPK–HDAC5 enhanced, Hsp70/Hsp90 executed posttranslational processing of HIF-1α. AMPK serves as a sensor of multiple types of stresses, which promotes the cytosolic localization of HDAC4 and HDAC5, depending on which is expressed in a specific type of cells. HDAC4 and HDAC5 catalyzed deacetylation of Hsp70 enhances the efficiency of posttranslational processing of HIF-1α, minimizing pre-mature degradation.

such as steroid hormone receptors, transcription factors, and kinases, to fold properly into their active conformation by consuming energy from ATP hydrolysis, which buffers proteostasis against environmental stress [Whitesell and Lindquist, 2005]. Usually Hsp90 does not recognize client proteins in the nascent state; it interacts with other co-chaperones, which guide the client recognition and delivery of client proteins. Hsp70 is a well-known co-chaperone that works with Hsp90 to form the chaperone cycle [Pratt and Toft, 2003; Wegele et al., 2004]. The monomeric Hsp70 recognizes short hydrophobic motifs in client proteins, which are commonly exposed in nascent polypeptide chains. The newly synthesized client proteins then associate with Hsp70 to form an early complex, leading to the delivery of client proteins to Hsp90 to form the mature complex [Pratt and Toft, 2003; Wegele et al., 2004; Taipale et al., 2010]. The Hsp90 oligomeric double ring structure encloses the entire nascent client protein and ensures the correct folding [Pratt and Toft, 2003; Wegele et al., 2004; Taipale et al., 2010]. The dynamic interaction between HIF-1α and Hsp90 was found to facilitate the stabilization of HIF-1α [Katschinski et al., 2004], indicating HIF-1α is one of the client proteins of the Hsp70/Hsp90 system. This was further supported by the evidence that Hsp90 inhibitors such as 17-allylaminogeldanamycin (17-AAG) induce proteasomal degradation of HIF-1α in the absence of oxygen and in a VHL-independent manner [Isaacs et al., 2002; Mabjeesh et al., 2002; Zagzag et al., 2003; Kong et al., 2006].

Another group of compounds, the histone deacetylase (HDAC) inhibitors, including trichostatin A (TSA), SAHA (vorinostat), sodium butyrate and LAQ824, were also reported to induce proteasomal degradation of HIF-1α in a VHL-independent manner similar to Hsp90 inhibitors [Fath et al., 2006; Qian et al., 2006] (Table I). HDACIs that cause a suppressive effect on HIF-1 usually non-selectively inhibit all Class I and Class II HDACs, including HDAC1-9 [Yang and Seto, 2007; Chen and Sang, 2011]. Recently, a member of Class IIa HDACs, HDAC5, has been identified as the specific HDAC member that facilitates the stabilization and nuclear accumulation of HIF-1α protein [Chen et al., 2015]. HDAC5 dynamically shuttles between the nucleus and the cytosol and has relatively weak enzymatic activity on the histones [McKinsey et al., 2001; Fischle et al., 2002]. New findings reveal that Hsp70 is a cytosolic substrate of HDAC5 [Chen et al., 2015], and deacetylation of the Hsp70 by HDAC5 promotes HIF-1α interaction with Hsp90, thus facilitating the rapid nuclear accumulation of HIF-1α [Chen et al., 2015]. Retrospectively, both HDAC4 and HDAC6 were proposed to destabilize HIF-1α and repress HIF-1 function [Kong et al., 2006; Qian et al., 2006; Geng et al., 2011]. HDAC4 is highly homologous to HDAC5 [McKinsey et al., 2001]. We found that the knockdown of either HDAC4 or HDAC5 reduces HIF-1α protein levels and suppresses HIF-1 function (Fig. 5A, B). Moreover, expression of an HDAC4 mutant S265/266A, which is exclusively localized in the cytosol, is sufficient to stabilize HIF-1α (Fig. 5C). This indicates that cells expressing HDAC4 might facilitate HIF-1α stabilization through a similar mechanism. However, hypoxia only increases the protein level of HDAC5 [Chen et al., 2015], not HDAC4 (Fig. 5A). Their tissue-specific expression levels in different tissues also vary dramatically; HDAC4 is highly expressed in myeloid, whereas HDAC5 is highly expressed in heart, neuron, muscle, lung, and placenta, which represent the tissues most sensitive to physiological fluctuation of oxygen levels and metabolic stress [Chang et al., 2004]. Therefore, both HDAC4 and HDAC5 may be involved in the regulation of posttranslational processing of HIF-1α by regulating the Hsp70/Hsp90 system, but it is likely that HDAC5 plays a more important role in facilitating HIF-1α folding in response to hypoxic stress. HDAC6 inhibtion was proposed to increase the acetylation level of Hsp90, thus impairing Hsp90

