四川大学学报（医学版） 2024，55（6）：1436－1445
J Sichuan Univ（Med Sci）

在线全文

• 高原医学 •

‖ 文献综述 ‖

高原缺氧应激与肝细胞癌研究进展*

梁钰博[1]，李凌娟[2]，刘柏杨[2]，高 洁[2]，陈星明[1]，李 进[1]，柯 阳[1△]，陈勇彬[2,3△]

1. 昆明医科大学第二附属医院 肝胆胰外科（昆明 650101）；2. 郑州大学第一附属医院（郑州 450052）；
3. 中国科学院昆明动物研究所（昆明 650223）

【摘要】 肝细胞癌是全球常见且致死率高的恶性肿瘤之一，在我国的疾病负担尤为严重。世居高原地区的居民肝细胞癌的发病率和死亡率相较平原地区居民低，这可能归因于世居高原地区居民对缺氧应激产生适应性进化。高原缺氧应激与肝细胞癌发生发展相关，缺氧应激可通过调控肝癌细胞的衰老、死亡、代谢、肿瘤微环境和肿瘤免疫等方面参与肝细胞癌的发生发展。此外，最新临床证据显示高原缺氧环境对肝细胞癌切除术后的肝再生也具有重要影响。然而，关于高原缺氧应激在肝细胞癌的发展中是起促进作用还是抑制作用，目前仍存在争议。本文从世居高原地区居民对高原缺氧应激的适应性进化对肝细胞癌发生发展的影响，缺氧对肝癌细胞衰老、死亡、肿瘤微环境、肿瘤代谢和肿瘤免疫的影响，高原缺氧应激对肝细胞癌切除术后肝再生的影响三个方面讨论氧浓度，细胞背景和组织微环境的不同对肝细胞癌发生发展的影响，以及研究高原缺氧应激机制在优化肝细胞癌治疗中的潜在应用。

【关键词】 高原 缺氧应激 肝细胞癌 发生发展 肝再生 综述

Research Advances in the Roles of High-Altitude Hypoxic Stress in Hepatocellular Carcinoma

LIANG Yubo[1], *LI Lingjuan*[2], *LIU Baiyang*[2], *GAO Jie*[2], *CHEN Xingming*[1], *LI Jin*[1], *KE Yang*[1△], *CHEN Yongbin*[2,3△]. 1. *Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University*, Kunming 650101, China; 2. *The First Affiliated Hospital of Zhengzhou University*, Zhengzhou 450052, China; 3. *Kunming Institute of Zoology, CAS*, Kunming 650223, China

△ Corresponding author, KE Yang, E-mail: keyang@kmmu.edu.cn; CHEN Yongbin, E-mail: ybchen@mail.kiz.ac.cn

【**Abstract**】 Hepatocellular carcinoma (HCC), one of the most prevalent malignant tumors causing the highest mortality globally, imposes an especially heavy burden of disease in China. Individuals living in high-altitude areas have a lower incidence of and mortality resulting from HCC compared with those in low-altitude regions do, potentially due to adaptive evolution in responses to hypoxic stress. Notably, high-altitude hypoxic stress is associated with the development and progression of HCC. Hypoxic stress may be involved in the development and progression of HCC by modulating the senescence, apoptosis, metabolism, tumor microenvironment, and tumor immunity of HCC cells. Additionally, the latest clinical findings indicate that high-altitude hypoxic environment has a significant impact on liver regeneration after HCC resection surgery. However, there is still a debate going on regarding whether high-altitude hypoxic stress promotes or inhibits the progression of HCC. This review covers three main aspects, the impact of adaptive evolution to high-altitude hypoxic stress on the development and progression of HCC in long-term residents of high-altitude areas, the effects of high-altitude hypoxic stress on the senescence, apoptosis, metabolism, tumor microenvironment, tumor metabolism, and tumor immunity of HCC cells, and the effect of high-altitude hypoxic stress on liver regeneration after HCC resection. We discussed the effect of changes in oxygen concentrations, cellular context, and tissue microenvironment on HCC development and progression. Moreover, we highlighted the potential for using research findings on mechanisms underlying high-altitude hypoxic stress to optimize HCC treatment strategies.

【**Key words**】 High altitude Hypoxic stress Hepatocellular carcinoma Development and progression Liver regeneration Review

原发性肝癌在全球癌症发病率中列第6位，死亡率列第3位[1-2]。原发性肝癌的病理类型中，肝细胞癌（hepatocellular carcinoma, HCC）占85% ~ 90%，故本文聚焦于HCC及高原医学主题进行综述。依据生物在不同海拔的反应，医学上通常将海拔3 000 m以上地区称为高原地区[3]。高原环境下，人体处于缺氧状态，氧分压降低，人体在海拔5800 m时的动脉血氧分压几乎与处于海平面时的静脉血氧分压相等[4]。高原缺氧环境与HCC高代谢、高增殖所造成的缺氧微环境相似，且高原缺氧应激与HCC

* 国家自然科学基金（No. 82103173、No. 82460461），云南省中青学术和技术带头人后备人才项目（No. 202205AC160063）和云南省基础研究计划优秀青年基金（No. 202401AW070003）资助

△ 通信作者，柯阳，E-mail：keyang@kmmu.edu.cn；陈勇彬，E-mail：ybchen@mail.kiz.ac.cn

出版日期：2024-11-20

发生发展及疾病转归有重要联系，为研究缺氧应激提供了独特的自然条件。本文旨在梳理近年来国内外关于高原和平原地区人群对缺氧应激的耐受性，以及对HCC发生发展的影响；深入讨论高原缺氧如何造成肿瘤细胞衰老死亡、肿瘤代谢、肿瘤微环境、肿瘤免疫等应激反应；以及高原缺氧应激对HCC切除术后肝再生的影响，从而影响HCC的转归，以期为未来HCC的诊治研究提供新思路。

1　高原和平原地区人群对缺氧应激耐受性

高原环境具有低氧、低气压、高寒、强紫外线照射等特点，其中缺氧应激是最常见的高原应激类型之一[5]。缺氧应激指缺氧状态下，细胞无法有效地通过常规氧气依赖性代谢途径有效产生能量，进而触发一系列的适应反应和变化[6-8]。从低海拔地区急进高原地区的人群可面临高原缺氧应激反应，易引起急性高原肺水肿、高原脑水肿、高原红细胞增多症、高原肺动脉高压等多种急慢性高原病[5]。相较于世居低海拔地区的人群，世居高原地区的人群对高原环境发生了从基因到生理性状上的整体适应性进化[9]。研究表明，生活在海拔3 000 m以上的藏族人群比平原地区人群有着更强的摄氧能力与心输出量[10]，同一做功下消耗更少的氧气[11]，且有着更平衡稳定的氧自由基代谢[3]，说明世居高原人群对于缺氧环境有着更强的耐受性。一项针对世居高原的藏族人、安第斯人、埃塞俄比亚人、夏尔巴人等人群与平原人群的多组学研究发现，缺氧诱导因子(hypoxia-inducible factor, HIF)调控下的氧感应、红细胞生成、血管生成、氧化还原稳态调节等过程的相关基因表达水平存在显著差异，并通过蛋白组学鉴定出血红蛋白β亚基(HBB)、转铁蛋白(TF)、血管生成素样蛋白4(ANGPTL4)、细胞分裂周期因子42(CDC42)、维生素D结合蛋白(DBP)、胰岛素样生长因子结合蛋白1(IGFBP1)、胰岛素样生长因子结合蛋白2(IGFBP2)七个与基因组学差异一致的蛋白，可能促进了世居高原人群对其所处环境的适应[12]。

流行病学调查表明高海拔人群中HCC、肺癌、乳腺癌、结直肠癌等常见肿瘤发病率和死亡率显著低于低海拔人群[13-14]，这可能与世居高原人群对缺氧的耐受性和适应性进化导致应激反应与平原人群不同有关[15-16]。例如，促癌基因*YTHDF1*在HCC、肺癌、结直肠癌等多种低氧实体瘤中高表达，与不良的临床预后相关，但其在高原哺乳动物缺氧适应性进化中选择性低表达[15]，解析这种高原缺氧适应性进化的分子机制有望为低氧实体瘤治疗靶点的选择提供新的见解。另外，我们推测：世居高原地区人群的免疫系统较平原地区人群对低氧环境有更好适应，可在实体瘤低氧微环境中发挥更好的抗肿瘤作用，也可能是造成以上流行病学差异重要原因之一，但该推论及潜在的驱动分子机制尚待进一步研究。

2　缺氧应激与HCC衰老和新型死亡

缺氧引起HCC生长过程中的多种应激反应，包括既往已大量报道的HCC细胞的增殖、自噬、凋亡和坏死[17-24]，近年来研究发现缺氧还会影响HCC细胞的衰老和新的死亡形式，如铁死亡(ferroptosis)、铜死亡(cuproptosis)[25-33](图1)。

2.1　缺氧应激与HCC衰老

世居高原的人群和其他哺乳动物有着更长寿命，这可能与长期缺氧应激下衰老相关基因的进化有关[34]。对

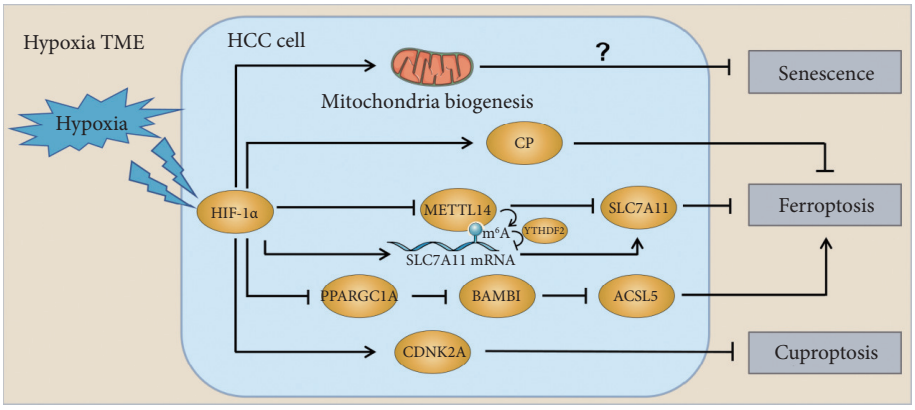


图 1　缺氧应激与HCC衰老、铁死亡和铜死亡

Fig 1　The effect of hypoxia on senescence, ferroptosis, and cuproptosis in HCC

TME: tumor microenvironment; ACSL5: acyl-CoA synthetase long chain family member 5; BAMBI: BMP and activin membrane bound inhibitor; CDNK2A: cyclin dependent kinase inhibitor 2A; CP: ceruloplasmin; HCC: hepatocellular carcinoma; HIF-1α: hypoxia inducible factor 1 subunit alpha; m6A: N6-methyladenosine; METTL14: methyltransferase- like 14; PPARGC1A: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SLC7A11: solute carrier family 7 member 11; TME: tumor microenvironment; YTHDF2: YTH N6-methyladenosine RNA binding protein 2.

于肿瘤而言，衰老被视为一种抑瘤机制[35-36]，另外，免疫系统对衰老过程的监视在抑制HCC发生过程中具有重要意义[37]。研究发现，在多种肿瘤中，缺氧可以激活HIF-1α，以维持和增强线粒体的生物合成，从而阻止肿瘤细胞的衰老[25]。HIF-1α在HCC发生发展中具有重要作用[26]，缺氧环境可能通过激活HIF-1α抑制HCC的衰老过程，导致HCC进展[27]。

