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A compendium of proteins that interact with HIF-1α

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Abstract

Hypoxia-inducible factor 1 (HIF-1) is the founding member of a family of transcription factors that function as master regulators of oxygen homeostasis. HIF-1 is composed of an O_2-regulated HIF-1α subunit and a constitutively expressed HIF-1β subunit. This review provides a compendium of proteins that interact with the HIF-1α subunit, many of which regulate HIF-1 activity in either an O_2-dependent or O_2-independent manner.

Keywords

Oxygen biology; Transcriptional regulation

Cells of metazoan species require a constant supply of O_2 as a substrate for metabolic reactions, principally mitochondrial oxidative phosphorylation. Hypoxia-inducible factors (HIFs) regulate the transcription of hundreds of genes in order to maintain a balance between O_2 supply and demand in every cell. The founding member of the HIF family, HIF-1, is composed of HIF-1α and HIF-1β subunits, each of which contains basic helix-loop-helix (bHLH) and Per-ARNT-Sim homology (PAS) domains that together mediate dimerization and DNA binding [1,2]. HIF-1β, which is also known as the aryl hydrocarbon nuclear translocator (ARNT) protein, heterodimerizes with several different bHLH-PAS proteins, whereas HIF-1α is the HIF-1-specific and O_2-regulated subunit. HIF-1 activity is regulated by the interaction of HIF-1α with many other proteins [3–156], which are listed in Table 1. This list, which continues to grow rapidly, is intended to be illustrative rather than comprehensive. For many of these proteins, the site of interaction has been localized to specific amino acid residues or to a particular domain within HIF-1α, such as the bHLH-PAS domain (amino acid residues 1–390 approximately), PAS-B subdomain (residues 200–330 approximately), O_2-dependent degradation domain (residues 390–575 approximately), or C-terminal transactivation domain (residues 786–826).

The majority of HIF-1α-interacting proteins that have been identified thus far regulate the stability of HIF-1α in either an O_2-dependent or O_2-independent manner. O_2-dependent degradation is triggered by the prolyl hydroxylase domain proteins PHD1-3 [88,102]. Hydroxylation of HIF-1α at proline residue 402 or 564 facilitates binding of the von Hippel-Lindau protein (VHL), which recruits an E3 ubiquitin-protein ligase complex that catalyzes the covalent linkage of ubiquitin to lysine residues in HIF-1α, which serves as a signal for proteasomal degradation (151).

HIF-1α-interacting proteins that facilitate O_2-dependent degradation may do so by stabilizing interactions between components of the hydroxylation complex or by stimulating

ubiquitination of hydroxylated HIF-1α (Table 2). Many HIF-1α-interacting proteins that inhibit O_2-dependent degradation do so by blocking the action of the VHL-E3 ligase complex or by catalyzing deubiquitination (Table 3). Other HIF-1α-interacting proteins facilitate O_2-independent degradation (Table 4) by stimulating ubiquitination, SUMOylation, proteasomal degradation, or chaperone-mediated autophagy (lysosomal degradation). HIF-1α-interacting proteins that inhibit O_2-independent degradation do so by altering ubiquitination or by catalyzing deSUMOylation (Table 5). Another large group of HIF-1α-interacting proteins serve as co-activators or co-repressors to regulate transactivation mediated by HIF-1α (Table 6).

Many of the proteins that interact with HIF-1α regulate HIF-1 activity by either promoting or inhibiting the interaction of HIF-1α with other proteins, as described above. In contrast, other HIF-1α-interacting proteins have a catalytic activity, such as acetylation, deacetylation, demethylation, phosphorylation, or ubiquitination, leading to post-translational modification of HIF-1α that alters its stability, subcellular localization, or transactivation function (Table 7).

In the era of Big Data Science, it is often frustrating that large projects to characterize gene expression, transcription factor binding, or protein-protein interactions often do not include HIF-1 because the experiments were performed using tissue culture cells cultured at 20% O_2. The data presented here represent a compilation of studies using many different cell types and the observed protein interactions will of course only be observed in those cell types in which both proteins are expressed. In addition, the interaction of HIF-1α with its interacting proteins may be regulated by post-translational modification of one or both proteins, which may occur in a cell-type or stimulus-specific manner. Finally, it should be noted that many HIF-1α-interacting proteins are the products of HIF-1 target genes and participate in feed-forward or feedback loops that serve to amplify or extinguish cellular responses to hypoxia [163].

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Table 1

Proteins that interact with hypoxia-inducible factor 1α (HIF-1α).