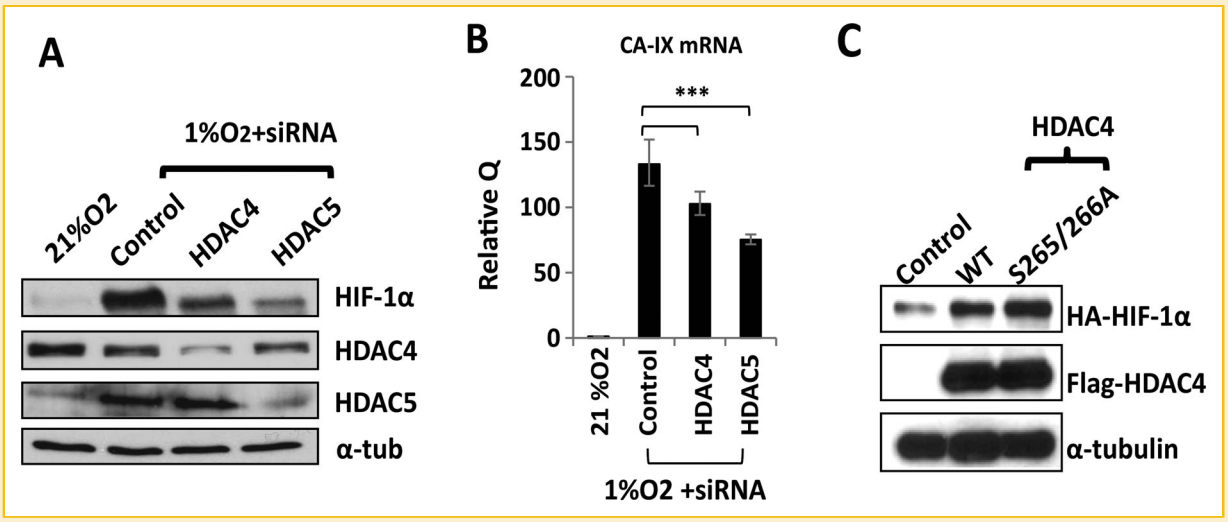

Fig. 5. Cytosolic HDAC4 and HDAC5 contribute to hypoxic stabilization of HIF-1α and functional activation of HIF-1. Knockdown of either HDAC4 or HDAC5 attenuates hypoxia triggered HIF-1α accumulation. Hep3B cells were transfected with indicated siRNA . After 42 h, cells were exposed to hypoxia (1% O2) for 6 h. (A) Western blotting showing the protein levels of HIF-1α, HDAC4 and HDAC5. The protein levels of α-tubulin were determined as a loading control. Note that hypoxia enhanced HDAC5 but not HDAC4. (B) Total RNA was collected, and quantitative real time PCR was performed following reverse transcription to determine the mRNA levels of CA-IX as an indicator of HIF-1 function. (C) Cytosolic HDAC4 mutant (S265/266A) is sufficient to stabilize HIF-1α. Hep3B cells were cotransfected with 2 μg of HA-HIF-1α together with 2 μg of either control vector, Flag-HDAC4(WT), or cytosolic mutant HDAC4-S265/266A. HIF-1α and Flag-tagged HDAC4 were detected by Western blotting.

function [Kovacs et al., 2005; Fath et al., 2006]. However, romidepsin (FK228,depsipeptide), an HDAC inhibitor that has very weak repressive effect on HDAC6, effectively destabilizes HIF-1α, making it possible that it also destabilizes HIF-1α through inhibiting HDAC5 or HDAC4, leading to Hsp70 hyperacetylation [Wang et al., 2007; To et al., 2011].

AMPK, the master regulator of cellular energy homeostasis, is activated by nutrient insufficiency including low glucose, low glutamine and hypoxia [Laderoute et al., 2006; Jibb and Richards, 2008; Mungai et al., 2011; Davie et al., 2015]. AMPK is a highly conserved serine or threonine heterotrimeric kinase consisting of α, β, and γ subunits [Winder and Hardie, 1999]. Nutrient insufficiency causes an increase of intracellular AMP; the binding of AMP to AMPK-γ subunit exposes the catalytic domain on AMPK-α, thus activating AMPK [Adams et al., 2004]. The cannonical function of AMPK activation is to maintain the intracellular ATP homeostasis by stimulating ATP producing catabolic pathways but inhibiting ATP consuming biosynthetic pathways. Interestingly, AMPK is also activated when cells are exposed to cell damage factors such as increased work load, heat, radiation and pathogenic microbials. This indicates that AMPK activation may have a universal and critical role in cells′ survival strategy upon being stressed.

