BBA - Molecular Cell Research 1871 (2024) 119683

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr

Minireview

A reductionist perspective on HIF-1α's role in cell proliferation under non-hypoxic conditions

Jan Dreute [1], Maximilian Pfisterer [1], M. Lienhard Schmitz [*]

Institute of Biochemistry, Justus-Liebig-University Giessen, Germany

ARTICLE INFO

Keywords:
HIF-1α
Cell proliferation
cancer
Normoxia
Physioxia

ABSTRACT

The role of hypoxia-inducible factor (HIF)-1α in the control of proliferation under non-hypoxic conditions has been investigated in numerous studies, but does not yield a coherent picture. Therefore, we conducted this meta-analysis of existing literature to systematically evaluate the role of HIF-1α, based on a number of inclusion and exclusion criteria. Studies analyzing non-transformed, primary cells showed a largely heterogeneous distribution of pro-proliferative, anti-proliferative or absent functions for HIF-1α, which are co-determined by several parameters, including the type and age of the cell and its localization in tissues and organs. In contrast, the analyses of tumor cells showed a predominantly pro-proliferative role of HIF-1α by cell-intrinsic and cell-extrinsic molecular mechanism not yet understood.

1. Introduction

Conditions of low oxygen availability (hypoxia) lead to the stabilization of the hypoxia inducible factor (HIF) family of transcription factors. HIF-1 and HIF-2 are heterodimers composed of an oxygen-regulated HIF-α subunits (HIF-1α and HIF-2α) and a constitutively expressed and stable HIF-1β (ARNT) subunit [1]. The molecular mechanisms leading to oxygen-dependent stabilization of HIFα subunits depend on regulated hydroxylation and ubiquitination, as summarized in a number of excellent reviews [2,3]. HIF stabilization can also occur by oxygen-independent mechanisms under physiological conditions [4] or in diseases such as cancer [5,6].

Oxygen-independent HIF stabilization employs a number of different pathways, including *de novo* transcription and translation [7,8] and regulation of protein stability by posttranslational modifications such as phosphorylation and non-degradative ubiquitination [9,10]. In addition, the association with further proteins can either antagonize HIF function as exemplified by COMMD1-mediated disruption of HIF-1α/β dimerization [11] or promote HIF function, *e.g.* through PIN1 mediated stabilization [12]. The activated HIF dimer associates with its cognate genomic binding sites to regulate expression of its numerous target genes with important roles in metabolic adaptation, energy homeostasis, angiogenesis and erythropoiesis and the control of cell survival and proliferation [13]. However, HIF also has functions that do not depend on DNA-binding, as exemplified by its ability to limit DNA replication under hypoxic conditions upon interaction with the MCM DNA helicase complex and the helicase loading factor cell division cycle 6 (CDC6) [14,15].

The relevance of HIF-1α in the absence of pronounced oxygen shortage was revealed through gene deletion in mice. Global knockout of the HIF-1α encoding *HIF1A* gene is embryonically lethal at E11 and leads to multiple defects in the development of the neural and cardiovascular systems [16]. Similarly, organ- or tissue-specific *HIF1A* deletion results in multiple developmental defects [17–22]. While many of these changes can be attributed to the well-established roles of HIF-1α in angiogenesis and energy metabolism, a number of studies have also observed alterations in cell proliferation. While hypoxia frequently results in a HIF-dependent decrease of cell proliferation [23], the function of this transcription factor for the control of cell division under normoxic conditions is far from clear. Thus, we re-examined the literature on the role of the central and extensively studied HIF-1α subunit in the regulation of proliferation under non-hypoxic conditions. These are represented by normoxia and physioxia, the latter referring to lower oxygen concentrations that occur in organs and tissues under physiological conditions [24]. Furthermore, the following criteria were defined to minimize the contribution of HIF-1α-independent effects:

---

[*] Corresponding author.
E-mail address: lienhard.schmitz@biochemie.med.uni-giessen.de (M.L. Schmitz).

[1] Equal contribution.

https://doi.org/10.1016/j.bbamcr.2024.119683
Received 18 October 2023; Received in revised form 18 January 2024; Accepted 20 January 2024

Table 1
The proliferative role of HIF-1α in non-transformed, primary cells. GOF: gain-of-function, LOF: loss-of-function, the arrows symbolize HIF-1α's functional role.