2.2 缺氧应激与HCC铁死亡

铁死亡是一种细胞内铁离子依赖性、脂质过氧化驱动的死亡形式，在索拉非尼、仑伐替尼和抗PD-1/PD-L1药物治疗HCC的过程中起着关键作用[28, 38-39]。一项高通量预测模型研究发现，铁死亡相关基因(*FRGs*)联合缺氧相关基因(*HRGs*)构建的预后模型能预测HCC患者预后，且缺氧状态和铁死亡抑制状态是HCC患者预后不良的关键因素[40]。在机制上，HIF-1α通过抑制METTL14通路，抑制*SLC7A11* mRNA m6A甲基化修饰，减少YTHDF2依赖的SLC7A11降解，进而抑制HCC铁死亡，导致HCC的恶性进展[29]；缺氧还通过PPARGC1A/BAMBI/ACSL5轴抑制肝癌细胞铁死亡，导致仑伐替尼治疗耐药[28]。此外，HIF-1α的活化还可以通过促进Bcl-2相互作用蛋白3(BNIP3)启动子的甲基化[30]、促进铜蓝蛋白(CP)[31]与SLC7A11表达上调，减少脂质过氧化物酶的积累[31-32]等途径抑制HCC铁死亡，引起HCC治疗中索拉非尼耐药与放疗抵抗。

2.3 缺氧应激与HCC铜死亡

铜死亡是近年新提出的一种细胞程序性死亡方式，主要通过铜靶向线粒体三羧酸循环中硫辛酰化蛋白，造成脂酰化蛋白质聚集和铁硫簇蛋白丢失，诱导细胞死亡[41]。目前关于缺氧与HCC铜死亡相关性的报道尚少，一项铜相关基因特征预测HCC患者预后的研究发现，铜死亡负调控基因——*CDKN2A*的高表达是HCC预后不良的因素，且与HCC缺氧呈正相关，这提示缺氧可能通过上调CDKN2A抑制铜死亡，导致HCC生长和进展的风险增加[33]。

3 缺氧应激与HCC代谢

缺氧条件下HCC细胞仍会通过不完全的电子传递链产生能量，导致更多活性氧(reactive oxygen species, ROS)的生成，造成氧化应激(oxidative stress, OS)[42]。过量的ROS一方面可以激活HIF-1α以调节相关代谢酶，整合新的代谢网络，另一方面可以直接损害包括糖类、脂质和蛋白质等诸多细胞组分[43](图2)。

3.1 缺氧应激与HCC糖代谢

肿瘤细胞在缺氧或即使是氧气充足情况下，优先通过糖酵解产生乳酸获取能量而不是通过三羧酸循环获取能量，以满足肿瘤快速生长对能量的需求，这种现象称为

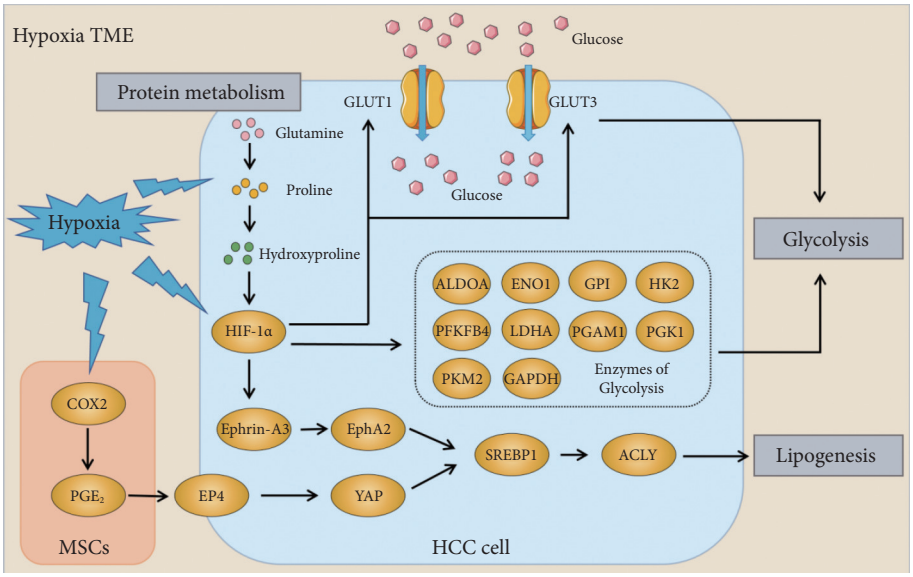


图 2 缺氧应激与HCC代谢

Fig 2 The effect of hypoxic stress on the metabolism of HCC

ACLY: ATP citrate lyase; ALDOA: aldolase, fructose-bisphosphate A; COX2: cyclooxygenase 2; ENO1: enolase 1; EP4: prostaglandin receptor 4; EphA2: EPH receptor A2; Ephrin-A3: EPH-related receptor tyrosine kinase ligand 3; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; GLUT1: glucose transporter 1; GLUT3: glucose transporter 3; GPI: glucose-6-phosphate isomerase; HCC: hepatocellular carcinoma; HIF-1α: hypoxia inducible factor 1 subunit alpha; HK2: hexokinase 2; LDHA: lactate dehydrogenase A; MSCs: mesenchymal stem cells; PFKFB4: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; PGAM1: phosphoglycerate mutase 1; PGE_2: prostaglandin E_2; PGK1: phosphoglycerate kinase 1; PKM2: pyruvate kinase M2; SREBP1: sterol regulatory element-binding protein 1; TME: tumor microenvironment; YAP: Yes-associated protein.

瓦博格效应[44]。缺氧状态下, HCC细胞可通过HIF-1α生成ALDOA、ENO1、GPI、HK2、GAPDH、PFKFB4、LDHA、PGAM1、PGK1和PKM2等糖酵解途径关键酶促进糖酵解[45-46]; 此外, 缺氧还能通过激活HIF-1α增加葡萄糖转运蛋白1(GLUT1)、葡萄糖转运蛋白3(GLUT3)的表达, 促进缺氧状态下HCC对葡萄糖的摄取, 促进HCC发生发展[47]。

3.2　缺氧应激与HCC脂质代谢

脂肪生成被认为能够促进肿瘤细胞的增殖与能量储存[48]。临床发现HCC患者肿瘤中有较高的胆固醇、甘油三酯水平, 以及脂肪生成相关蛋白表达增高, 且脂质形成增加与HCC预后不良相关[49]。在缺氧下HCC细胞Ephrin-A3表达增加, 与EphA2受体作用, 通过固醇调节元件结合蛋白1(SREBP1)促进脂肪生成酶ACLY转录, 合成脂肪酸及胆固醇, 促进HCC癌症干性[50]; 缺氧可以增加间充质干细胞(MSCs)中环氧合酶2(COX2)的表达, 促进胞内前列腺素E_2(PGE_2)的合成与分泌, PEG_2通过HCC细胞EP4蛋白激活Yes相关蛋白(YAP), YAP通过AKT/mTOR/SREBP1介导脂肪生成, 且通过TEAD介导肿瘤细胞增殖, 促进HCC进展[51]; HIF-1α的活化还可调节葡萄糖和心磷脂合成代谢的整合, 引起HCC放射治疗抵抗[52]。