As an ATP conserving strategy, AMPK activation inhibits general protein translation by suppressing mTOR signaling pathways, including HIF-1α [Shackelford and Shaw, 2009]. However, HIF-1 is the major driver of glucose utilization, which provides rapid ATP generation for cells to survive and sustain certain key functions under stressful conditions [Chen et al., 2015; Davie et al., 2015]. It had been unclear until recently how HIF-1 function is sustained under the stress conditions. In fact, activated AMPK phosphorylates and promotes the nuclear export of HDAC5 and perhaps HDAC4 as well [McKinsey et al., 2001]. In the cytosol, HDAC4 and HDAC5 stabilize HIF-1α by deacetylating Hsp70, promoting the transfer of HIF-1α from Hsp70 to Hsp90 for the completion of the maturation process. Therefore, while the AMPK may reduce the translation of HIF-1α, it compensates by enhacing the efficiency of posttranslational folding of HIF-1α, thus ensuring HIF-1 activation under stressful conditions [Chen et al., 2015].

It is important to point out that for normal cells under physiological conditions, a basal level of Hsp70/Hsp90 activity may be sufficient to process newly synthesized proteins. However, under conditions that new proteins are translated in large quantities (proliferative biosynthesis, overexpressing recombinant proteins), an enhanced capacity of Hsp70/Hsp90 may become crucial for the processing of newly synthesized critical proteins such as HIF-1α. Hence, suppression of the enhancement of Hsp70/Hsp90 function may disrupt the formation of correctly folded, functional active HIF-1α, leading to disposal of misfolded HIF-1α by a quality control system. This disposal appears to involve a hydroxylation-independent and ubiquitination-independent proteasome degradation (UIP) [Kong et al., 2006; Liang et al., 2006; Lao et al., 2012], hence being mechanistically distinguishable from the oxygen-triggered degradation (Fig. 1). Blocking this process with proteasome inhibitors or overexpressing HIF-1α increases the total levels of HIF-1α, but may not significantly activate HIF-1 function [Kaluz et al., 2006; Chen et al., 2015], demonstrating the importance of the posttranslational processing mediated by Hsp70/Hsp90. Therefore, the stress-activated AMPK-HDAC5-Hsp70/Hsp90-HIF-1 pathway may function as a critical but universal survival strategy for cells to cope with a variety of stresses, including but not limited to hypoxia.

In addition to the enhanced Hsp70/Hsp90 function, selective translation of ATF4, a transcription factor often activated during

endoplasmic reticulum stress and unfolded protein response, also occurs as a result of cellular stress and mTORC1 inhibition [Rutkowski and Kaufman, 2003]. It has been shown that the activation of ATF4 is critical for cell adaptation to nutrient depletion [Ye et al., 2010]. Well known target genes activated by ATF4 are DDIT3 (CHOP) and stanniocalcin 2 (STC2). However, it remains unclear if there is a link among the ATF4-pathway, AMPK activation and HIF-1 activation. Finally, it is reported that a stress-activated protein kinase, JNK1, is required for HIF-1α stabilization in hypoxic tissues [Antoniou et al., 2009], providing another link between cell stress and HIF-1 activation.

RELEVANCE OF HIF-1 ACTIVATION IN TUMORS

In solid tumors, oncogenic pathways drive rapid cell proliferation, which demands for more nutrients, particularly molecular oxygen, glucose and amino acids. However, the abnomral vascular structure limits the nutrient delivery, resulting in nutrient insufficiency [Chen and Sang, 2011]. While hypoxia is the major cause of HIF-1α stabilization, recently it became clear that the lack of glucose or amino acids may also contribute to HIF-1 activation. It has been well known that HIF-1 activation plays an important role for hypoxic cell survival and migration [Vaupel, 2009]. HIF-1α overexpression and HIF-1 activation have been observed in varieties of solid tumors [Zhong et al., 2000; Semenza, 2004, 2006; Vaupel et al., 2007]. Of the more than 1,000 HIF-1 target genes that have been identified [Manalo et al., 2005; Xia et al., 2009; Schodel et al., 2011], many are implicated in adaptive strategies including metabolic reprogramming, survival, angiogenesis, and migration; enhanced surivival and migration directly contribute to tumor metastasis and resistance to radiation and chemotherapy [Hockel and Vaupel, 2001; Semenza, 2003, 2004, 2010; Lee et al., 2009; Harada et al., 2012]. Accordingly, it has been proposed that repressing HIF-1 function may improve the therapeutical outcome of tumors [Semenza, 2003, 2009, 2010].