HIF-1α manipulation	Organism	Effect	Role in proliferation	Ref.
		Cell-intrinsic mechanism		
LOF, collagen 2a1-Cre	Mouse	increased proliferation of chondrocytes from periphery of cartilaginous growth plate $p57^{Kip2}$ expression	↓	[21]
LOF, Pdgfra-CreER	Mouse	increased proliferation of fibroblasts after post-ischemic activation limitation of reactive oxygen species (ROS)	↓	[50]
GOF, HIF-1a (stabilized)	Mouse	decreased proliferation of NIH3T3 fibroblasts $p27^{Kip1}$ expression	↓	[29]
LOF, siRNA	Human	loss of the antiproliferative effect of IFNα in umbilical vein endothelial cells unknown	↓	[51]
GOF, keratin-14 promoter-HIF-1a (stabilized)	Mouse	O_2-induced proliferation decreased in lenses from older animals (>8 months), but not in younger animals proposed: $p27^{Kip1}$ expression	↓→	[22]
GOF, HIF-1α (stabilized)	Mouse	decreased proliferation of lung epithelial cells, no effect in lung mesenchymal cells $p21^{Waf}$ expression	→↓	[18]
LOF, knockout	Mouse	increased proliferation in embryoid bodies, no effect in embryonic stem cells	→↓	[31]
LOF, Nkx2-5-Cre	Mouse	hypoplasia of fetal cardiomyocytes $p21^{Waf}$, $p57^{Kip2}$ & Tob2 expression	↑	[19]
LOF, Islet1-Cre	Mouse	decreased proliferation of sympathetic neuronal progenitors unknown	↑	[17]
LOF, Cre	Mouse	decreased proliferation of embryonic fibroblasts unknown	↑	[52]
LOF, Sftpc-CreER	Mouse	reduced LPS-induced proliferation of primary alveolar type II cells unknown	↑	[53]
LOF, knockout	Mouse	reduced proliferation of embryonic stem cells expression of glycolytic enzymes	↑	[16]
LOF, siRNA	Mouse	reduced proliferation of mesenchymal stem cell unknown	↑	[54]
LOF, siRNA	Human	decreased proliferation in primary keratinocytes unknown	↑	[55]
LOF, siRNA	Human	decreased proliferation in HaCaT keratinocytes $p21^{Waf}$ expression	↑	[32]
LOF, shRNA	Human	decreased FGF-2/PDGF-induced proliferation in primary pulmonary artery smooth muscle cells proposed: cyclin A expression	↑	[56]
LOF, Nestin-Cre	Mouse	decreased proliferation of midbrain-derived neural precursor cells, no effects in frontal neural precursor cells	↑→	[20]
LOF, nestin-CreER	Mouse	unknown	No effect in neural stem cells	→
[57]				
LOF, Vav-Cre	Mouse	No effect in hematopoietic stem cells	→	[35]
LOF, Ncr1-Cre	Mouse	No effect in NK cells	→	[58]
LOF, siRNA	Human	immortalized endothelial cells (EA. hy926 &HMEC1)	→	[59]

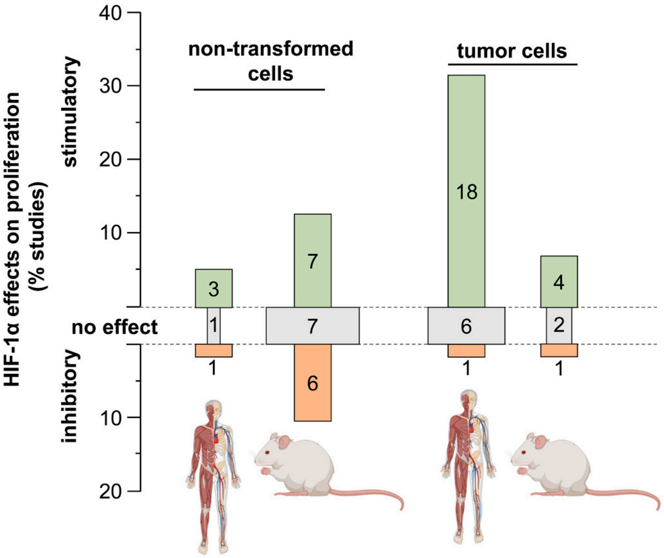

Fig. 1. Graphic summary of the role of HIF-1α in cell proliferation under non-hypoxic conditions. The percentage of studies revealing different roles in the regulation of proliferation and the model organisms from which these results were derived are displayed. The numbers represent the absolute count of publications.

1) Manipulation of HIF-1α levels using genetic tools only, as chemical compounds frequently have off-target effects.
2) No indirect manipulation of HIF levels by targeting its regulators to avoid indirect effects.
3) Analysis of HIF function in the absence of cellular stress or any type of damage, as such events also influence cell proliferation.

2. HIF-1α-dependent regulation of proliferation in healthy cells

As these criteria reduce complexity and allow direct conclusions about the respective role of HIF-1α, we analyzed publications that examined the effects of genetic HIF-1α (de)activation in primary, non-oncogenically transformed human and murine cells. This literature analysis revealed a similar distribution of studies showing a stimulatory, inhibitory or absent role of HIF-1α for proliferation under non-hypoxic conditions (Table 1, Fig. 1). Interestingly, this analysis revealed several parameters that influence HIF-1α-dependent proliferation. For instance, the overexpression of HIF-1α in the lenses of older mice resulted in reduced proliferation of lens epithelial cells, while younger animals showed no effects [22]. Another overexpression model demonstrated decreased proliferation of lung epithelial cells, with no

Table 2

The proliferative role of HIF-1α in tumor cells. GOF: gain-of-function, LOF: loss-of-function, the arrows symbolize HIF-1α's functional role.

HIF-1α manipulation	Tumor model Cell-intrinsic mechanism	Effect	Role in proliferation	Ref.
LOF, AAV-mediated knockout	Human colon cancer cell lines (HCT116 & RKO) unknown	Decreased proliferation	↑	[60]
LOF, siRNA	Human gastric cancer cell lines (AGS & SNU-1) proposed: PI3K/AKT signaling	Decreased proliferation	↑	[61]
LOF, siRNA	Human osteosarcoma (U2OS) and cervix carcinoma cell lines (Hela) $p21^{Waf}$ & $p27^{Kip1}$ expression	Decreased proliferation	↑	[30]
LOF, siRNA	Human circulating breast cancer cells proposed: metabolic changes	Decreased proliferation in brain	↑	[62]
LOF, shRNA	Human breast cancer cell line (MDA-MB-231) unknown	Decreased proliferation	↑	[63]
LOF, siRNA	Human cervical cancer cell line (CaSki) unknown	Decreased proliferation	↑	[37]
LOF, siRNA	Haemangioma endothelial cells Cyclin D1 & p53 expression	Decreased proliferation	↑	[41]
LOF, siRNA	Human esophageal squamous carcinoma cell lines (T.Tn & TE1) Wnt/ß-catenin signaling	Decreased proliferation	↑	[39]
GOF, HIF-1α	Human adenocarcinoma cell line 786-O HECTD2 expression	Increased proliferation	↑	[64]
LOF, siRNA	Human clear cell renal carcinoma cell lines (Caki-1 & OSRC-2) unknown	Decreased proliferation	↑	[65]
LOF, siRNA	Human bladder cancer cell lines T24 and BIU-87 unknown	Decreased proliferation	↑	[66]
LOF, siRNA	Human lung cancer cell line H358 proposed: metabolic changes	Decreased proliferation	↑	[67]
LOF, siRNA	Human thyroid cancer cell lines (MZ-CRC-1 & TT) WWP2 & WWP9 expression	Decreased proliferation	↑	[68]
LOF, siRNA	Human glioblastoma cell line U251 unknown	Decreased proliferation	↑	[69]
LOF, siRNA	Human chronic myelogenous leukemia cell line K562 $p21^{Waf}$ expression	Decreased proliferation	↑	[34]
LOF, siRNA	Human esophagus carcinoma cell lines (Eca109 & TE13) proposed: TCF4 expression and Wnt signaling	Decreased proliferation	↑	[70]
LOF, siRNA	Human retinoblastoma cell line Y-79 unknown	Decreased proliferation	↑	[71,72]
LOF, miRNA	Human Oral squamous cell carcinoma cell lines (SCC3 & CAL27) Kv3.4 expression	Decreased proliferation	↑	[73]
LOF, p48-Cre	Mouse pancreatic cancer expressing $Kras^{G12D}$ unknown	Decreased proliferation	↑	[38]
LOF, siRNA	Mouse $Jak2^{V617F}$-expressing myeloblast-like 32D cells metabolic changes	Decreased proliferation	↑	[36]
LOF, Vav-Cre	Mouse leukemia stem cells expressing BCR-ABL $p16^{Ink4a}$ & $p19^{Arf}$ expression	Decreased proliferation	↑	[35]
LOF, Cre	Mouse embryonic fibroblasts, H-ras transformed unknown	Decreased proliferation	↑	[74]
LOF, Villin-Cre	Mouse colorectal cancer	No effect	→	[75]
LOF, CD19-Cre	Mouse Chronic lymphatic leukemia cells expressing Eμ-TCL1	No effect	→	[76]
LOF, siRNA	Human lung small cell carcinoma cell line U-1906	No effect	→	[77]
LOF, HIF-1α Auxin degron	Human colon cancer cell line HCT116	No effect	→	[43]
LOF, siRNA	Human Pancreas adenocarcinoma cell line BxPC-3	No effect	→	[78]
LOF, miRNA	Human lung carcinoma cell line A549	No effect	→	[79]
LOF, Crispr	Human glioblastoma cells	No effect	→	[80]
GOF, HIF-1α	Human Neuroblastoma cell lines (SH-SY5Y or IMR32)	No effect	→	[81]
GOF, HIF-1α (stabilized)	Human colon cancer cell line HCT116 $p21^{Waf}$ expression	Decreased proliferation	↓	[33]
LOF, Mx1-Cre	Mouse acute myeloid leukemia unknown	Increased proliferation	↓	[82]

effect on lung mesenchymal cells [18]. Cell type-specific effects were also observed in another model, where the knockout of HIF-1α resulted in decreased proliferation of midbrain-derived neural precursor cells without affecting the cell cycle in frontal neural precursor cells [20]. HIF-1α knockout in the developing bone revealed increased proliferation of chondrocytes only from the periphery, but not the center of the

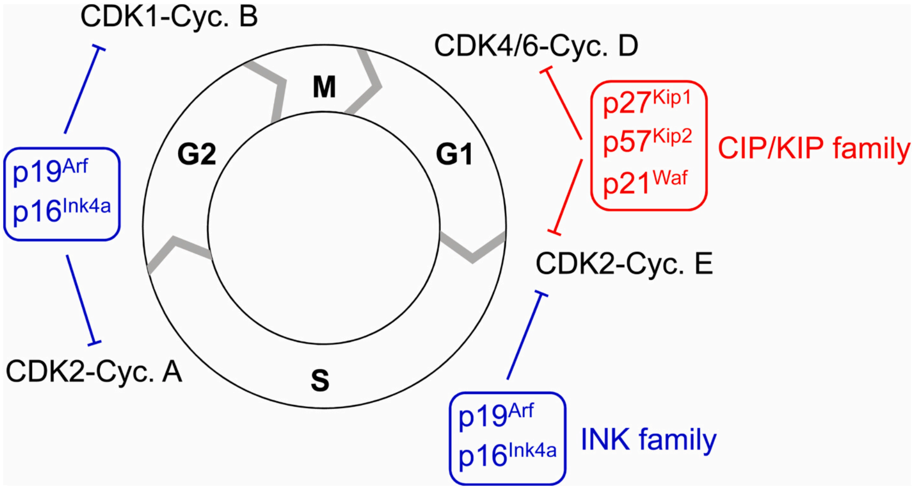

Fig. 2. Summary of the HIF-1α-dependent regulation of CDKIs and their inhibitory effects on various CDK/cyclin complexes in the cell cycle.

cartilaginous growth plate [21]. It is therefore safe to say that the role of HIF depends on the cell type, species and on further parameters such as age or localization within the organ.

3. HIF-1α-dependent regulation of proliferation in tumor cells

The role of HIF in tumor cells was analyzed separately, as they differ from non-transformed cells in many ways, including metabolic rewiring, chromatin packaging, signaling and gene expression, amongst further hallmarks of cancer cells [25]. Studies measuring proliferation of solid tumors were excluded, as these often contain areas with low oxygen availability [26]. Meta-analysis of these studies revealed a proliferation-supportive role of HIF-1α in the vast majority of tumor cells of different origins, while only 2 studies showed an antiproliferative role of HIF-1α (Table 2, Fig. 2). In agreement with a largely proliferation-supportive function of HIF-1α, many tumors show elevated protein levels of HIF-1α [27,28].

The molecular mechanisms allowing HIF-1α-mediated control of cell proliferation are not well understood. It is commonly observed that changes in HIF-1α levels cause alterations in the levels of CDK inhibitors (CDKIs) such as $p57^{Kip2}$ [19,21], $p27^{Kip1}$ [29,30], $p21^{Waf}$ [18,19,30–34], $p16^{Ink4a}$ and $p19^{Arf}$ [35,36]. These HIF-1α-regulated CDKIs belong to the CDK-interacting protein/kinase inhibitory protein (CIP/KIP) family ($p21^{Waf}$, $p27^{Kip1}$ and $p57^{Kip2}$) and the inhibitor of kinase (INK) family ($p16^{Ink4a}$ & $p19^{Arf}$), which target distinct CDK/cyclin complexes, as illustrated in Fig. 2. All HIF-1α-dependent CDKIs target the CDK2/Cyclin E complex which promotes G1/S progression and accordingly the inactivation of HIF-1α frequently results in a G1 arrest [30,32,37–41].

4. Emerging mechanisms of HIF-1α-dependent regulation of proliferation

The stark evidence for the role of CDKIs is contrasted by a lack of mechanistic insights for these regulations, as exemplified by the control of $p21^{Waf}$ levels. On the one hand, HIF-1α stabilization can trigger $p21^{Waf}$ expression either directly by binding to its promoter [42] or indirectly by displacement of Myc [33]. On the other hand, also downregulation of HIF-1α leads to an increase of $p21^{Waf}$ [18,30–32], but the underlying mechanisms explaining why both up- and down-regulation of a transcription factor can cause $p21^{Waf}$ upregulation are not known. As only few of the HIF target genes have a function in cell cycle control [13], HIF-1α may regulate cell proliferation indirectly by cell-intrinsic or cell-extrinsic mechanisms. In this context, HIF-1α-dependent reprogramming of metabolic networks, such as the enhancement of glycolysis, could potentially meet the demand for metabolites arising from cell division. Such a metabolic function was also assigned to the recently reported transient stabilization of HIF-1α in the G1 phase of different cell lines grown under normoxic conditions [43]. It will be interesting to investigate whether the reported association of HIF-1α with CDK1 [44,45], CDK5 [46] and CDK8 [47] also occurs under normoxic conditions and whether these interactions contribute to HIF's role in the regulation of cell proliferation.

5. Concluding remarks

While some cell cycle regulatory proteins such as CDK1 are indispensable for proliferation, others such as interphase CDKs are only essential for proliferation of specialized cells and tumors [48]. HIF-1α clearly belongs to the latter group, and has therefore been proposed as a relevant target for the treatment of HIF-1α-dependent tumors [31,49]. To selectively target tumor cell-specific HIF-1α functions without compromising the proliferation of normal cells and tissues, it will be important to identify tumor cell-specific HIF-1α interdependencies with other factors and signaling pathways using synthetic lethal screens.

CRediT authorship contribution statement

Jan Dreute: Writing – review & editing. **Maximilian Pfisterer:** Formal analysis. **M. Lienhard Schmitz:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We apologize to all authors whose important work could not be cited due to space constraints and hope that we haven't missed relevant manuscripts. This research was funded by the grants from the Deutsche Forschungsgemeinschaft: GRK 2573 (RP4, project 416910386) and the excellence cluster CPI (project 390649896).

References

[1] C.J. Hu, L.Y. Wang, L.A. Chodosh, B. Keith, M.C. Simon, Differential roles of hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-2alpha in hypoxic gene regulation, Mol. Cell. Biol. 23 (2003) 9361–9374.

[2] W.G. Kaelin Jr., P.J. Ratcliffe, Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway, Mol. Cell 30 (2008) 393–402.

[3] G.L. Semenza, The genomics and genetics of oxygen homeostasis, Annu. Rev. Genomics Hum. Genet. 21 (2020) 183–204.

[4] A.F. McGettrick, L.A.J. O'Neill, The role of HIF in immunity and inflammation, Cell Metab. 32 (2020) 524–536.

[5] G. Xiong, R.L. Stewart, J. Chen, T. Gao, T.L. Scott, L.M. Samayoa, K. O'Connor, A. N. Lane, R. Xu, Collagen prolyl 4-hydroxylase 1 is essential for HIF-1alpha stabilization and TNBC chemoresistance, Nat. Commun. 9 (2018) 4456.

[6] K. Shigeta, M. Hasegawa, T. Hishiki, Y. Naito, Y. Baba, S. Mikami, K. Matsumoto, R. Mizuno, A. Miyajima, E. Kikuchi, H. Saya, T. Kosaka, M. Oya, IDH2 stabilizes HIF-1alpha-induced metabolic reprogramming and promotes chemoresistance in urothelial cancer, EMBO J. 42 (2023) e110620.

[7] A. Görlach, Regulation of HIF-1alpha at the transcriptional level, Curr. Pharm. Des. 15 (2009) 3844–3852.

[8] M. Carbonaro, A. O'Brate, P. Giannakakou, Microtubule disruption targets HIF-1alpha mRNA to cytoplasmic P-bodies for translational repression, J. Cell Biol. 192 (2011) 83–99.

[9] T. Kietzmann, D. Mennerich, E.Y. Dimova, Hypoxia-inducible factors (HIFs) and phosphorylation: impact on stability, localization, and transactivity, Front Cell Dev Biol 4 (2016) 11.

[10] L.A. Daly, P.J. Brownridge, M. Batie, S. Rocha, V. See, C.E. Eyers, Oxygen-dependent changes in binding partners and post-translational modifications regulate the abundance and activity of HIF-1alpha/2alpha, Sci. Signal. 14 (2021).

[11] B. van de Sluis, X. Mao, Y. Zhai, A.J. Groot, J.F. Vermeulen, E. van der Wall, P. J. van Diest, M.H. Hofker, C. Wijmenga, L.W. Klomp, K.R. Cho, E.R. Fearon, M. Vooijs, E. Burstein, COMMD1 disrupts HIF-1alpha/beta dimerization and inhibits human tumor cell invasion, J. Clin. Invest. 120 (2010) 2119–2130.

[12] H.J. Han, N. Kwon, M.A. Choi, K.O. Jung, J.Y. Piao, H.K. Ngo, S.J. Kim, D.H. Kim, J.K. Chung, Y.N. Cha, H. Youn, B.Y. Choi, S.H. Min, Y.J. Surh, Peptidyl prolyl isomerase PIN1 directly binds to and stabilizes hypoxia-inducible factor-1alpha, PLoS One 11 (2016) e0147038.

[13] Y. Benita, H. Kikuchi, A.D. Smith, M.Q. Zhang, D.C. Chung, R.J. Xavier, An integrative genomics approach identifies Hypoxia Inducible Factor-1 (HIF-1)-target genes that form the core response to hypoxia, Nucleic Acids Res. 37 (2009) 4587–4602.

[14] M.E. Hubbi, W. Luo, J.H. Baek, G.L. Semenza, MCM proteins are negative regulators of hypoxia-inducible factor 1, Mol. Cell 42 (2011) 700–712.

[15] M.E. Hubbi, D.M. Kshitiz, C.C. Rey, W. Wong, D.H. Luo, C.V. Kim, A. Dang, G.L. Semenza Levchenko, A nontranscriptional role for HIF-1alpha as a direct inhibitor of DNA replication, Sci. Signal. 6 (2013) ra10.

[16] N.V. Iyer, L.E. Kotch, F. Agani, S.W. Leung, E. Laughner, R.H. Wenger, M. Gassmann, J.D. Gearhart, A.M. Lawler, A.Y. Yu, G.L. Semenza, Cellular and developmental control of O2 homeostasis by hypoxia-inducible factor 1 alpha, Genes Dev. 12 (1998) 149–162.

[17] R. Bohuslavova, R. Cerychova, F. Papousek, V. Olejnickova, M. Bartos, A. Gorlach, F. Kolar, D. Sedmera, G.L. Semenza, G. Pavlinkova, HIF-1alpha is required for development of the sympathetic nervous system, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 13414–13423.

[18] J.P. Bridges, S. Lin, M. Ikegami, J.M. Shannon, Conditional hypoxia inducible factor-1alpha induction in embryonic pulmonary epithelium impairs maturation and augments lymphangiogenesis, Dev. Biol. 362 (2012) 24–41.

[19] N. Guimarães-Camboa, J. Stowe, I. Aneas, N. Sakabe, P. Cattaneo, L. Henderson, M. S. Kilberg, R.S. Johnson, J. Chen, A.D. McCulloch, M.A. Nobrega, S.M. Evans, A. C. Zambon, HIF1alpha represses cell stress pathways to allow proliferation of hypoxic fetal cardiomyocytes, Dev. Cell 33 (2015) 507–521.

[20] J. Milosevic, M. Maisel, F. Wegner, J. Leuchtenberger, R.H. Wenger, M. Gerlach, A. Storch, J. Schwarz, Lack of hypoxia-inducible factor-1 alpha impairs midbrain neural precursor cells involving vascular endothelial growth factor signaling, J. Neurosci. 27 (2007) 412–421.

[21] E. Schipani, H.E. Ryan, S. Didrickson, T. Kobayashi, M. Knight, R.S. Johnson, Hypoxia in cartilage: HIF-1alpha is essential for chondrocyte growth arrest and survival, Genes Dev. 15 (2001) 2865–2876.

[22] Y.B. Shui, J.M. Arbeit, R.S. Johnson, D.C. Beebe, HIF-1: an age-dependent regulator of lens cell proliferation, Invest. Ophthalmol. Vis. Sci. 49 (2008) 4961–4970.

[23] M.E. Hubbi, G.L. Semenza, Regulation of cell proliferation by hypoxia-inducible factors, Am. J. Phys. Cell Phys. 309 (2015) C775–C782.

[24] A. Carreau, B. El Hafny-Rahbi, A. Matejuk, C. Grillon, C. Kieda, Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia, J. Cell. Mol. Med. 15 (2011) 1239–1253.

[25] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.

[26] C. Liao, X. Liu, C. Zhang, Q. Zhang, Tumor hypoxia: from basic knowledge to therapeutic implications, Semin. Cancer Biol. 88 (2023) 172–186.

[27] E.E. Wicks, G.L. Semenza, Hypoxia-inducible factors: cancer progression and clinical translation, J. Clin. Invest. 132 (2022).

[28] L. Schito, G.L. Semenza, Hypoxia-inducible factors: master regulators of cancer progression, trends, Cancer 2 (2016) 758–770.

[29] T. Hackenbeck, K.X. Knaup, R. Schietke, J. Schodel, C. Willam, X. Wu, C. Warnecke, K.U. Eckardt, M.S. Wiesener, HIF-1 or HIF-2 induction is sufficient to achieve cell cycle arrest in NIH3T3 mouse fibroblasts independent from hypoxia, Cell Cycle 8 (2009) 1386–1395.

[30] C. Culver, A. Melvin, S. Mudie, S. Rocha, HIF-1alpha depletion results in SP1-mediated cell cycle disruption and alters the cellular response to chemotherapeutic drugs, Cell Cycle 10 (2011) 1249–1260.

[31] P. Carmeliet, Y. Dor, J.M. Herbert, D. Fukumura, K. Brusselmans, M. Dewerchin, M. Neeman, F. Bono, R. Abramovitch, P. Maxwell, C.J. Koch, P. Ratcliffe, L. Moons, R.K. Jain, D. Collen, E. Keshert, Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis, Nature 394 (1998) 485–490.

[32] Y.S. Cho, J.M. Bae, Y.S. Chun, J.H. Chung, Y.K. Jeon, I.S. Kim, M.S. Kim, J.W. Park, HIF-1alpha controls keratinocyte proliferation by up-regulating p21(WAF1/Cip1), Biochim. Biophys. Acta 1783 (2008) 323–333.

[33] M. Koshiji, Y. Kageyama, E.A. Pete, I. Horikawa, J.C. Barrett, L.E. Huang, HIF-1alpha induces cell cycle arrest by functionally counteracting Myc, EMBO J. 23 (2004) 1949–1956.

[34] H. Chen, Y. Shen, F. Gong, Y. Jiang, R. Zhang, HIF-alpha promotes chronic myelogenous leukemia cell proliferation by upregulating p21 expression, Cell Biochem. Biophys. 72 (2015) 179–183.

[35] H. Zhang, H. Li, H.S. Xi, S. Li, HIF1alpha is required for survival maintenance of chronic myeloid leukemia stem cells, Blood 119 (2012) 2595–2607.

[36] J. Baumeister, N. Chatain, A. Hubrich, T. Maie, I.G. Costa, B. Denecke, L. Han, C. Kustermann, S. Sontag, K. Sere, K. Strathmann, M. Zenke, A. Schuppert, T. H. Brummendorf, K.R. Kranc, S. Koschmieder, D. Gezer, Hypoxia-inducible factor 1 (HIF-1) is a new therapeutic target in JAK2V617F-positive myeloproliferative neoplasms, Leukemia 34 (2020) 1062–1074.

[37] L. Jiang, S. Shi, Q. Shi, H. Zhang, R. Hu, M. Wang, Similarity in the functions of HIF-1alpha and HIF-2alpha proteins in cervical cancer cells, Oncol. Lett. 14 (2017) 5643–5651.

[38] K.E. Lee, M. Spata, L.J. Bayne, E.L. Buza, A.C. Durham, D. Allman, R. H. Vonderheide, M.C. Simon, Hif1a deletion reveals pro-neoplastic function of B cells in pancreatic neoplasia, Cancer Discov. 6 (2016) 256–269.

[39] K. Tang, T. Toyozumi, K. Murakami, H. Sakata, M. Kano, S. Endo, Y. Matsumoto, H. Suito, M. Takahashi, N. Sekino, R. Otsuka, K. Kinoshita, S. Hirasawa, J. Hu, M. Uesato, K. Hayano, H. Matsubara, HIF-1alpha stimulates the progression of oesophageal squamous cell carcinoma by activating the Wnt/beta-catenin signalling pathway, Br. J. Cancer 127 (2022) 474–487.

[40] M. Vukovic, A.V. Guitart, C. Sepulveda, A. Villacreces, E. O'Duibhir, T. I. Panagopoulou, A. Ivens, J. Menendez-Gonzalez, J.M. Iglesias, L. Allen, F. Glykofrydis, C. Subramani, A. Armesilla-Diaz, A.E. Post, K. Schaak, D. Gezer, C. W. So, T.L. Holyoake, A. Wood, D. O'Carroll, P.J. Ratcliffe, K.R. Kranc, Hif-1alpha and Hif-2alpha synergize to suppress AML development but are dispensable for disease maintenance, J. Exp. Med. 212 (2015) 2223–2234.

[41] W. Zhang, L. Sun, H. Gao, S. Wang, Mechanism of the HIF-1alpha/VEGF/VEGFR-2 pathway in the proliferation and apoptosis of human haemangioma endothelial cells, Int. J. Exp. Pathol. 104 (2023) 258–268.

[42] K. Salnikow, M. Costa, W.D. Figg, M.V. Blagosklonny, Hyperinducibility of hypoxia-responsive genes without p53/p21-dependent checkpoint in aggressive prostate cancer, Cancer Res. 60 (2000) 5630–5634.

[43] R. Belapurkar, M. Pfisterer, J. Dreute, S. Werner, S. Zukunft, I. Fleming, M. Kracht, M.L. Schmitz, A transient increase of HIF-1alpha during the G1 phase (G1-HIF) ensures cell survival under nutritional stress, Cell Death Dis. 14 (2023) 477.

[44] N.A. Warfel, N.G. Dolloff, D.T. Dicker, J. Malysz, W.S. El-Deiry, CDK1 stabilizes HIF-1alpha via direct phosphorylation of Ser668 to promote tumor growth, Cell Cycle 12 (2013) 3689–3701.

[45] M.E. Hubbi, D.M. Gilkes, H. Hu, I. Kshitiz, G.L. Semenza Ahmed, Cyclin-dependent kinases regulate lysosomal degradation of hypoxia-inducible factor 1alpha to promote cell-cycle progression, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E3325–E3334.

[46] J. Herzog, S.M. Ehrlich, L. Pfitzer, J. Liebl, T. Frohlich, G.J. Arnold, W. Mikulits, C. Haider, A.M. Vollmar, S. Zahler, Cyclin-dependent kinase 5 stabilizes hypoxia-inducible factor-1alpha: a novel approach for inhibiting angiogenesis in hepatocellular carcinoma, Oncotarget 7 (2016) 27108–27121.

[47] M.D. Galbraith, M.A. Allen, C.L. Bensard, X. Wang, M.K. Schwinn, B. Qin, H. W. Long, D.L. Daniels, W.C. Hahn, R.D. Dowell, J.M. Espinosa, HIF1A employs CDK8-mediator to stimulate RNAPII elongation in response to hypoxia, Cell 153 (2013) 1327–1339.

[48] M. Malumbres, M. Barbacid, Cell cycle, CDKs and cancer: a changing paradigm, Nat. Rev. Cancer 9 (2009) 153–166.

[49] H.E. Ryan, J. Lo, R.S. Johnson, HIF-1 alpha is required for solid tumor formation and embryonic vascularization, EMBO J. 17 (1998) 3005–3015.

[50] V. Janbandhu, V. Tallapragada, R. Patrick, Y. Li, D. Abeygunawardena, D. T. Humphreys, E. Martin, A.O. Ward, O. Contreras, N. Farbehi, E. Yao, J. Du, S. L. Dunwoodie, N. Bursac, R.P. Harvey, Hif-1a suppresses ROS-induced proliferation of cardiac fibroblasts following myocardial infarction, Cell Stem Cell 29 (2022) 281–297 e212.

[51] S.A. Gerber, J.S. Pober, IFN-alpha induces transcription of hypoxia-inducible factor-1alpha to inhibit proliferation of human endothelial cells, J. Immunol. 181 (2008) 1052–1062.

[52] S.M. Welford, B. Bedogni, K. Gradin, L. Poellinger, M. Broome Powell, A.J. Giaccia, HIF1alpha delays premature senescence through the activation of MIF, Genes Dev. 20 (2006) 3366–3371.

[53] J. McClendon, N.L. Jansing, E.F. Redente, A. Gandjeva, Y. Ito, S.P. Colgan, A. Ahmad, D.W.H. Riches, H.A. Chapman, R.J. Mason, R.M. Tuder, R.L. Zemans, Hypoxia-inducible factor 1alpha signaling promotes repair of the alveolar epithelium after acute lung injury, Am. J. Pathol. 187 (2017) 1772–1786.

[54] Y. Xue, Z. Li, Y. Wang, X. Zhu, R. Hu, W. Xu, Role of the HIF-1alpha/SDF-1/CXCR4 signaling axis in accelerated fracture healing after craniocerebral injury, Mol. Med. Rep. 22 (2020) 2767–2774.
[55] H.R. Rezvani, N. Ali, M. Serrano-Sanchez, P. Dubus, C. Varon, C. Ged, C. Pain, M. Cario-Andre, J. Seneschal, A. Taieb, H. de Verneuil, F. Mazurier, Loss of epidermal hypoxia-inducible factor-1alpha accelerates epidermal aging and affects re-epithelialization in human and mouse, J. Cell Sci. 124 (2011) 4172–4183.
[56] K. Schultz, B.L. Fanburg, D. Beasley, Hypoxia and hypoxia-inducible factor-1alpha promote growth factor-induced proliferation of human vascular smooth muscle cells, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) H2528–H2534.
[57] L. Li, K.M. Candelario, K. Thomas, R. Wang, K. Wright, A. Messier, L. A. Cunningham, Hypoxia inducible factor-1alpha (HIF-1alpha) is required for neural stem cell maintenance and vascular stability in the adult mouse SVZ, J. Neurosci. 34 (2014) 16713–16719.
[58] F. Victorino, T.M. Bigley, E. Park, C.H. Yao, J. Benoit, L.P. Yang, S.J. Piersma, E. J. Lauron, R.M. Davidson, G.J. Patti, W.M. Yokoyama, HIF1alpha is required for NK cell metabolic adaptation during virus infection, Elife 10 (2021).
[59] L. Chen, J.H. Qiu, L.L. Zhang, X.D. Luo, Adrenomedullin promotes human endothelial cell proliferation via HIF-1alpha, Mol. Cell. Biochem. 365 (2012) 263–273.
[60] D.T. Dang, F. Chen, L.B. Gardner, J.M. Cummins, C. Rago, F. Bunz, S.V. Kantsevoy, L.H. Dang, Hypoxia-inducible factor-1alpha promotes nonhypoxia-mediated proliferation in colon cancer cells and xenografts, Cancer Res. 66 (2006) 1684–1936.
[61] J. Zhang, J. Xu, Y. Dong, B. Huang, Down-regulation of HIF-1alpha inhibits the proliferation, migration, and invasion of gastric cancer by inhibiting PI3K/AKT pathway and VEGF expression, Biosci. Rep. 38 (2018).
[62] R.Y. Ebright, M.A. Zachariah, D.S. Micalizzi, B.S. Wittner, K.L. Niederhoffer, L. T. Nieman, B. Chirn, D.F. Wiley, B. Wesley, B. Shaw, E. Nieblas-Bedolla, L. Atlas, A. Szabolcs, A.J. Iafrate, M. Toner, D.T. Ting, P.K. Brastianos, D.A. Haber, S. Maheswaran, HIF1A signaling selectively supports proliferation of breast cancer in the brain, Nat. Commun. 11 (2020) 6311.
[63] S. Li, Q. Wei, Q. Li, B. Zhang, Q. Xiao, Down-regulating HIF-1alpha by lentivirus-mediated shRNA for therapy of triple negative breast cancer, Cancer Biol. Ther. 16 (2015) 866–875.
[64] D. Lv, T. Shen, J. Yao, Q. Yang, Y. Xiang, Z. Ma, HIF-1alpha induces HECTD2 up-regulation and aggravates the malignant progression of renal cell cancer via repressing miR-320a, Front. Cell Dev. Biol. 9 (2021) 775642.
[65] B. Zhan, X. Dong, Y. Yuan, Z. Gong, B. Li, hZIP1 inhibits progression of clear cell renal cell carcinoma by suppressing NF-kB/HIF-1alpha pathway, Front. Oncol. 11 (2021) 759818.
[66] N. Lu, M.H. Piao, C.S. Feng, Y. Yuan, Isoflurane promotes epithelial-to-mesenchymal transition and metastasis of bladder cancer cells through HIF-1alpha-beta-catenin/Notch1 pathways, Life Sci. 258 (2020) 118154.
[67] J. Li, J. Zhang, F. Xie, J. Peng, X. Wu, Macrophage migration inhibitory factor promotes Warburg effect via activation of the NF-kappaB/HIF-1alpha pathway in lung cancer, Int. J. Mol. Med. 41 (2018) 1062–1068.
[68] Z.Y. Ding, Y.J. Huang, J.D. Tang, G. Li, P.Q. Jiang, H.T. Wu, Silencing of hypoxia-inducible factor-1alpha promotes thyroid cancer cell apoptosis and inhibits invasion by downregulating WWP2, WWP9, VEGF and VEGFR2, Exp. Ther. Med. 12 (2016) 3735–3741.
[69] J.H. Tang, Z.X. Ma, G.H. Huang, Q.F. Xu, Y. Xiang, N. Li, K. Sidlauskas, E.E. Zhang, S.Q. Lv, Downregulation of HIF-1a sensitizes U251 glioma cells to the temozolomide (TMZ) treatment, Exp. Cell Res. 343 (2016) 148–158.
[70] N.N. Tang, H. Zhu, H.J. Zhang, W.F. Zhang, H.L. Jin, L. Wang, P. Wang, G.J. He, B. Hao, R.H. Shi, HIF-1alpha induces VE-cadherin expression and modulates vasculogenic mimicry in esophageal carcinoma cells, World J. Gastroenterol. 20 (2014) 17894–17904.
[71] Y. Gao, M. Jing, R. Ge, Z. Zhou, Y. Sun, Inhibition of hypoxia inducible factor 1alpha by siRNA-induced apoptosis in human retinoblastoma cells, J. Biochem. Mol. Toxicol. 28 (2014) 394–399.
[72] B.F. Fernandes, J. Coates, A.N. Odashiro, C. Quezada, A. Huynh, P.R. Odashiro, M. Odashiro, M.N. Burnier Jr., Hypoxia-inducible factor-1alpha and its role in the proliferation of retinoblastoma cells, Pathol. Oncol. Res. 20 (2014) 557–563.
[73] C. Qian, Y. Dai, X. Xu, Y. Jiang, HIF-1alpha regulates proliferation and invasion of oral cancer cells through Kv3.4 channel, Ann. Clin. Lab. Sci. 49 (2019) 457–467.
[74] H.E. Ryan, M. Poloni, W. McNulty, D. Elson, M. Gassmann, J.M. Arbeit, R. S. Johnson, Hypoxia-inducible factor-1alpha is a positive factor in solid tumor growth, Cancer Res. 60 (2000) 4010–4015.
[75] N. Rohwer, S. Jumpertz, M. Erdem, A. Egners, K.T. Warzecha, A. Fragoulis, A. A. Kuhl, R. Kramann, S. Neuss, I. Rudolph, T. Endermann, C. Zasada, I. Apostolova, M. Gerling, S. Kempa, R. Hughes, C.E. Lewis, W. Brenner, M.B. Malinowski, M. Stockmann, L. Schomburg, W. Faller, O.J. Sansom, F. Tacke, M. Morkel, T. Cramer, Non-canonical HIF-1 stabilization contributes to intestinal tumorigenesis, Oncogene 38 (2019) 5670–5685.
[76] S. Gonder, A. Largeot, E. Gargiulo, S. Pierson, I. Fernandez Botana, G. Pagano, J. Paggetti, E. Moussay, The tumor microenvironment-dependent transcription factors AHR and HIF-1alpha are dispensable for leukemogenesis in the Emicro-TCL1 mouse model of chronic lymphocytic leukemia, Cancers (Basel) 13 (2021).
[77] M. Munksgaard Thoren, M. Vaapil, J. Staaf, M. Planck, M.E. Johansson, S. Mohlin, S. Pahlman, Myc-induced glutaminolysis bypasses HIF-driven glycolysis in hypoxic small cell lung carcinoma cells, Oncotarget 8 (2017) 48983–48995.
[78] G. He, Y. Jiang, B. Zhang, G. Wu, The effect of HIF-1alpha on glucose metabolism, growth and apoptosis of pancreatic cancerous cells, Asia Pac. J. Clin. Nutr. 23 (2014) 174–180.
[79] W. Li, Y.Q. Chen, Y.B. Shen, H.M. Shu, X.J. Wang, C.L. Zhao, C.J. Chen, HIF-1alpha knockdown by miRNA decreases survivin expression and inhibits A549 cell growth in vitro and in vivo, Int. J. Mol. Med. 32 (2013) 271–280.
[80] P. Wang, L. Zhao, S. Gong, S. Xiong, J. Wang, D. Zou, J. Pan, Y. Deng, Q. Yan, N. Wu, B. Liao, HIF1alpha/HIF2alpha-Sox2/Klf4 promotes the malignant progression of glioblastoma via the EGFR-PI3K/AKT signalling pathway with positive feedback under hypoxia, Cell Death Dis. 12 (2021) 312.
[81] S. Chen, M. Zhang, L. Xing, Y. Wang, Y. Xiao, Y. Wu, HIF-1alpha contributes to proliferation and invasiveness of neuroblastoma cells via SHH signaling, PLoS One 10 (2015) e0121115.
[82] T. Velasco-Hernandez, A. Hyrenius-Wittsten, M. Rehn, D. Bryder, J. Cammenga, HIF-1alpha can act as a tumor suppressor gene in murine acute myeloid leukemia, Blood 124 (2014) 3597–3607.