Protein	Also known as	HIF-1α Residues[a]	Other Partner (s):	Reference(s)
ARD1	NAA10	401–603		[3,4]
ARNT	HIF–1β	1–390		[1,2]
ARNTL	BMAL1, MOP3	ND		[5,6]
ARNTL2	BMAL2, MOP9	ND		[7]
ARRB1	Arrestin-β1	ND	p300	[8,9]
ATP6V0C		1–16		[10]
BCL2		ND	HSP90	[11]
BHLHE41	DEC2, SHARP1	ND	20*S* proteasome	[12]
BRG1	SMARCA4	ND		[13]
CBP	CREBBP	531–584, 786–826		[14–17]
CBX4	Chromobox 4	299–604	PRC1	[18]
C/EBPα	CEBPA	1–302		[19,20]
CDC6		1–329	MCMs	[21]
CDK1		ND		[22,23]
CDK2		ND		[23]
CDK5		ND		[24,25]
CDK8		ND	Mediator	[26]
CJUN (non-phospho)		345–787		[27,28]
CK1δ		PAS-B[b]		[29]
COMMD1		1–300	HSP70	[30,31]
CRM1		616–658		[32]
CTNNB1	β-catenin	1–344		[33]
DROSHA		ND		[34]
E2F7		1–80		[35]
EAF2		(HIF–1α only)[c]	VHL	[36]
ERα	ESR1	ND		[37]
ERK1/2	MAPK3/1	616–658		[32]
ERRα,β,γ	ESRRA/B/G	HIF-α: HIF–1β	SRC–1/2; PGC–1α/β	[38,39]
ETV4		786–826		[40]
FBP1		604–786		[41]
FHL2		429–608		[42]
FIH–1		757–826	VHL	[43]
FLNA		(HIF–1α only)		[44]
FOXA2		1–390	p300	[45]
FOXP3		ND	VHL	[46]
GR	NR3C1	85–153, 238–346		[47]
GPD1L		ND		[48]
GSK3β	GSK3B	ND		[49]
HAF	SART1	298–400		[50,51]

Protein	Also known as	HIF-1α Residues[a]	Other Partner (s):	Reference(s)
HBV X		1–400		[52]
HDAC1		ODD		[53]
HDAC3		ODD		[53]
HDAC4		ND		[54,55]
HDAC6		ND		[54]
HDAC7		601–785		[56]
HDM2	MDM2	bHLH; 776–826	p53	[57]
HEXIM1		ND		[58]
HHV–8 vIRF		bHLH		[59]
HNF4		106–526		[60]
HPV E7		ND	excludes HDACs	[61]
HSPA8	HSC70	1–329; ^{529}NEFKL	CHIP, LAMP2A	[62,63]
HSP70		331–427	CHIP	[64]
HSP90		81–200		[65]
Importin 7		bHLH-PAS-A		[66]
ING1b	ING	ND		[67]
IRF1		ND		[68]
JAB1	COPS5, CSN5	401–603		[69]
JMJD2C	KDM4C	575–786		[70]
KAT5	TIP60	ND		[71]
KDM1A	LSD1	ND		[72,73]
KSHV LANA		300–530		[74]
KSHV vIRF		ND		[75]
LAMP2A		ND	HSC70	[62]
MAX		ND		[76]
MCM2		ND		[77]
MCM3		531–826		[77]
MCM5		ND		[77]
MCM7		201–329	VHL, Elongin C	[77]
MGCRACGAP		ND		[78]
MTA1		401–603; 576–785; 786–826	HDAC1	[79]
MUC1		ND	p300	[80]
MYC		1–329		[81]
NBS1		1–400		[82]
NECDIN		ODD		[83]
NEMO		ND	IKKβ	[84]
NOTCH		ND		[85]
NOTCH3		ND		[86]
NQO1		331–575		[87]
OS-9		692–826	PHD2, PHD3	[88]
OTUD7B		ND		[89]
P14^{ARF}		1–199, 463–452		[90]