Oncogenic activation of HIF-1, triggered by both hypoxia and hypoxia independent mechanisms, plays a critical role in metabolic transformation and tumor progression. The aerobic glycolysis caused by oncogenic activation of HIF-1 is best known as the Warburg effect. In addition to metabolic adaptation as discussed in introduction, angiogenesis and lymphogenesis are promoted by HIF-1. Deletion of HIF-1α dramatically inhibits solid tumor development *in vivo*, and reduces expression of pro-angiogenic factors, such as VEGF, which promotes the formation of capillaries, and fibroblast growth factor 1 (FGF-1), which primarily stimulates the formation of arterial vessels [Ryan et al., 1998, 2000; Hirota and Semenza, 2006]. HIF-1 activation also promotes cancer invasion and metastasis, a major obstacle to successful cancer therapy [Fidler, 2003; Huber et al., 2005; Polyak and Weinberg, 2009; Singh and Settleman, 2010]. HIF-1α overexpression is associated with more aggressive and invasive behaviors of human cancers [Zhong et al., 1999; Bos et al., 2001].

HIF-1 activation results in radiation resistance in solid tumors [Hockel and Vaupel, 2001]. Radiation reacts with intracellular molecules and molecular oxygen to cause DNA damage by forming oxygen free radicals [Hall and Giaccia, 2006]. In mouse model, HIF-1α null tumor xenografts show increased radiation sensitivity [Aebersold et al., 2001]. Clinical data also revealed that HIF-1α overexpression increased risk of failure to achieve complete remission after radiation therapy [Aebersold et al., 2001]. One study reports that cancer cells require HIF-1 activation for metastasis after surviving radiation [Harada et al., 2012].

While radiation resistance may involve mutliple pathways including the established ATR/ATM-DNA repair response [Choudhury et al., 2006], radiation also increases HIF-1 activity and promotes endothelial cell survival [Moeller et al., 2004], which may form another adaptive strategy for tumor cells to survive the radiation. How radiation activates HIF-1 remains unclear; it has been reported that radiation activates AMPK and the ATF4 pathway [Fels and Koumenis, 2006; Lee et al., 2008; Cao and Wan, 2009; Sanli et al., 2010, 2012; Zhang et al., 2010; Zannella et al., 2011; Kim et al., 2014], and overexpression of STC2, an ATF4 target, positively correlates to radiation resistance [Smith et al., 2006; Lin et al., 2014]. It is interesting to note that an intriguing similarity exists between the radiation-triggered and the nutrient insufficiency-triggered cellular responses: both induce cell cycle inhibition, activation of AMPK, activation of ATF4 pathways [Meng et al., 2010; Qie et al., 2012; Davie et al., 2015], and most importnatly, activation of HIF-1. However, a mechanistic link among those responses remains unclear. Further investigation is needed to address if this similarity explains the radiation resistance of tumor cells exposed to nutrient insufficiency.

Considering the role of HIF-1 in cells′ survival strategy, researchers are actively exploring HIF-1 as a target for cancer therapy either alone or as a sensitizer for chemoradiation [Welsh et al., 2004; Kong et al., 2005; Tan et al., 2005]. Current strategies include suppressing HIF-1α translation, increasing HIF-1α degradation and inhibiting HIF-1 transcription activity [Semenza, 2007]. For example, mTOR inhibitors have been tested to inhibit HIF-1α translation [Majumder et al., 2004; Thomas et al., 2006]. Other compounds including HDACIs [Marks et al., 2001; Johnstone and Licht, 2003; Drummond et al., 2005], Hsp90 inhibitors [Miyata, 2005; Neckers and Neckers, 2005], proteasome inhibitors [Sunwoo et al., 2001; Bazzaro et al., 2006; Joazeiro et al., 2006; Ishii et al., 2007] and microtubule inhibitors [Mabjeesh et al., 2003; Escuin et al., 2005; Newcomb et al., 2006] were found to destabilize HIF-1α or inhibit HIF-1 function (Table I). Echinomycin, an antibiotic peptide, supresses HIF-1 function by reducing HIF-1α binding to DNA [Kong et al., 2005]; PX478 and 103D5R showed the ability to inhibit HIF-1 function through unkown mechanisms [Welsh et al., 2004; Kong et al., 2005; Tan et al., 2005]. While these approaches have demonstrated to be effective, severe adverse effects on normal tissues limit their clinical application. Particularly, several compounds directly targeting the Hsp70/Hsp90 system or HIF-1 have proven effective for cancers. However, since a basal level of Hsp70/Hsp90 activity may be required for normal cells under physiological conditions to process newly synthesized proteins, it would not be surprising to find that directly and completely disrupting the Hsp70/Hsp90 has various side effects on normal tissues. Since tumor cells frequently experience nutrient insufficiency and therapy-elicited stresses, refolding or disposal of stress-triggered misfolded or damaged proteins may effectively overwhelm the basal level of Hsp70/Hsp90 function. Accordingly, it is expected that targeting the AMPK-HDAC5 or AMPK-HDAC4-enhanced Hsp70/Hsp90 activity