3.3　缺氧应激与HCC蛋白质代谢

HCC对葡萄糖的高需求量使得蛋白质分解为氨基酸, 从而进行糖异生供能[53], 是HCC患者发生肌少症(sarcopenia)、恶病质的重要原因[54]。代谢组学发现HCC患者肿瘤组织中有着较高水平的谷氨酰胺、谷胱甘肽和缬氨酸、亮氨酸、异亮氨酸等支链氨基酸[53]。缺氧促进HCC中谷氨酰胺、脯氨酸的生物合成, 脯氨酸可进一步形成羟脯氨酸, 羟脯氨酸可以抑制HIF-1α蛋白的羟基化以稳定HIF-1α, 促进HCC的存活与索拉非尼耐药[55]; 缺氧还可诱导甲硫氨酸腺苷转移酶2A(MAT2A)表达, 减少S-腺苷甲硫氨酸(SAM)稳态, 从而诱导基因组DNA去甲基化, 促进HCC发生发展[56]。

4　缺氧应激与HCC肿瘤微环境

肿瘤微环境由肿瘤细胞、癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)、肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)等免疫细胞、内皮细胞和细胞外基质(extracellular matrix, ECM)等构成, 发挥促肿瘤和抗肿瘤的双重作用[57-59]。缺氧可以诱导HCC肿瘤微环境中多种因子的表达促进血管生成[60-62], 还会影响ECM、CAFs、TAMs, 导致HCC发生发展(图3)。

4.1　缺氧应激与HCC ECM重塑

缺氧状态的肿瘤可以分泌基质金属蛋白酶(MMPs)、前胶原赖氨酸羟化酶家族(PLODs)、赖氨酰氧化酶(LOXs)、脯氨酰4-羟基酶(P4Hs)等多种酶[63-64], 调节

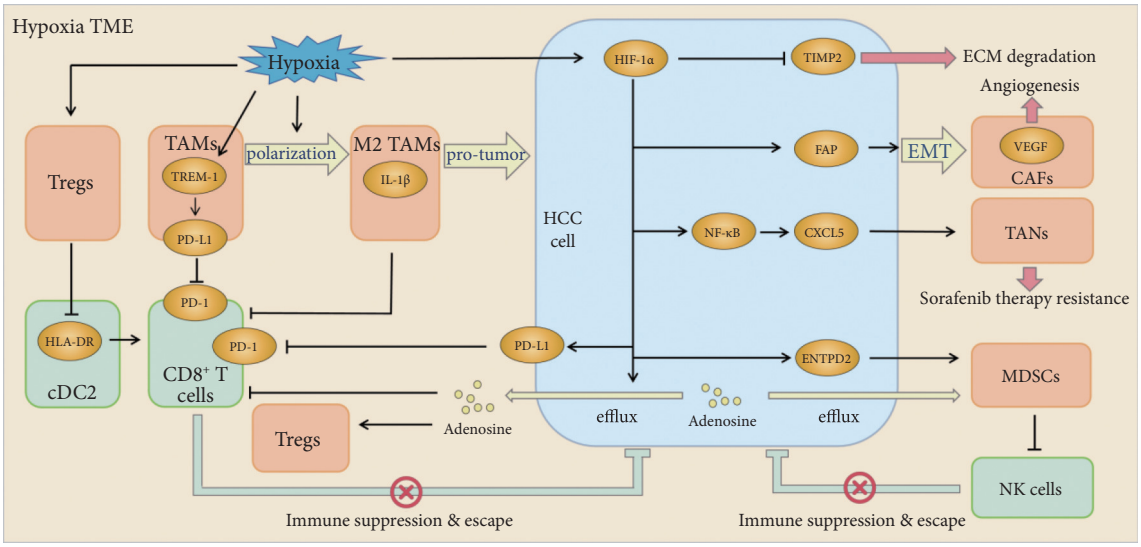


图 3　缺氧应激与HCC肿瘤微环境和免疫

Fig 3　The effect of hypoxic stress on tumor microenvironment and tumor immunology in HCC

CAFs: cancer associated fibroblasts; $CD8^+$ T cells: cluster of differentiation 8 positive T cells; cDC2: type 2 conventional dendritic cell; CXCL5: C-X-C motif chemokine ligand 5; ENTPD2: ectonucleoside triphosphate diphosphohydrolase 2; FAP: fibroblast activation protein alpha; HCC: hepatocellular carcinoma; HLA-DR: human leukocyte antigen-DR; HIF-1α: hypoxia-inducible factor-1 alpha; IL-1β: interleukin-1 beta; MDSCs: myeloid-derived suppressor cells; NF-κB: nuclear factor kappa-B; NK cells: natural killer cells; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; TAMs: tumor-associated macrophages; TANs: tumor-associated neutrophils; TEM: tumor microenvironment; TIMP2: tissue inhibitor of metalloprotease-2; Tregs: regulatory T cells; TREM-1: triggering receptor expressed on myeloid cells 1; VEGF: vascular endothelial growth factor.

ECM硬度和降解变化,即ECM重塑,对肿瘤的生长、侵袭和转移有重要影响[65]。在HCC中,缺氧通过HIF-1α抑制金属蛋白酶组织抑制因子2(TIMP2)表达,增强HCC细胞降解ECM的能力,促进HCC转移[66]。

4.2 缺氧应激与HCC CAFs

CAFs是肿瘤微环境中最常见的基质细胞,相比正常成纤维细胞具有较强的代谢活性与分泌能力,能够产生ECM蛋白、生长因子、细胞因子和细胞外囊泡,重塑ECM[67-68]。HCC中的CAFs来源于肝星状细胞、发生上皮间质转化的HCC细胞、间充质基质细胞等多种细胞[67]。缺氧能促进HCC细胞发生上皮间质转化,成为高表达成纤维细胞活化蛋白(FAP)的CAFs样细胞,促进HCC进展[69];经过缺氧激活的CAFs可以分泌促血管生成因子,促进HCC肿瘤微环境中血管生成[70]。

4.3 缺氧应激与HCC TAMs

TAMs是肿瘤微环境中含量最丰富的免疫细胞,TAMs经诱导可极化为M1样抗肿瘤状态或M2样促肿瘤状态[71]。缺氧能够通过多种途径诱导TAMs向M2极化,抑制免疫功能,促进肿瘤生长[72]。缺氧条件下,HCC肿瘤微环境中的TAMs可以上调TREM-1表达,进而上调PD-L1表达、招募CCR6$^+$Foxp3$^+$调节性T细胞(Tregs),从而损害CD8$^+$ T细胞的细胞毒性功能并诱导CD8$^+$ T细胞凋亡,导致免疫抑制,并造成抗PD-L1治疗的耐药性[73];缺氧还促使M2极化的TAMs分泌IL-1β诱导HCC上皮间质转化,促进HCC转移[74]。

5 缺氧应激与HCC肿瘤免疫

HCC肿瘤微环境中存在T淋巴细胞、B淋巴细胞、TAMs、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)、树突状细胞(dendritic cells, DCs)、肿瘤相关中性粒细胞(tumor-associated neutrophils, TANs)和自然杀伤细胞(nature killer, NK)等多种免疫细胞以及它们分泌的细胞因子和趋化因子[75-77]。缺氧可以引起HCC募集多种免疫抑制性细胞,释放多种免疫抑制因子,产生免疫抑制性肿瘤微环境[78](图3)。

5.1 缺氧与HCC免疫细胞

MDSCs是骨髓来源的一群抑制性细胞,是DCs、巨噬细胞和(或)粒细胞的前体,具有显著抑制NK细胞等免疫细胞应答的能力[79],缺氧通过HIF-1α诱导HCC胞外酶ENTPD2表达,ENTPD2抑制MDSCs分化维持其前体状态,引起HCC免疫逃逸[80]。DCs是负责抗原递呈的关键细胞,缺氧可以耗竭HCC中CD8$^+$ T淋巴细胞,并引起Tregs和经典树突状细胞亚群2(cDC2)富集与相互作用,使cDC2上专职抗原递呈的人类白细胞DR抗原(HLA-DR)丢失,驱动HCC的免疫抑制[78]。TANs是肿瘤微环境中重要炎症细胞,索拉非尼的抗血管作用可以引起瘤内缺氧,缺氧会使HCC细胞激活NF-κB信号传导,进而分泌CXCL5,从而促进TANs募集、抑制TANs凋亡,进而招募M2型TAMs和Tregs,促进索拉非尼治疗耐药[81-82]。

5.2 缺氧与HCC免疫抑制因子

免疫抑制因子包括CTLA-4、PD-1、TIM-3、LAG-3、BTLA等免疫检查点因子和精氨酸酶1(ARG1)、集落刺激因子-1(CSF-1)、乳酸、腺苷、半乳糖凝集素、IL-4、IL-8、IL-10等免疫调节因子,能够形成HCC免疫抑制性肿瘤微环境[83-84]。缺氧能促进HCC中CCL20和CXCL5的表达,促进Tregs和TANs的募集,驱动免疫抑制[78]。缺氧可以通过HIF-1α增加TAMs、MDSCs和肿瘤细胞中PD-L1的表达引起免疫逃逸[73, 85-86];索拉非尼治疗引起的缺氧同样可以增加HCC中PD-L1表达引起免疫抑制[82]。缺氧还促进HCC细胞腺苷的产生和细胞外积累,从而减少CD4$^+$ T细胞、CD8$^+$ T细胞和DCs的肿瘤浸润,促进Tregs和MDSCs细胞群的积累,引起HCC免疫抑制[87]。

6 高原缺氧与HCC切除术后肝再生

肝切除术是治疗HCC的重要手段[88],术后残肝的再生程度对肝功能恢复、预防术后肝衰竭以及远期预后有重要影响[89-90]。最新临床证据显示,西藏高原地区的HCC患者,接受联合肝脏离断和门静脉结扎二步肝切除术,与平原地区接受相同手术的HCC患者相比术后残肝再生不良,而增加氧疗显著增加高原地区HCC患者术后残肝再生程度[91]。在机制上,肝部分切除术后可迅速激活残肝细胞内c-Met和EGFR等信号通路,促进残肝的再生过程[92-93],高原缺氧可能抑制了肝硬化肝脏由HGF-c-Met介导的再生过程[94]。但也有研究持相反的观点:认为缺氧促进肝脏再生[95]。缺氧可以通过HIF-1α增加肝切除术后残肝中VEGF与flt-1的表达,促进肝窦内皮细胞再生[96],并调节糖异生以维持肝再生过程中的能量代谢[97],这提示缺氧对HCC切除术后肝再生过程的影响具有两面性,可能是由于世居高原人群针对缺氧应激的进化与新进高原人群或平原地区人群不同导致的。目前,尚缺乏随机对照试验或其他高级别循证证据,以进一步确认高原人群与平原人群在HCC切除术后肝再生水平上的差异,以及高海拔引起的缺氧应激对HCC切除术后肝再生的影响。

7 总结与展望

本文深入探讨了高原缺氧应激与HCC衰老、死亡、

代谢、微环境和免疫多方面之间的相关性, 一方面世居高原环境的人群HCC发生率较平原环境的人群低, 且世居高原环境的HCC患者生存率较平原环境的HCC患者高; 临床也观察到巨大HCC因严重缺氧导致肿瘤中心部位出现液化坏死, 提示对高原缺氧应激的适应或者严重缺氧应激本身对HCC患者具有保护性作用; 另一方面, 大量基础研究表明一定程度的缺氧会影响HCC的衰老、死亡、代谢、微环境和免疫, 促进HCC增殖、侵袭和转移, 且高原缺氧环境可能对HCC肝部分切除术后肝再生有明显影响, 提示这些条件下, 缺氧是导致HCC预后不良的危险因素。因此, 缺氧是否促进或抑制HCC的发生发展仍然存在悖论。笔者认为, 不同氧浓度、不同细胞背景和组织微环境下, 缺氧可能对HCC的发生发展产生不同的影响。

目前, 已有多种针对缺氧相关靶点的药物开发[98], 包括: 32-134D是一种低分子量化合物, 可有效抑制HCC细胞中HIF-1和HIF-2介导的基因表达, 并阻断小鼠HCC肿瘤的生长, 与抗PD-1疗法联合使用可将肿瘤清除率从25%提高到67%, 但缺乏临床数据[99]; EZN-2968是一种基于锁核酸的寡脱氧核苷酸, 能与*HIF-1α* mRNA特异性结合, 抑制HIF-1α表达, EZN-2968在治疗HCC的Ⅰb期临床试验(NCT02564614)的8例患者中发现1例达到部分缓解, 1例达到疾病稳定, 且部分缓解和疾病稳定患者肿瘤活检显示*HIF-1α* mRNA明显减少[100]; Minnelide是一种水溶性雷公藤内酯前体药物, 能靶向缺氧的下游热休克蛋白HSP70, 在细胞实验和动物实验中具有抗胰腺癌的作用, 但尚无HCC研究数据[101-102]。总之, 高原缺氧应激及适应性进化机制尚需进一步研究, 为未来开发针对缺氧相关靶点的精准治疗策略提供科学依据。

*　　*　　*

作者贡献声明　梁钰博负责调查研究、研究方法、可视化和初稿写作, 李凌娟、高洁、陈星明和李进负责调查研究、研究方法和初稿写作, 刘柏杨负责调查研究、研究方法、初稿写作和审读与编辑写作, 柯阳负责论文构思、经费获取、监督指导和审读与编辑写作, 陈勇彬负责论文构思、监督指导和审读与编辑写作。所有作者已经同意将文章提交给本刊, 且对将要发表的版本进行最终定稿, 并同意对工作的所有方面负责。

Author Contribution　LIANG Yubo is responsible for investigation, methodology, visualization, and writing-original draft. LI Lingjuan, GAO Jie, CHEN Xingming, and LI Jin are responsible for investigation, methodology, and writing-original draft. LIU Baiyang is responsible for investigation, methodology, writing-original draft, and writing-review and editing. KE Yang is responsible for conceptualization, funding acquisition, supervision, and writing-review and editing. CHEN Yongbin is responsible for conceptualization, supervision, and writing-review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突　所有作者均声明不存在利益冲突

Declaration of Conflicting Interests　All authors declare no competing interests.

参　考　文　献

[1] SUNG H, FERLAY J, SIEGEL R L, *et al*. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2021, 71(3): 209-249. doi: 10.3322/caac.21660.

[2] HAN B F, ZHENG R S, ZENG H M, *et al*. Cancer incidence and mortality in China, 2022. J Natl Cancer Cent, 2024, 4(1): 47-53. doi: 10.1016/j.jncc.2024.01.006.

[3] 侯少范, 王五一, 李海蓉, 等. 高原环境因素与自由基反应. 地理科学进展, 2006, 25(1): 82-89. doi: 10.3969/j.issn.1007-6301.2006.01.009.
HOU S F, WANG W Y, LI H R, *et al*. The environmental factors of high altitude and free radical reactions. Prog Geogr, 2006, 25(1): 82-89. doi: 10.3969/j.issn.1007-6301.2006.01.009.

[4] PEACOCK A J. ABC of oxygen: oxygen at high altitude. BMJ, 1998, 317(7165): 1063-1066. doi: 10.1136/bmj.317.7165.1063.

[5] 黄灿华. 应激医学与人类健康. 四川大学学报(医学版), 2021, 52(1): 1-4. doi: 10.12182/20210160501.
HUANG C H. Stress medicine and human health. J Sichuan Univ (Med Sci), 2021, 52(1): 1-4. doi: 10.12182/20210160501.

[6] MAJMUNDAR A J, WONG W J, SIMON M C. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell, 2010, 40(2): 294-309. doi: 10.1016/j.molcel.2010.09.022.

[7] HOTOKEZAKA Y, Van LEYEN K, LO E H, *et al*. alphaNAC depletion as an initiator of ER stress-induced apoptosis in hypoxia. Cell Death Differ, 2009, 16(11): 1505-1514. doi: 10.1038/cdd.2009.90.

[8] MAGALHÃES J, ASCENSÃO A, SOARES J M C, *et al*. Acute and severe hypobaric hypoxia increases oxidative stress and impairs mitochondrial function in mouse skeletal muscle. J Appl Physiol (1985), 2005, 99(4): 1247-1253. doi: 10.1152/japplphysiol.01324.2004.

[9] 吴奇胜, 刘培桑, 杨翠萍, 等. 高原低氧适应与低氧实体瘤. 四川大学学报(医学版), 2021, 52(1): 50-56. doi: 10.12182/20210160504.
WU Q S, LIU P S, YANG C P, *et al*. A review of high-altitude hypoxia adaptation and hypoxic solid tumor. J Sichuan Univ (Med Sci), 2021, 52(1): 50-56. doi: 10.12182/20210160504.

[10] STORZ J F, CHEVIRON Z A. Physiological Genomics of Adaptation to High-Altitude Hypoxia. Annu Rev Anim Biosci, 2021, 9: 149-171. doi: 10.1146/annurev-animal-072820-102736.

[11] 吴天一. 高原低氧环境对人类的挑战. 医学研究杂志, 2006, 35(10): 1-3. doi: 10.3969/j.issn.1673-548X.2006.10.001.
WU T Y. The challenges of high-altitude hypoxic environments for humans. J Med Res, 2006, 35(10): 1-3. doi: 10.3969/j.issn.1673-548X.2006.10.001.

[12] SHARMA V, VARSHNEY R, SETHY N K. Human adaptation to high

altitude: a review of convergence between genomic and proteomic signatures. Hum Genomics, 2022, 16(1): 21. doi: 10.1186/s40246-022-00395-y.

[13] THIERSCH M, SWENSON E R. High altitude and cancer mortality. High Alt Med Biol, 2018, 19(2): 116-123. doi: 10.1089/ham.2017.0061.

[14] ZHOU M, WANG H, ZHU J, *et al*. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet, 2016, 387(10015): 251-272. doi: 10.1016/S0140-6736(15)00551-6.

[15] SHI Y, FAN S, WU M, *et al*. YTHDF1 links hypoxia adaptation and non-small cell lung cancer progression. Nat Commun, 2019, 10(1): 4892. doi: 10.1038/s41467-019-12801-6.

[16] XIONG Q, LIU B, DING M, *et al*. Hypoxia and cancer related pathology. Cancer Lett, 2020, 486: 1-7. doi: 10.1016/j.canlet.2020.05.002.

[17] XIAO Y, SUN Y, LIU G, *et al*. Androgen receptor (AR)/miR-520f-3p/SOX9 signaling is involved in altering hepatocellular carcinoma (HCC) cell sensitivity to the Sorafenib therapy under hypoxia via increasing cancer stem cells phenotype. Cancer Lett, 2019, 444: 175-187. doi: 10.1016/j.canlet.2018.11.004.

[18] JING L, RUAN Z, SUN H, *et al*. Epithelial-mesenchymal transition induced cancer-stem-cell-like characteristics in hepatocellular carcinoma. J Cell Physiol, 2019, 234(10): 18448-18458. doi: 10.1002/jcp.28480.

[19] CUI C P, WONG C C L, KAI A K L, *et al*. SENP1 promotes hypoxia-induced cancer stemness by HIF-1α deSUMOylation and SENP1/HIF-1α positive feedback loop. Gut, 2017, 66(12): 2149-2159. doi: 10.1136/gutjnl-2016-313264.

[20] CHEN C, LOU T. Hypoxia inducible factors in hepatocellular carcinoma. Oncotarget, 2017, 8(28): 46691-46703. doi: 10.18632/oncotarget.17358.

[21] TONG Y, YANG H, XU X, *et al*. Effect of a hypoxic microenvironment after radiofrequency ablation on residual hepatocellular cell migration and invasion. Cancer Sci, 2017, 108(4): 753-762. doi: 10.1111/cas.13191.

[22] LI J Q, WU X, GAN L, *et al*. Hypoxia induces universal but differential drug resistance and impairs anticancer mechanisms of 5-fluorouracil in hepatoma cells. Acta Pharmacol Sin, 2017, 38(12): 1642-1654. doi: 10.1038/aps.2017.79.

[23] PIRET J P, MINET E, COSSE J P, *et al*. Hypoxia-inducible factor-1-dependent overexpression of myeloid cell factor-1 protects hypoxic cells against tert-butyl hydroperoxide-induced apoptosis. J Biol Chem, 2005, 280(10): 9336-9344. doi: 10.1074/jbc.M411858200.

[24] CHANG Y, YAN W, HE X, *et al*. miR-375 inhibits autophagy and reduces viability of hepatocellular carcinoma cells under hypoxic conditions. Gastroenterology, 2012, 143(1): 177-187.e8. doi:10.1053/j.gastro.2012.04.009.

[25] LIU J, HUANG X, LIU D, *et al*. Demethyleneberberine induces cell cycle arrest and cellular senescence of NSCLC cells via c-Myc/HIF-1α pathway. Phytomedicine, 2021, 91: 153678. doi: 10.1016/j.phymed.2021.153678.

[26] FENG W, XUE T, HUANG S, *et al*. HIF-1α promotes the migration and invasion of hepatocellular carcinoma cells via the IL-8-NF-κB axis. Cell Mol Biol Lett, 2018, 23: 26. doi: 10.1186/s11658-018-0077-1.

[27] GWAK G Y, YOON J H, KIM K M, *et al*. Hypoxia stimulates proliferation of human hepatoma cells through the induction of hexokinase Ⅱ expression. J Hepatol, 2005, 42(3): 358-364. doi: 10.1016/j.jhep.2004.11.020.

[28] ZHANG Q, XIONG L, WEI T, *et al*. Hypoxia-responsive PPARGC1A/BAMBI/ACSL5 axis promotes progression and resistance to lenvatinib in hepatocellular carcinoma. Oncogene, 2023, 42(19): 1509-1523. doi: 10.1038/s41388-023-02665-y.

[29] FAN Z, YANG G, ZHANG W, *et al*. Hypoxia blocks ferroptosis of hepatocellular carcinoma via suppression of METTL14 triggered YTHDF2-dependent silencing of SLC7A11. J Cell Mol Med, 2021, 25(21): 10197-10212. doi: 10.1111/jcmm.16957.

[30] MÉNDEZ-BLANCO C, FONDEVILA F, FERNÁNDEZ-PALANCA P, *et al*. Stabilization of hypoxia-inducible factors and BNIP3 promoter methylation contribute to acquired sorafenib resistance in human hepatocarcinoma cells. Cancers (Basel), 2019, 11(12): 1984. doi: 10.3390/cancers11121984.

[31] YANG M, WU X, HU J, *et al*. COMMD10 inhibits HIF1α/CP loop to enhance ferroptosis and radiosensitivity by disrupting Cu-Fe balance in hepatocellular carcinoma. J Hepatol, 2022, 76(5): 1138-1150. doi: 10.1016/j.jhep.2022.01.009.

[32] LI Y, YANG W, ZHENG Y, *et al*. Targeting fatty acid synthase modulates sensitivity of hepatocellular carcinoma to sorafenib via ferroptosis. J Exp Clin Cancer Res, 2023, 42(1): 6. doi: 10.1186/s13046-022-02567-z.

[33] SHI H, HUANG J, WANG X, *et al*. Development and validation of a copper-related gene prognostic signature in hepatocellular carcinoma. Front Cell Dev Biol, 2023, 11: 1157841. doi: 10.3389/fcell.2023.1157841.

[34] LI Y, WANG M S, OTECKO N O, *et al*. Hypoxia potentially promotes Tibetan longevity. Cell Res, 2017, 27(2): 302-305. doi: 10.1038/cr.2016.105.

[35] CALCINOTTO A, KOHLI J, ZAGATO E, *et al*. Cellular senescence: aging, cancer, and injury. Physiol Rev, 2019, 99(2): 1047-1078. doi: 10.1152/physrev.00020.2018.

[36] SONG K X, WANG J X, HUANG D. Therapy-induced senescent tumor cells in cancer relapse. J Natl Cancer Cent, 2023, 3(4): 273-278. doi: 10.1016/j.jncc.2023.09.001.

[37] KANG T W, YEVSA T, WOLLER N, *et al*. Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature, 2011, 479(7374): 547-551. doi: 10.1038/nature10599.

[38] LOUANDRE C, EZZOUKHRY Z, GODIN C, *et al*. Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. Int J

Cancer, 2013, 133(7): 1732-1742. doi: 10.1002/ijc.28159.

[39] JIANG Z, LIM S O, YAN M, *et al*. TYRO3 induces anti-PD-1/PD-L1 therapy resistance by limiting innate immunity and tumoral ferroptosis. J Clin Invest, 2021, 131(8): e139434. doi:10.1172/JCI139434.

[40] WEN K, YAN Y, SHI J, *et al*. Construction and validation of a combined ferroptosis and hypoxia prognostic signature for hepatocellular carcinoma. Front Mol Biosci, 2021, 8: 809672. doi: 10.3389/fmolb.2021.809672.

[41] TSVETKOV P, COY S, PETROVA B, *et al*. Copper induces cell death by targeting lipoylated TCA cycle proteins. Science, 2022, 375(6586): 1254-1261. doi: 10.1126/science.abf0529.

[42] FRUEHAUF J P, MEYSKENS F L. Reactive oxygen species: a breath of life or death? Clin Cancer Res, 2007, 13(3): 789-794. doi:10.1158/1078-0432.CCR-06-2082.

[43] MOLONEY J N, COTTER T G. ROS signalling in the biology of cancer. Semin Cell Dev Biol, 2018, 80: 50-64. doi: 10.1016/j.semcdb.2017.05.023.

[44] SAMUDIO I, FIEGL M, ANDREEFF M. Mitochondrial uncoupling and the Warburg effect: molecular basis for the reprogramming of cancer cell metabolism. Cancer Res, 2009, 69(6): 2163-2166. doi: 10.1158/0008-5472.CAN-08-3722.

[45] SIN S Q, MOHAN C D, GOH R M W J, *et al*. Hypoxia signaling in hepatocellular carcinoma: challenges and therapeutic opportunities. Cancer Metastasis Rev, 2023, 42(3): 741-764. doi: 10.1007/s10555-022-10071-1.

[46] GUO Y, XIAO Z, YANG L, *et al*. Hypoxia-inducible factors in hepatocellular carcinoma (Review). Oncol Rep, 2020, 43(1): 3-15. doi: 10.3892/or.2019.7397.

[47] XIA H, CHEN J, GAO H, *et al*. Hypoxia-induced modulation of glucose transporter expression impacts 18F-fluorodeoxyglucose PET-CT imaging in hepatocellular carcinoma. Eur J Nucl Med Mol Imaging, 2020, 47(4): 787-797. doi: 10.1007/s00259-019-04638-4.

[48] RÖHRIG F, SCHULZE A. The multifaceted roles of fatty acid synthesis in cancer. Nat Rev Cancer, 2016, 16(11): 732-749. doi: 10.1038/nrc.2016.89.

[49] CALVISI D F, WANG C, HO C, *et al*. Increased lipogenesis, induced by AKT-mTORC1-RPS6 signaling, promotes development of human hepatocellular carcinoma. Gastroenterology, 2011, 140(3): 1071-1083. doi: 10.1053/j.gastro.2010.12.006.

[50] HUSAIN A, CHIU Y T, SZE K M F, *et al*. Ephrin-A3/EphA2 axis regulates cellular metabolic plasticity to enhance cancer stemness in hypoxic hepatocellular carcinoma. J Hepatol, 2022, 77(2): 383-396. doi: 10.1016/j.jhep.2022.02.018.

[51] LIU Y, REN H, ZHOU Y, *et al*. The hypoxia conditioned mesenchymal stem cells promote hepatocellular carcinoma progression through YAP mediated lipogenesis reprogramming. J Exp Clin Cancer Res, 2019, 38(1): 228. doi: 10.1186/s13046-019-1219-7.

[52] FANG Y, ZHAN Y, XIE Y, *et al*. Integration of glucose and cardiolipin anabolism confers radiation resistance of HCC. Hepatology, 2022, 75(6): 1386-1401. doi: 10.1002/hep.32177.

[53] HUANG Q, TAN Y, YIN P, *et al*. Metabolic characterization of hepatocellular carcinoma using nontargeted tissue metabolomics. Cancer Res, 2013, 73(16): 4992-5002. doi: 10.1158/0008-5472.CAN-13-0308.

[54] FUJIWARA N, NAKAGAWA H, KUDO Y, *et al*. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol, 2015, 63(1): 131-140. doi: 10.1016/j.jhep.2015.02.031.

[55] TANG L, ZENG J, GENG P, *et al*. Global metabolic profiling identifies a pivotal role of proline and hydroxyproline metabolism in supporting hypoxic response in hepatocellular carcinoma. Clin Cancer Res, 2018, 24(2): 474-485. doi: 10.1158/1078-0432.CCR-17-1707.

[56] LIU Q, LIU L, ZHAO Y, *et al*. Hypoxia induces genomic DNA demethylation through the activation of HIF-1α and transcriptional upregulation of MAT2A in hepatoma cells. Mol Cancer Ther, 2011, 10(6): 1113-1123. doi: 10.1158/1535-7163.MCT-10-1010.

[57] De VISSER K E, JOYCE J A. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell, 2023, 41(3): 374-403. doi: 10.1016/j.ccell.2023.02.016.

[58] CHUNG A, NASRALLA D, QUAGLIA A. