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缺氧诱导因子对肿瘤的影响及其对胃肠道间质瘤的作用

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[摘 要] 在缺氧环境下，细胞为作出适应性反应而产生了缺氧诱导因子(hypoxia-inducible factors，HIFs)。HIF不仅是细胞适应低氧和营养缺乏环境的主要调控因子，还是促进许多肿瘤发展的重要转录因子。HIF可在代谢、转移、耐药等多方面调节靶基因的活性，进而影响肿瘤的进展，对患者的预后产生较大影响。HIF的破坏可以直接抑制肿瘤细胞的增殖。目前，HIF已成为新型抗肿瘤药物的作用靶点。有研究表明，HIF参与了部分类型胃肠道间质瘤的发病。HIF与胃肠道间质瘤(gastrointestinal stromal tumors，GIST)之间的关系值得被深入研究。

[关键词] 缺氧诱导因子；肿瘤；胃肠道间质瘤；靶基因

Effect of hypoxia-inducible factors on tumors and its role in gastrointestinal stromal tumors

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Abstract Hypoxia-inducible factors (HIFs) are produced by cells in response to hypoxia. HIF is not only a major regulator of cell adaptation to hypoxic and nutrient-deficient environments, but also an important transcription factor that promotes the development of many tumors. HIF can regulate the activity of target genes in many aspects such as metabolism, metastasis, and drug resistance, which in turn affects the progression of tumors and has a greater impact on the prognosis of patients. The disruption of HIF can directly inhibits the proliferation of tumor cells. At present, HIF has become a target for new anti-tumor drugs. Current studies have shown that HIF is involved in the pathogenesis of some types of gastrointestinal stromal tumors. The study of the relationship between HIF and gastrointestinal stromal tumors (GIST) is worthy of further exploration.

Keywords hypoxia-inducible factors; tumor; gastrointestinal stromal tumors; target gene

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缺氧常见于许多实体肿瘤中。缺氧时产生的缺氧诱导因子(hypoxia-inducible factors，HIFs)在许多肿瘤的进展过程中起调节作用。胃肠道间质瘤(gastrointestinal stromal tumors，GIST)是胃肠道最常见的间叶组织肿瘤[1-2]。HIF不仅参与了部分GIST患者的发病，还与GIST的进展情况密切相关。因而研究HIF对肿瘤的影响及其对GIST的作用具有重大意义。

1 HIF的结构、功能及调节因子

哺乳动物的细胞需要持续供氧作为代谢反应的底物。HIFs正向调节数百个基因的转录以维持每个细胞的氧气供求平衡。HIF由Wang等[3]于1995年发现。到目前为止，在哺乳动物中已鉴定出3个HIF家族成员，分别为HIF-1，HIF-2和HIF-3[4]。HIF-1是HIF家族的创始者，转录因子家族的基础成员，氧稳态的主要调节因子。HIF-1由一个特异性的、进行氧调节的HIF-1α亚单位和一个组成性表达的HIF-1β亚单位组成的异二聚体蛋白[5]。HIF-1α与HIF-1β的分子质量分别约为120 kD(1 D=1 u)和90 kD[3]。许多HIF-1α相互作用蛋白质是HIF-1靶基因的产物，参与前馈或反馈通路，来增强或抑制细胞对缺氧的反应。

HIF-α可以HIF-1α，HIF-2α或HIF-3α形式存在[6]。在常氧状态下，HIF-1α或HIF-2α在Fe^{2+}、维生素C、细胞酮戊二酸脱氢酶(α-ketoglutarate dehydrogenase，α-KGDH)的存在下被脯氨酰羟化酶结构域(prolyl hydroxylase domain，PHD)羟基化、VHL(von Hippel-Lindau)识别和泛素化，导致被蛋白酶体降解，降解速率十分迅速，约5 min。在缺氧状态下，稳定的HIF-1α转移到细胞核中与HIF-1β形成异二聚体，在协同激活剂P300(300-kD protein)和cAMP反应元件结合蛋白(cAMP response element-binding protein，CREB)结合蛋白CBP(CREB-binding protein)的帮助下，与靶基因启动子结合，形成缺氧反应元件(hypoxia-responsive element，HRE)序列，以激活大量基因转录[7-10]。HIF-3α的作用是对抗HRE的基因表达[11]。

PHD依赖性羟基化、VHL依赖性泛素化和缺氧诱导因子抑制因子(factor-inhibiting hypoxia-inducible factor 1，FIH-1)依赖性羟基化是调节HIF-1活性的传统机制。同时，HIF-1的活性还受到多种因子的调控，如信号转导和转录激活因子-1(signal transducer and activator of transcription-1，STAT1)/STAT2/干扰素反应因子-9(interferon response factor-9，IRF9)，STAT3或核因子-κB(nuclear factor-kappa B，NF-κB)等转录因子组成的干扰素刺激基因因子-3(interferon-stimulated gene factor-3，ISGF3)复合物，与*HIF-1α*基因的启动子区域结合，可以激活其转录起始。磷酸肌醇-3激酶/蛋白激酶B，又称碱性磷酸酶/蛋白激酶C/组蛋白去乙酰化酶(phosphoinositide-3 kinase/protein kinase B，PKB，又称AKT/protein kinase C/histone deacetylases，PI3K/AKT/PKC/HDAC)通路也可以诱导HIF-1α转录的上调[10,12]。核呼吸因子1(nuclear respiratory factor 1，NRF-1)则可抑制HIF-1α转录的起始。PI3K/AKT通路、Y盒结合蛋白-1(Y box-binding protain-1，Yb-1)、ATM和Rad3相关基因(ATM and Rad3-related gene，ATR)均可以上调HIF-1α蛋白的翻译起始。另外，通过核异位、异二聚体形成或者HIF-1α蛋白的激活活性等方面对HIF-1α起正向调节作用的有Dynein，腺苷-磷酸活化蛋白激酶/组蛋白去乙酰化酶(adenosine monophosphate-activated protein kinase/histone deacetylase，AMPK/HDAC)通路、X-盒结合蛋白1(X-box binding protein 1，XBP1)、异柠檬酸脱氢酶3(isocitrate dehydrogenase 3，IDH3)，对HIF-1α起负向调节作用的有丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)、酪蛋白激酶1δ(casein kinase 1 delta，CK1δ)、FIH-1、III类去乙酰化酶(surtuin 1，SIRT1)等。Koyasu等[12]研究发现IDH3、泛素羧基末端水解酶L1(ubiquitin carboxy-terminal hydrolase L1，UCHL1)和淋巴细胞抗原6复合体E(lymphocyte antigen 6 complex, locus E，*LY6E*)基因都是HIF-1新的激活因子。肿瘤坏死因子α(tumor necrosis factor α，TNF-α)也可以通过激活磷脂酰肌醇3-激酶-AKT-哺乳动物雷帕霉素靶蛋白(phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin，PI3K-AKT-mTOR)和丝裂原活化蛋白激酶-细胞外信号调节蛋白激酶(mitogen-activated protein kinase-extracellular signal-regulated protein kinase，MAPK-ERK)通路来上调HIF-1α的表达。活化的NF-κB也可以增强HIF-1α的活性表达[8]。

2 HIF的靶基因及其对肿瘤的影响

HIF是肿瘤内缺氧的主要调节因子，控制肿瘤中缺氧环境下的病理过程，包括代谢重编程、细胞转移/侵袭、酸碱平衡、血管生成、抑制凋亡、

免疫逃避、干细胞多能性和治疗抵抗等[13-14]，从而影响患者预后。

2.1 HIF对肿瘤的代谢的影响

HIF-1可以通过调节葡萄糖代谢、线粒体活性、脂质代谢和磷酸戊糖途径来进一步调节癌细胞的代谢，使之对缺氧产生适应性反应[15-16]。上百个与这些途径相关的靶基因均受HIF-1的正向调节[7-8]。Warburg[17]认为：肿瘤的产生是由于细胞内糖无氧酵解增强加上氧耗量降低造成的。在缺氧环境下，HIF-1直接上调与糖酵解相关基因的表达，包括葡萄糖转运蛋白1和3(glucose transporter 1 and 3，GLUT1/3)和糖酵解酶己糖激酶-1(hexokinase-1，HK1)、HK2、糖基磷脂酰肌醇(glycosylphosphatidylinositol，GPI)、磷酸果糖激酶(phosphofructokinase，PFKL)、醛缩酶A(aldolase A，ALDOA)、磷酸丙糖异构酶(triosephosphate isomerase，TPI)、甘油醛-3-磷酸脱氢酶(glyceraldehyde-3-phosphate dehydrogenase，GAPDH)、磷酸甘油酸激酶1(phosphoglycerate kinase 1，PGK1)、磷酸甘油酸变位酶1(phosphoglycerate mutase 1，PGAM1)、α-烯醇化酶(enolase 1-alpha，ENO1)、丙酮酸激酶M2(pyruvate kinase M2，PKM2)和乳酸脱氢酶A(lactate dehydrogenase A，LDHA)，为肿瘤的增殖提供能量[15]。Choudhry等[18]认为缺氧会以HIF-1α依赖的方式诱导基因间非编码RNA-p21(intergenic non-coding RNA-p21，lincRNA-p21)的表达，后者与VHL和HIF-1α结合，引起VHL和HIF-1α的解离，从而抑制低氧条件下HIF-1α的蛋白酶体依赖性降解，lincRNA-p21通过调节一系列糖酵解相关基因的表达，从而在Warburg效应中起作用。HIF-1可以调节与线粒体活性相关的基因最大交互因子-1(max interactor-1，MXI-1)、过氧化物酶体增殖物激活受体-γ共激活子-1β(peroxisome proliferator activated receptor-γ coactivator-1β，PGC-1β)、细胞色素C氧化酶亚基4-亚型1和2(cytochrome c oxidase subunit 4-isoform 1 and 2，COX4-1/2)、bcl-2/腺病毒E1B 19-KDA相互作用蛋白3(bcl-2/adenovirus E1B 19-kD interacting protein 3，BNIP3)、bcl-2/E1B 19 kDA-相互作用蛋白3样(bcl-2/E1B 19 kD-interacting protein 3-like，BNIP3L)、NADH脱氢酶(泛醌)1A亚复合物4样2[NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4-like 2，NDUFA4L2]、微小RNA-210(microRNA-210，miR-210)、铁硫簇组装酶-1和2(iron-sulfur cluster assembly enzyme-1 and 2，ISCU-1/2)的表达，来调节癌细胞对缺氧的适应性反应[15-16]。HIF-1可以通过调节与脂质代谢相关的基因脂肪酸结合蛋白3和7(fatty acid-binding protein 3 and 7，FABP3/7)、脂肪分化相关蛋白(adipose differentiation-related protein，ADRP)、中链酰基COA脱氢酶(medium-chain acyl-CoA dehydrogenase，MCAD)和长链酰基COA脱氢酶(long-chain acyl-CoA dehydrogenase，LCAD)，为癌细胞增殖提供脂质。HIF-1还可以调节与丝氨酸生物合成途径相关的基因磷酸甘油酸脱氢酶(phosphoglycerate dehydrogenase，PHGDH)、丝氨酸羟甲基转移酶2(serine hydroxymethyltransferase 2，SHMT2)，为癌细胞增殖提供核苷酸[15]。

2.2 HIF对肿瘤的转移/侵袭的影响

在缺氧环境下，HIF-1会影响肿瘤转移的多个步骤，包括上皮-间质转移(epithelial-mesenchymal transition，EMT)、血管内、外渗和转移前生态位形成[15]。在EMT方面，HIF-1通过诱导Snail，锌指E盒结合同源框1(zinc-finger E- box binding homeobox 1，ZEB1)，Twist，转化生长因子(transforming growth factor，TGF)3和E-钙黏蛋白靶基因的表达而起作用[15,19]。在血管内、外渗方面，HIF-1可以调节基质金属蛋白酶2和9(matrix metalloproteinase 2 and 9，MMP2/9)、纤溶酶原激活剂尿激酶受体(plasminogen activator urokinase receptor，PLAUR)、脯氨酰4-羟化酶亚基A1和2(prolyl 4-hydroxylase subunit alpha 1 and 2，P4HA1/2)、前胶原-赖氨酸,2-氧代戊二酸5-双加氧酶1和2(procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 and 2，PLOD1/2)、L1神经元细胞黏附分子(L1 neuronal cell adhesion molecule，LICAM)、血管生成素样4(angiopoietin-like 4，ANGPTL4)、基质细胞衍生因子-1/CXC趋化因子受体4(stromal cell-derived factor-1/CXC chemokine receptor 4，SDF1/CXCR4)靶基因的表达。在转移前生态位形成方面，HIF-1通过调节赖氨酰化氧(lysyl oxidase，LOX)，LOX2，LOX4，血管内皮生长因子(vascular endothelial growth factor，VEGF)靶基因的表达而起作用。琥珀酸脱氢酶(succinate dehydrogenase，SDH)、延胡索酸水合酶(fumarate hydratase，FH)、异柠檬酸脱氢酶(isocitrate dehydrogenase，IDH)和PKM2等代谢酶也通过HIF-1调节肿瘤转移[15]。激酶激活的长非编码RNA(long-intergenic noncoding RNA for kinase activation，long non-coding RNA，LINK-A lncRNA)可能通过上调HIF1α在骨肉瘤[20]的转移以及三阴性乳腺癌[21]的致癌中起作用。Thomas等[22]发现在膀胱和前列腺癌的临床前模型中，CD24是HIF-1的直接靶点，促进HIF-1驱动的转移。Chiou等[23]研究发现：在胰腺导管

腺癌转移干细胞转移中，B淋巴细胞诱导成熟蛋白-1(B lymphocyte-induced maturation protein-1，BLIMP1)作为HIF-1的新靶点而起作用，它是胰腺导管腺癌转移性干细胞具备转移潜能所必需的转录因子。Lange等[24]研究证明：在鳞状细胞癌中存在一些与肿瘤转移有关的HIF-1α依赖性因子，包括赖氨酰氧化酶样2(lysyl oxidase-like 2，LOXL2)、血小板反应蛋白1(thrombospondin 1，THBS1)、ANGPTL4、二肽基肽酶-4(dipeptidyl peptidase-4，DPP4)、TWIST-相关蛋白1(Twist-related protein 1，TWIST1)、转化生长因子β2(transforming growth factor beta 2，TGF-β2)和CXC趋化因子受体-4(CXC chemokine receptor-4，CXCR4)。这些因素在转移发展的不同阶段起着中心作用。

缺氧环境下，HIF-1还促进脂肪酸结合蛋白4(fatty acid-binding protein 4，FABP4)、3-磷酸肌醇依赖性蛋白激酶1(3-phosphoinositide-dependent protein kinase 1，PDK1)和醛缩酶B(aldolase B，ALDOB)靶基因的表达，有利于癌细胞的远距离生长[13,15]。

2.3 HIF 对肿瘤的酸碱平衡的影响

在缺氧环境下，HIF-1可以通过钠氢泵调节酸碱度，降低细胞外pH值。HIF也可以诱导胞外酶碳酸酐酶IX(carbonic anhydrase IX，CA IX)或胞外酶碳酸酐酶XII(carbonic anhydrase XII，CA XII)将扩散的二氧化碳转化为碳酸，从而降低细胞外pH，有利于肿瘤细胞生长[16]。

2.4 HIF 对肿瘤的血管生成与细胞凋亡的影响

HIF-1α通路与促进肿瘤血管生成、生长、转移和抑制细胞凋亡密切相关[25-30]。HIF-1α的靶基因还包括抗凋亡的促红细胞生成素(erythropoietin，EPO)，血管生成的VEGF，血小板源性生长因子(platelet-derived growth factor，PDGF)、血管生成素-2(angiopoietin-2，ANG2)、内皮素-1(endothelin-1，ET-1)，细胞增殖的表皮生长因子受体(epidermal growth factor receptor，EGFR)等[8]。Luo等[13]认为HIF-1和HIF-2在血管通透性、内皮细胞增殖、基底膜降解、发芽、细胞迁移和导管形成等方面均起重要作用，有利于肿瘤新血管的形成。Lange等[24]用转录测序和基因本体聚类分析的方法，证明了包括HIF-1α和VEGF在内的诸多低氧相关因子在鳞状细胞癌中显著增加，可能有助于肿瘤增殖、血管生成和转移。Zhu等[31]证明在实体肿瘤微环境中，低氧可通过激活HIF-1α/VEGF通路促进细胞生长和抑制细胞凋亡。确定了HIF-1α/VEGF通路与放疗反应的关系及其在肺癌血管生成中的作用。HIF-1α/VEGF通路可能成为肺癌抗血管生成治疗的靶点。Ye等[32]证明了lincRNA-p21可以通过靶向HIF-1α降低VEGF水平，从而抑制细胞增殖和侵袭能力。

HIF-2α也能够促进参与抑制凋亡、肿瘤发生和血管生成的基因激活[33]。在许多血管化肿瘤中，HIF-2α的表达与血管生成因子VEGF和内皮细胞生长因子(endothelial cell growth factor，ECGF)的表达呈正相关，表明HIF-2α在肿瘤血管生成中起着关键作用。在非小细胞肺癌、子宫内膜癌、鳞状细胞头颈部癌、星形细胞瘤、结直肠癌、胆囊癌和乳腺癌等多种肿瘤类型中曾检测到HIF-2α的过度表达[34]。

2.5 HIF 对肿瘤的免疫逃避的影响

人类肿瘤可以下调主要组织相容性复合物(major histocompatibility complex，MHC)I类表达。Hatfield等[35]发现在体内缺氧的肿瘤细胞有较低水平的MHC I类表达。Escors等[36]研究认为，MHC表达减少或丢失的肿瘤细胞能够避免免疫监视，并且不具备足够的免疫原性来激活抗肿瘤免疫反应。Sethumadhavan等[37]发现：在活体及体外培养中肿瘤微环境中的低氧张力通过下调肽-MHC复合物的表面展示所需要的抗原呈递蛋白，如与抗原加工1和2相关的转运蛋白(transporter associated with antigen processing 1 and 2，TAP 1/2)和低分子量蛋白7(low molecular mass protein7，LMP7)，而负向调节HIF依赖性的MHC表达。该研究还发现由于*VHL*基因丢失，HIF-1α的组成性表达的肿瘤细胞MHC I类水平降低；*HIF-1α*基因表达下调的肿瘤细胞MHC I类水平升高。这些发现共同支持了HIF-1α可以使肿瘤细胞难以被识别，从而促进肿瘤逃避的观点。

2.6 HIF 对肿瘤干细胞多能性的影响

HIF在多能干细胞和多能干细胞的维持中起重要作用。造血干细胞(hematopoietic stem cell，HSCs)，胚胎干细胞(embryonic stem cells，ESCs)和诱导多能干细胞(induced pluripotent stem cells，iPSCs)维持多能性均需要HIF。目前已有研究确定HIF在胶质母细胞瘤(glioblastoma stem cells，GSCs)、白血病/淋巴瘤和乳腺癌肿瘤干细胞的维持中具有重要作用[38]。HIF-1α和HIF-2α对于具有高度致瘤性的肿瘤干细胞获得更多的恶性表型起关键作用。在肿瘤干细胞及其分化后代的发

育过程中，HIF-1α和HIF-2α在调控干细胞特性和改变其代谢途径中具有关键作用[39]。在缺氧条件下，HIF-1α与Notch信号相互作用，并通过允许参与干细胞维持和分化的相关基因的表达来促进干细胞的维持。HIF-1α通过重编程葡萄糖代谢使干细胞在缺氧条件下存活。HIF-2α直接参与*Oct4*(Octamer-4)基因的激活。*Oct4*基因是干细胞因子，对维持干细胞非常重要[40]。HIF还可以通过Wnt/β-catenin信号通路在干细胞维持中起作用。HIF促进细胞质中β-catenin水平的升高，并在细胞核中易位。在细胞核中，β-catenin 与T细胞因子/淋巴增强因子(T cell factor/lymphoid enhancer factor，TCF/LEF)结合并促进包括*c-Myc*基因在内的参与干细胞维持的靶基因的转录[41]。

2.7 HIF 对肿瘤的治疗及耐药的影响

Wiedmann等[42]认为，在分子水平上，HIF抑制剂chetomin可以破坏P300的CH1结构域，阻止其对HIF的帮助作用，从而减弱缺氧诱导转录。全身注射该HIF抑制剂可以抑制肿瘤内缺氧诱导转录，抑制肿瘤生长。HIF-1在现在已被证实成为新型抗肿瘤药物的作用靶点[14,43]。Renfrow等[44]证实了HIF2α的表达是治疗胶质瘤的一个特异性的药物新靶点。有临床试验正在研究阻断HIF-2α和HIF-1β异二聚化的一种HIF-2抑制剂是否能够治疗透明细胞肾细胞癌[45]。研究[46]表明：HIF-2α的表达与肿瘤患者预后较差相关。HIF-1α或HIF-2α的过度表达与肿瘤的进展密切相关[47]。*HIF-1α*，*HIF-2α*基因的破坏直接抑制了肿瘤细胞的增殖。

HIF-1诱导的血管内皮生长因子A(vascular endothelial growth factor A，VEGFA)和碱性成纤维细胞生长因子(basic fibroblast growth factor，bFGF)可以促进内皮细胞的存活，从而降低肿瘤对放射的敏感性。HIF-1是抗放射治疗中不可缺少的因子[13]。

低氧诱导转录因子HIF-1和HIF-2与多种肿瘤类型的癌干细胞转移和耐药性有关。有研究确定了与癌干细胞表型相关的化学药物治疗抵抗中，HIF起促进作用[48]。

2.8 HIF 对肿瘤患者预后的影响

有荟萃分析分别研究了HIF-1α在食管癌[49]、口腔鳞癌[50]、肺癌[51]、胶质瘤[52]、鼻咽癌[53]等肿瘤中的预后意义，这些研究均表明HIF-1α的表达与预后不良相关。Xie等[53]研究认为HIF-1α与较高的淋巴结转移率和较晚期的肿瘤分期有关，但与局部复发或远处转移无关。

3 胃肠道间质瘤概况

1983年，Mazur等[54]首次描述了GIST，它是胃肠道最常见的间叶组织肿瘤[1-2]，约占软组织肉瘤的8%[55]。

20世纪90年代，人们发现GIST来源于肠壁上的Cajal间质细胞(interstitial cells of Cajal，ICCS)[54,56-57]，后者是位于肠神经细胞和胃肠道平滑肌之间的起搏器细胞，可以调节肠道运动。GIST的发病率为每年10~15/100万[58-59]。GIST可以出现在包括新生儿在内的所有年龄段中，中位数为65岁，>70岁时患病率和发病率最高[58]，不到10%的GIST患者年龄<40岁[60]。GIST按病理组织形态主要分为梭形细胞和上皮样细胞类型[61]。用于鉴别诊断GIST与其它肿瘤的免疫组织化学指标有CD117(c-KIT)，Desmin，S100，α-SMA，CD34，DOG1，STAT6，β-catenin，ALK，SDHB，Ki-67等[62]。CT[63-64]，MRI[65-66]，内镜超声[67]，PET-CT[68]等检查在GIST的诊断及预测靶向治疗效果中也起较为重要的作用。

4 HIF 与 GIST 的关系

基因突变检测[69-70]结果表明：85%~90%的GIST存在c-KIT或血小板源性生长因子受体α(platelet-derived growth factor receptor alpha，*PDGFR-α*)基因突变。其余GIST称为野生型GIST，分为琥珀酸脱氢酶复合物亚基B(succinate dehydrogenase complex subunits B，SDHB)阴性与SDHB阳性两类。近年来，SDHB阴性的GIST得到越来越多的关注。在SDHB阴性的野生型GIST中，*SDHB*基因的突变抑制了HIF-α脯氨酰羟化酶(prolyl hydroxylases domain，PHDs)的活性，导致HIF-1/2α羟基化不足，HIF-1/2α变的更加稳定，HIF-1α与HIF1β二聚形成完整的HIF，HIF与缺氧反应元件HRE的结合，从而使包括胰岛素样生长因子(insulin-like growth factor，IGF)和VEGF在内的下游低氧相关基因上调，导致肿瘤发生[71-75]。故HIF-α参与了SDH缺陷型的野生型胃肠道间质瘤的发病。

另外，有研究[76-78]认为，在低氧环境下，ET-1可以增加HIF-1α的稳定性，HIF-1α可促进*VEGF*基因上调，在GIST中促进肿瘤血管发生以及血道转移、对抗凋亡，对GIST预后情况的评估和分子

靶向治疗的研究有提示作用。张天彪等[78]认为：HIF-1α的水平与GIST的恶性程度分级、浸润、转移程度关系密切。HIF-1α，一氧化氮合酶2(nitric oxide synthase 2，NOS2)与VEGF三者表达呈正相关，共同促进GIST的发展。Bai等[79]研究发现叉头框蛋白M1(forkhead box M1，FoxM1)对GIST的细胞增殖、侵袭和转移起明显促进作用。在缺氧条件下，HIF-1α和HIF-2α上调Foxm1。同时下调HIF-1α和HIF-2α的水平时，可以抑制GIST肿瘤生长。故HIF-α可能是GIST患者对低氧适应性反应的重要调节因子。HIF-1α/HIF-2α-Foxm1轴对预防和治疗GIST有值得肯定的意义。Tella等[80]认为HIF-2α拮抗剂对HIF二聚体有抑制作用，从而抑制了包括间质瘤在内的多种肿瘤的发生。Chen等[81]研究认为，HIF-1α的表达率与肿瘤侵袭性风险呈正比，与复发/远处转移的发生率呈正比。HIF-1α可以成为预测肿瘤危险性行为的辅助指标，它可能是GIST的独立预测参考因子。

甲磺酸伊马替尼是治疗GIST的一线靶向药物，也是治疗实体肿瘤的最为广泛应用的药物。但是，GIST在伊马替尼治疗后耐药较为常见，是GIST治疗的一大难题[82]。Yan等[83]认为，HIF-1途径是伊马替尼耐药的一种假定介质。某些lncRNAs可以调节HIF-1信号通路。LncRNAs可能在GIST的发生和伊马替尼的继发耐药中起促进的作用。

目前，在伊马替尼耐药或不耐受的情况下，用二线治疗药物——多靶向受体酪氨酸激酶(receptor tyrosine kinases，RTK)抑制剂舒尼替尼治疗后，可使患者获得约8个月的中位无进展生存期(progression-free survival，PFS)[84]。在常氧或缺氧条件，舒尼替尼可以通过降低HIF-1α mRNA表达及降解HIF-1α蛋白本身来下调HIF-1α蛋白的水平[85]。

另外，Hu等[86]研究发现赖氨酸特异性去甲基化酶4D(lysine-specific demethylase 4D，KDM4D)/HIF-1β/VEGFA作为新的调控途径参与GIST的进展，它可能成为GIST患者潜在的治疗靶点。

5 结语

在缺氧条件下，HIF通过上调大量参与代谢重编、细胞侵袭、酸碱平衡、血管生成、抑制凋亡、免疫逃避、干细胞多能性和治疗抵抗等相关靶基因的活性，协助多种肿瘤生长并促进其进一步发展。HIF的持续激活或过度表达与许多癌症的进展具有直接正相关的关系，对患者的预后有不良影响。抑制HIF的活性表达已成为新型肿瘤靶向药物的治疗目的。关于HIF在GIST中作用的研究尚在较不完善阶段。目前已有报道[76-77]指出HIF-1α可以评估胃肠道间质瘤患者的预后。但HIF在GIST中的表达机制有待进一步研究，HIF是否可以作为GIST的肿瘤标志物应用还未被明确，还需大量后期试验来进一步了解它们之间的关系。

参考文献

1. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour[J]. Lancet, 2013, 382(9896): 973-983.
2. Schmieder M, Henne-Bruns D, Mayer B, et al. Comparison of different risk classification systems in 558 patients with gastrointestinal stromal tumors after R0-resection[J]. Front Pharmacol, 2016, 7: 504.
3. Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1[J]. J Biol Chem, 1995, 270(3): 1230-1237.
4. Gu YZ, Moran SM, Hogenesch JB, et al. Molecular characterization and chromosomal localization of a third alpha-class hypoxia inducible factor subunit, HIF3alpha[J]. Gene Expression, 1998, 7(3): 205-213.
5. Semenza GL. A compendium of proteins that interact with HIF-1α[J]. Exp Cell Res, 2017, 356(2): 128-135.
6. Suzuki N, Gradin K, Poellinger L, et al. Regulation of hypoxia-inducible gene expression after HIF activation[J]. Exp Cell Res, 2017, 356(2): 182-186.
7. Bhattarai D, Xu XZ, Lee K. Hypoxia-inducible factor-1 (HIF-1) inhibitors from the last decade (2007 to 2016): A "structure-activity relationship" perspective[J]. Med Res Rev, 2018, 38(4): 1404-1442.
8. Ajith TA. Current insights and future perspectives of hypoxia-inducible factor-targeted therapy in cancer[J]. J Basic Clin Physiol Pharmacol, 2018, 30(1): 11-18.
9. Renfrow JJ, Soike MH, Debinski W, et al. Hypoxia-inducible factor 2α: a novel target in gliomas[J]. Future Med Chem, 2018, 10(18): 2227-2236.
10. Iommarini L, Porcelli AM, Gasparre G, et al. Non-canonical mechanisms regulating hypoxia-inducible factor 1 alpha in cancer[J]. Front Oncol, 2017, 7: 286.
11. Gu YZ, Moran SM, Hogenesch JB, et al. Molecular characterization and chromosomal localization of a third alpha-class hypoxia inducible factor subunit, HIF3alpha[J]. Gene Expr, 1998, 7(3): 205-213.
12. Koyasu S, Kobayashi M, Goto Y, et al. Regulatory mechanisms of hypoxia-inducible factor 1 activity: two decades of knowledge[J]. Cancer Sci, 2018, 109(3): 560-571.
13. Luo W, Wang Y. Hypoxia mediates tumor malignancy and therapy resistance[J]. Adv Exp Med Biol, 2019, 1136: 1-18.
14. Li J, Xi WL, Li XF, et al. Advances in inhibition of protein-protein interactions targeting hypoxia-inducible factor-1 for cancer therapy[J].

Bioorg Med Chem, 2019, 27(7): 1145-1158.

15. Zhang T, Suo CX, Zheng CY, et al. Hypoxia and metabolism in metastasis[J]. Adv Exp Med Biol, 2019, 1136: 87-95.
16. Singh D, Arora R, Kaur P, et al. Overexpression of hypoxia-inducible factor and metabolic pathways: possible targets of cancer[J]. Cell Biosci, 2017, 7: 62.
17. Warburg O. On the origin of cancer cells[J]. Science, 1956, 123(3191): 309-314.
18. Choudhry H, Harris AL. Advances in hypoxia-inducible factor biology[J]. Cell Metab, 2018, 27(2): 281-298.
19. Qian J, Rankin EB. Hypoxia-induced phenotypes that mediate tumor heterogeneity[J]. Adv Exp Med Biol, 2019, 1136: 43-55.
20. Zhao B, Liu K, Cai L. LINK-A lncRNA functions in the metastasis of osteosarcoma by upregulating HIF1α[J]. Oncol Lett, 2019, 17(6): 5005-5011.
21. Lin A, Li C, Xing Z, et al. The LINK-A lncRNA activates normoxic HIF1α signalling in triple-negative breast cancer[J]. Nat Cell Biol, 2016, 18(2): 213-224.
22. Thomas S, Harding MA, Smith SC, et al. CD24 is an effector of HIF-1-driven primary tumor growth and metastasis[J]. Cancer Res, 2012, 72(21): 5600-5612.
23. Chiou SH, Risca VI, Wang GX, et al. BLIMP1 induces transient metastatic heterogeneity in pancreatic cancer[J]. Cancer Discov, 2017, 7(10): 1184-1199.
24. Lange CAK, Lehnert P, Boneva SK, et al. Increased expression of hypoxia-inducible factor-1 alpha and its impact on transcriptional changes and prognosis in malignant tumours of the ocular adnexa[J]. Eye (Lond), 2018, 32(11): 1772-1782.
25. Sun Y, Wang H, Liu M, et al. Resveratrol abrogates the effects of hypoxia on cell proliferation, invasion and EMT in osteosarcoma cells through downregulation of the HIF-1α protein[J]. Mol Med Rep, 2015, 11(3): 1975-1981.
26. Chang J, Erler J. Hypoxia-mediated metastasis[J]. Adv Exp Med Biol, 2014, 772: 55-81.
27. Xiang L, Gilkes DM, Chaturvedi P, et al. Ganetespib blocks HIF-1 activity and inhibits tumor growth, vascularization, stem cell maintenance, invasion, and metastasis in orthotopic mouse models of triple-negative breast cancer[J]. J Mol Med (Berl), 2014, 92(2): 151-164.
28. Guan G, Zhang Y, Lu Y, et al. The HIF-1α/CXCR4 pathway supports hypoxia-induced metastasis of human osteosarcoma cells[J]. Cancer Lett, 2015, 357(1): 254-264.
29. Spirina LV, Usynin YA, Yurmazov ZA, et al. Transcription factors NF-kB, HIF-1, HIF-2, growth factor VEGF, VEGFR2 and carboanhydrase IX mRNA and protein level in the development of kidney cancer metastasis[J]. Mol Biol (Mosk), 2017, 51(2): 372-377.
30. Zhang B, Li YL, Zhao JL, et al. Hypoxia-inducible factor-1 promotes cancer progression through activating AKT/Cyclin D1 signaling pathway in osteosarcoma[J]. Biomed Pharmacother, 2018, 105: 1-9.
31. Zhu H, Zhang S. Hypoxia inducible factor-1α/vascular endothelial growth factor signaling activation correlates with response to radiotherapy and its inhibition reduces hypoxia-induced angiogenesis in lung cancer[J]. J Cell Biochem, 2018, 119(9): 7707-7718.
32. Ye Y, Peng Y, Li Y, et al. Effect of lincRNA-p21 targeting HIF-1α on biological functions of liver cancer cells[J]. Oncol Lett, 2019, 17(6): 4964-4968.
33. Vicha A, Taieb D, Pacak K. Current views on cell metabolism in SDHx-related pheochromocytoma and paraganglioma[J]. Endocr Relat Cancer, 2014, 21(3): R261-R277.
34. Befani C, Liakos P. The role of hypoxia-inducible factor-2 alpha in angiogenesis[J]. J Cell Physiol, 2018, 233(12): 9087-9098.
35. Hatfield SM, Kjaergaard J, Lukashev D, et al. Systemic oxygenation weakens the hypoxia and hypoxia inducible factor 1α-dependent and extracellular adenosine-mediated tumor protection[J]. J Mol Med (Berl), 2014, 92(12): 1283-1292.
36. Escors D. Tumour immunogenicity, antigen presentation, and immunological barriers in cancer immunotherapy[J]. New J Sci, 2014, 2014: 734515.
37. Sethumadhavan S, Silva M, Philbrook P, et al. Hypoxia and hypoxia-inducible factor (HIF) downregulate antigen-presenting MHC class I molecules limiting tumor cell recognition by T cells[J]. PLoS One, 2017, 12(11): e0187314.
38. Semenza GL. Dynamic regulation of stem cell specification and maintenance by hypoxia-inducible factors[J]. Mol Aspects Med, 2016, 47-48: 15-23.
39. Mimeault M, Batra SK. Hypoxia-inducing factors as master regulators of stemness properties and altered metabolism of cancer- and metastasis-initiating cells[J]. J Cell Mol Med, 2013, 17(1): 30-54.
40. Covello KL, Kehler J, Yu H, et al. HIF-2alpha regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth[J]. Genes Dev, 2006, 20(5): 557-570.
41. Vadde R, Vemula S, Jinka R, et al. Role of hypoxia-inducible factors (HIF) in the maintenance of stemness and malignancy of colorectal cancer[J]. Crit Rev Oncol Hematol, 2017, 113: 22-27.
42. Wiedmann MW, Caca K. Molecularly targeted therapy for gastrointestinal cancer[J]. Curr Cancer Drug Targets, 2005, 5(3): 171-193.
43. Zhang LH, Zhang ZH, Li MY, et al. Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives[J]. Bioorg Med Chem Lett, 2019, 29(12): 1440-1445.
44. Renfrow JJ, Soike MH, Debinski W, et al. Hypoxia-inducible factor 2α: a novel target in gliomas[J]. Future Med Chem, 2018, 10(18): 2227-2236.
45. Courtney KD, Infante JR, Lam ET, et al. Phase I dose-escalation trial

of PT2385, a first-in-class hypoxia-inducible factor-2α antagonist in patients with previously treated advanced clear cell renal cell carcinoma[J]. J Clin Oncol, 2018, 36(9): 867-874.

46. Moreno Roig E, Yaromina A, Houben R, et al. Prognostic role of hypoxia-inducible factor-2α tumor cell expression in cancer patients: a Meta-analysis[J]. Front Oncol, 2018, 8: 224.
47. Burkitt K, Chun SY, Dang DT, et al. Targeting both HIF-1 and HIF-2 in human colon cancer cells improves tumor response to sunitinib treatment[J]. Mol Cancer Ther, 2009, 8(5): 1148-1156.
48. Qian J, Rankin EB. Hypoxia-induced phenotypes that mediate tumor heterogeneity[J]. Adv Exp Med Biol, 2019, 1136: 43-55.
49. Jing SW, Wang J, Xu Q. Expression of hypoxia inducible factor 1 alpha and its clinical significance in esophageal carcinoma: A meta-analysis[J]. Tumour Biol, 2017, 39(7): 1010428317717983.
50. Zhou J, Huang S, Wang L, et al. Clinical and prognostic significance of HIF-1α overexpression in oral squamous cell carcinoma: a Meta-analysis[J]. World J Surg Oncol, 2017, 15(1): 104.
51. Yang SL, Ren QG, Wen L, et al. Clinicopathological and prognostic significance of hypoxia-inducible factor-1 alpha in lung cancer: a systematic review with Meta-analysis[J]. J Huazhong Univ Sci Technolog Med Sci, 2016, 36(3): 321-327.
52. Liu Q, Cao P. Clinical and prognostic significance of HIF-1alpha in glioma patients: a meta-analysis[J]. Int J Clin Exp Med, 2015, 8(12): 22073-22083.
53. Xie W, Liu L, He H, et al. Prognostic value of hypoxia-inducible factor-1 alpha in nasopharyngeal carcinoma: a meta-analysis[J].Int J Biol Markers, 2018, Epub ahead of print.
54. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis[J]. Am J Surg Pathol, 1983, 7(6): 507-519.
55. Brennan MF, Antonescu CR, Moraco N, et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma[J].Ann Surg, 2014, 260(3): 416-421.
56. Barnett CM, Corless CL, Heinrich MC. Gastrointestinal stromal tumors: molecular markers and genetic subtypes[J]. Hematol Oncol Clin North Am, 2013, 27(5): 871-888.
57. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor[J]. J Surg Oncol, 2011, 104(8): 865-873.
58. Søreide K, Sandvik OM, Søreide JA, et al.Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies[J]. Cancer Epidemiol, 2016, 40: 39-46.
59. Yang ML, Wang JC, Zou WB, et al. Clinicopathological characteristics and prognostic factors of gastrointestinal stromal tumors in Chinese patients[J]. Oncol Lett, 2018, 16(4): 4905-4914.
60. Kramer K, Knippschild U, Mayer B, et al. Impact of age and gender on tumor related prognosis in gastrointestinal stromal tumors (GIST)[J]. BMC Cancer, 2015, 15: 57.
61. Hirota S. Differential diagnosis of gastrointestinal stromal tumor by histopathology and immunohistochemistry[J]. Transl Gastroenterol Hepatol, 2018, 3: 27.
62. Chen Q, Li R, Zhang ZG, et al. Oncogene mutational analysis in Chinese gastrointestinal stromal tumor patients[J].Onco Targets Ther, 2018, 11: 2279-2286.
63. Li H, Ren G, Cai R, et al. A correlation research of Ki67 index, CT features, and risk stratification in gastrointestinal stromal tumor[J]. Cancer Med, 2018, 7(9): 4467-4474.
64. Valsangkar N, Sehdev A, Misra S, et al. Current management of gastrointestinal stromal tumors: Surgery, current biomarkers, mutations, and therapy[J]. Surgery, 2015, 158(5): 1149-1164.
65. Bano S, Puri SK, Upreti L, et al. Gastrointestinal stromal tumors (GISTs): an imaging perspective[J]. Jpn J Radiol, 2012, 30(2): 105-115.
66. Tang L, Li J, Li ZY, et al. MRI in predicting the response of gastrointestinal stromal tumor to targeted therapy:a patient-based multi-parameter study[J]. BMC Cancer, 2018, 18(1): 811.
67. Chen TH, Hsu CM, Chu YY, et al. Association of endoscopic ultrasonographic parameters and gastrointestinal stromal tumors (GISTs): can endoscopic ultrasonography be used to screen gastric GISTs for potential malignancy?[J]. Scand J Gastroenterol, 2016, 51(3): 374-377.
68. Yoshikawa K, Shimada M, Kurita N, et al. Efficacy of PET-CT for predicting the malignant potential of gastrointestinal stromal tumors[J]. Surg Today, 2013, 43(10): 1162-1167.
69. Celestino R, Lima J, Faustino A, et al. Molecular alterations and expression of succinate dehydrogenase complex in wild-type KIT/PDGFRA/BRAF gastrointestinal stromal tumors[J]. Eur J Hum Genet, 2013, 21(5): 503-510.
70. Boikos SA, Pappo AS, Killian JK, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the national institutes of health gastrointestinal stromal tumor clinic[J]. JAMA Oncol, 2016, 2(7): 922-928.
71. Vicha A, Taieb D, Pacak K. Current views on cell metabolism in SDHx-related pheochromocytoma and paraganglioma[J]. Endocr Relat Cancer, 2014, 21(3): R261-R277.
72. Wang YM, Gu ML, Ji F. Succinate dehydrogenase-deficient gastrointestinal stromal tumors[J]. World J Gastroenterol, 2015, 21(8): 2303-2314.
73. 姜铨, 童汉兴, 陆维祺. 琥珀酸脱氢酶缺陷型胃肠间质瘤研究进展[J]. 中国实用外科杂志, 2016, 36(3): 344-347.
JIANG Quan, TONG Hanxing, LU Weiqi. Research progress of succinate dehydrogenase-deficient gastrointestinal stromal tumors[J]. Chinese Journal of Practical Surgery, 2016, 36(3): 344-347.
74. Huss S, Elges S, Trautmann M, et al. Classification of KIT/PDGFRA wild-type gastrointestinal stromal tumors: implications for therapy[J].

Expert Rev Anticancer Ther, 2015, 15(6): 623-628.

75. Niinuma T, Suzuki H, Sugai T. Molecular characterization and pathogenesis of gastrointestinal stromal tumor[J]. Transl Gastroenterol Hepatol, 2018, 3: 2.
76. 艾晓辉, 唐利立, 廖国庆, 等. 缺氧诱导因子1a在胃肠道间质瘤中的表达及其与血管内皮细胞生长因子的相关性[J]. 中国肿瘤临床与康复, 2014, 21(4): 385-388.
AI Xiaohui, TANG Lili, LIAO Guoqing. Expression and significance of HIF-1a and VEGF in gastrointestinal stromal tumors[J]. Chinese Journal of Clinical Oncology and Rehabilitation, 2014, 21(4): 385-388.
77. 艾晓辉, 刘蔚东, 谢钢, 等. 缺氧诱导因子1α和血管内皮素1及血管内皮生长因子在胃肠道间质瘤中的表达及意义[J]. 中华消化外科杂志, 2013, 12(4): 290-293.
AI Xiaohui, LIU Weidong, XIE Gang. Expression and significance of hypoxia inducible factor-1a and endothelin-1 and vascular endothelial growth factor in gastrointestinal stromal tumor[J]. Chinese Journal of Digestive Surgery, 2013, 12(4): 290-293.
78. 张天彪, 赵滢, 赵毅, 等. 胃肠道间质瘤促血管生成相关因子的检测及其意义[J]. 中国医科大学学报, 2010, 39(5): 359-361.
ZHANG Tianbiao, ZHAO Ying, ZHAO Yi. Detection and significance of angiogenic factors in gastrointestinal stromal tumor[J]. Journal of China Medical University, 2010, 39(5): 359-361.
79. Bai C, Liu X, Qiu C, et al. FoxM1 is regulated by both HIF-1α and HIF-2α and contributes to gastrointestinal stromal tumor progression[J]. Gastric Cancer, 2019, 22(1): 91-103.
80. Tella SH, David Taïeb, Pacak K. HIF-2alpha: Achilles' heel of pseudohypoxic subtype paraganglioma and other related conditions[J]. Eur J Cancer, 2017, 86: 1-4.
81. Chen WT, Huang CJ, Wu MT, et al. Hypoxia-inducible factor-1α is associated with risk of aggressive behavior and tumor angiogenesis in gastrointestinal stromal tumor[J]. Jpn J Clin Oncol, 2005, 35(4): 207-213.
82. Zhou Y, Chen J, Weng X, et al. Establishment of a GIST-T1 gastrointestinal stromal tumour cell line resistant to imatinib mesylate[J]. Oncol Lett, 2018, 15(5): 7589-7594.
83. Yan J, Chen D, Chen X, et al. Identification of imatinib-resistant long non-coding RNAs in gastrointestinal stromal tumors[J]. Oncol Lett, 2019, 17(2): 2283-2295.
84. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib[J]. Cancer, 2015, 121(9): 1405-1413.
85. Lai XM, Liu SY, Tsai YT, et al. HAF mediates the evasive resistance of anti-angiogenesis TKI through disrupting HIF-1α and HIF-2α balance in renal cell carcinoma[J]. Oncotarget, 2017, 8(30): 49713-49724.
86. Hu F, Li H, Liu L, et al. Histone demethylase KDM4D promotes gastrointestinal stromal tumor progression through HIF1β/VEGFA signalling[J]. Mol Cancer, 2018, 17(1): 107.

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