may specifically disrupt the survival strategy of tumor cells exposed to nutrient insufficiency, radiation and chemotherapy.

RELEVANCE OF HIF-1 ACTIVATION IN ISCHEMIC DISORDERS

Nutrient insufficiency, particularly hypoxia, is the initiator and major contributing factor of the pathology of ischemic disorders. As opposed to solid tumors, ischemic lesions will greatly benefit from a successful survival strategy to cope with the nutrient insufficiency. Animal studies showed that HIF-1 function plays an important role in ischemia-induced vascular remodeling [Rivard et al., 1999; Patel et al., 2005; Bosch-Marce et al., 2007; Rey et al., 2009, 2011]. HIF-1α -/- mice were found to be lethal, but HIF-1α +/− mice showed reduced blood flow recovery and increased tissue damage after femoral artery ligation compared with wildtype littermates [Bosch-Marce et al., 2007]. Intramuscularly expressing a constitutively active form of HIF-1α [Kelly et al., 2003] not only protects mice from age-dependent impairment of ischemia-induced vascular remodeling [Bosch-Marce et al., 2007], but also improves the recovery of blood flow in a rabbit model [Patel et al., 2005]. In addition, HIF-1 activation also mediates the protection induced by ischemic preconditioning [Murry et al., 1986]. After being exposed to short periods of ischemia and reperfusion, the heart suffered less injury from a subsequent prolonged ischemic insult, shown by a smaller infarct size. Loss of one allele of HIF-1α abolishes this protection [Cai et al., 2008], demonstrating the importance of HIF-1 activation in this protection. HIF-1 may also protect the heart from pressure overload heart failure [Sano et al., 2007]. Hypertension could form a compensatory left ventricular hypertrophy to maintain the ejection fraction at an early stage, but it will progress to an uncompensated state with a decreased ejection fraction and eventually lead to heart failure [Levy et al., 1990]. Tissue-specific knockout of HIF-1α in cardiacmyocytes rapidly induced cardiac hypertrophy [Sano et al., 2007]. Interestingly, HDAC5 knockout impairs heart adaptation to increased work load, phenocoping the heart-specific HIF-1α knockout [Chang et al., 2004]. Along with the fact that hypoxia upregulates HDAC5, these findings indicate that the AMPK-HDAC5 pathway may be also involved in HIF-1α stabilization and HIF-1 activation in ischemic lesions of normal tissues.

PERSPECTIVES

In summary, nutrient insufficiency frequently occurs in solid tumors and ischemic lesions. Activation of the AMPK pathway is a common response to nutrient insufficiency, which triggers multiple responses to maintain the ATP homeostasis. One of the AMPK-triggered cascades of events is the phosphorylation and cytosolic shuttling of HDAC4 and HDAC5, which enhances Hsp70/Hsp90 function. This facilitates the posttranslational processing and nuclear localization of HIF-1α, ensuring a rapid activation of HIF-1 as a survival strategy. The role of this AMPK-facilitated HIF-1 activation in tumor metastasis and resistance to radiation remains unclear. However, the identification of cytosolic HDAC4 and HDAC5 as key players in cells′ survival strategy provides new drug target to improve the specificity of cancer therapy; targeting the conditionally required cytosolic HDAC4 and HDAC5 is expected to have less adverse effects on normal tissues than non-selective HDACIs, AMPK inhibitors and Hsp90 inhibitors. The involvement of AMPK-HDAC5 or AMPK-HDAC4 pathways in HIF-1 activation under other conditions, such as ischemic disorders, immune response, wound healing and neurondegenerative disorders, remains to be explored.

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