Protein	Also known as	HIF-1α Residues[a]	Other Partner (s):	Reference(s)
P16		ND		[91]
P53	TP53	1–330		[92–94]
P300		786–826		[95,96]
PARP1		ND (HIF-–1α and HIF-2α)		[97,98]
PCAF		ND		[99]
PER1		ND		[100]
PER2		ND		[101]
PHD1		ND		[88,102]
PHD2		531–610	OS-9	[88,102]
PHD3		531–826	OS-9	[88,102]
PIASY		211–330, 331–698 (phosphorylated HIF–1α)		[104]
PIN1				[105]
PKM2		81–200; 201–329; 331–427;575–786	PHD3	[106]
PLD1		1–401	PHD2	[107]
PLK3		ND		[108]
PONTIN		ND	p300	[109]
PRDX1		ND		[110]
PRDX2		575–786		[110]
PRDX4		531–826		[110]
PRDX6		ND		[110]
PRKACA		1–200; 531–826	PRKAR1A	[111]
PS1-NTF		1–364	PS1-CTF/Aph1a, Nct, Pen2	[112]
PSMA7		726–785		[113]
RACK1	GNB2L1	81–200	Elongin C, RHBDF1	[114]
RAPTOR		ND		[115]
RB		530–694		[116]
REF-1		531–584, 776–826		[14]
REPTIN		ND	HDAC1	[117]
RHOBTB3		ND	PHD2, VHL, LIMD1	[118]
RND3	RHOE	ND		[119]
RON		ND		[120]
RSUME		ND	UBC9, VHL	[121,122]
RUNX1	AML1	ND		[123]
RUNX2		ODD		[124]
RUNX3		603–826	PHD2	[125]
SENP1		ODD		[126]
SEPT9_V1	SEPT9	HLH (HIF-1α only)	comp RACK1	[127,128]
SET7		1–80, 201–330, 400–575, 576–785		[71,129]
SIRT1		600–826		[99,130]
SIRT2		ND		[131]
SIRT6		ND		[132]
SIRT7		ND		[133]

Protein	Also known as	HIF-1α Residues[a]	Other Partner (s):	Reference(s)
SMAD3		ND		[134]
SP1		PAS-B		[81,135]
SPRY2		ND	VHL	[136]
SRC-1		776–826		[14]
SSAT1		201–329	RACK1	[137]
SSAT2		81–200	VHL, Elongin C	[138]
STAT3		(HIF-1α only)	CBP, P300	[139]
STUB1	CHIP	201–329	HSP70	[64]
SUMO-1		ND		[140]
TAp63		ND		[141]
TAp73		1–330	MDM2	[142]
TAZ		ND		[143]
TIF2		ND		[14]
TRAF6		ND		[144]
TSGA10		1–401(mHIF-1α I.2);PAS-B;TAD-C		[145,146]
UCHL1		ND		[147]
USP7	HAUSP	ND		[148]
USP8		ND		[149]
USP19		bHLH-PAS	SIAH1, SIAH2	[150]
VDU2	USP20	ND		[151]
VHL		402+ND; 549–582		[152]
WWOX		ND		[153]
XBP1s		(HIF-1α only)		[154]
YAP		ND		[155]
YY1		ND		[156]

[a] ND, not determined.

[b] In some papers, interacting proteins were shown to bind to truncated recombinant proteins containing only a certain domain or subdomain within HIF-1α (e.g. bHLH-PAS, ODD, or PAS-B) but the specific amino acid residues were not stated.

[c] HIF-2α was tested and did not bind to the HIF-1α-interacting protein.

Table 2

Interacting proteins that stimulate O_2- and PHD/VHL-dependent degradation of HIF-1α.

Protein	Mechanism of action	Reference
HEXIM1	Increased hydroxylation	[58]
MCM7	Increased ubiquitination	[77]
OS9	Increased hydroxylation	[88]
PLD1	Increased hydroxylation	[107]
RHOBTB3	Increased hydroxylation	[118]
RUNX3	Increased hydroxylation	[125]
SIRT2	Increased hydroxylation	[131]
SPRY2	Increased ubiquitination	[136]
SSAT2	Increased ubiquitination	[138]
WWOX	Increased hydroxylation	[153]

Table 3

Interacting proteins that inhibit O_2-dependent degradation of HIF-1α.

Protein	Mechanism of action	Reference
ATP6V0C	Competes with VHL for binding	[10]
NQO1	Competes with PHDs for binding	[87]
OTUD7B	Mediates deubiquitination of HIF-1α	[89]
RSUME	Inhibits VHL-E3 ligase complex	[122]
RUNX2	Competes with VHL for binding	[124]
SENP1	Mediates deSUMOylation of HIF-1α	[126]
UCHL1	Mediates deubiquitination of HIF-1α	[147]
USP8	Mediates deubiquitination of HIF-1α	[149]
USP20	Mediates deubiquitination of HIF-1α	[151]

Table 4

Interacting proteins that mediate O_2-independent degradation of HIF-1α.

Protein	Mechanism of action	Reference
BHLHE41	Interaction with proteasome	[12]
CDK2	Chaperone-mediated autophagy	[23]
CHIP/HSP70	Ubiquitination	[64]
CHIP/HSC70/LAMP2A	Chaperone-mediated autophagy	[62,63]
HAF	Ubiquitination	[50,51]
P53	MDM2-dependent ubiquitination	[94]
PIASY	SUMOylation	[104]
RACK1	Ubiquitination	[114]
SIRT1	ND	[130]
SIRT7	Proteasome/lysosome-independent degradation	[133]
SSAT1	RACK1-dependent ubiquitination	[137]
TAp73	MDM2-dependent ubiquitination	[142]

Table 5

Interacting proteins that inhibit O_2-independent degradation of HIF-1α.

Protein	Mechanism of action	Reference
BCL2	Inhibits ubiquitination by stabilizing HSP90 binding	[11]
CDK1	Inhibits chaperone-mediated autophagy	[22,23]
HSP90	Inhibits ubiquitination by RACK1	[65,114]
MUC1	Not determined	[80]
SEPT9	Inhibits ubiquitination by RACK1	[127,128]
TRAF6	Stabilizes HIF-1α via K63-linked polyubiquitination	[144]

Table 6

Interacting proteins that regulate transactivation by HIF-1α.

Protein	Mechanism of action	Reference
CBP	Coactivator; binds to non-hydroxylated C-terminal TAD[a]	[14–17]
COMMD1	Blocks HIF-1α: HIF-1β heterodimerization	[21,22]
EAF2	Disrupts interaction of CBP/p300 with HIF-1α	[36]
FBP1	Co-repressor; inhibits C-terminal TAD	[41]
FHL2	Co-repressor	[42]
FIH-1	Hydroxylates N803 to block binding of CBP/p300	[43,157]
JMJD2C	Coactivator; demethylates H3K9me3[b] at HREs[c]	[70]
KAT5	Coactivator; required for RNA Pol II activation	[71]
MCM7	Inhibits transactivation in a hydroxylation manner	[77]
MGCRACGAP	Blocks HIF-1α: HIF-1β heterodimerization	[78]
MUC1	Stabilizes interaction of p300 with HIF-1α	[80]
P300	Coactivator; binds to non-hydroxylated C-terminal TAD[b]	[95,96]
PARP1	Coactivator	[97,98]
PCAF	Coactivator; enhances p300 recruitment	[99]
PKM2	Coactivator; enhances HIF-1 binding, p300 recruitment	[106]
PONTIN	Coactivator; increases recruitment of p300	[109]
REPTIN	Recruits HDAC1 to a subset of HIF target genes	[117]
SET7	Blocks binding of HIF-1 to DNA	[71,129]
SIRT1	Deacetylates HIF-1α on K674 to inhibit p300 binding	[99]
SIRT6	Co-repressor	[132]
SRC1	Co-activator	[14]
STAT3	Co-activator	[139]
TAZ	Co-activator; increases HIF-1α binding to HREs	[143]
TIF2	Co-activator	[14]
TSGA10	Blocks nuclear localization	[145,146]
XBP1s	Co-activator; increases RNA Pol II recruitment	[154]

[a]TAD, transactivation domain.

[b]H3K9me3, histone 3, trimethylated on lysine 9.

[c]HREs, hypoxia response elements.

Table 7

Post-translational modification (PTM) of HIF-1α.

Interactor	Site of PTM (AA#)*	Type of PTM	Consequence	Ref
ATM	696	Phosphorylation	Stabilization	[158]
CBX4	391,477	Sumoylation	Transactivation	[18]
CDK1	668	Phosphorylation	Stabilization	[22]
CDK5	687	Phosphorylation	Stabilization	[25]
CK1δ	247	Phosphorylation	Dimerization blocked	[29,159]
CK2	796	Phosphorylation	Transactivation	[160,161]
ERK1/2	641,643	Phosphorylation	Nuclear localization	[32]
GSK-3β	551.555,589	Phosphorylation	Degradation	[49]
HDAC4	10,11,12,19,21	Deacetylation	Stabilization	[55]
LSD1	32	Demethylation	Stabilization	[161]
P300	709	Acetylation	Stabilization	[55]
PCAF	674	Acetylation	Transactivation	[99]
PIASY	ND (not 391,477)	Sumoylation	Degradation	[104]
PLK3	576,657	Phosphorylation	Degradation	[108]
PRKACA	63,692	Phosphorylation	Degradation	[111]
SENP1	ND	Desumoylation	Stabilization	[126]
SET7	32	Methylation	Repression	[129]
SET7	32	Methylation	Degradation	[161]
SIRT1	674	Deacetylation	Repression	[99]
SIRT2	709	Deacetylation	Degradation	[131]
STUB1	ND	Ubiquitination	Degradation	[64]
TRAF6	ND	Ubiquitination[a]	Stabilization	[144]
VHL	532,538,547	Ubiquitination*	Degradation	[162]

*(AA#), the amino acid number of the HIF-1α residue that is subject to PTM is shown, based on GenBank accession number U22431.1.

*K48-linked polyubiquitination.

[a]K63-linked polyubiquitination.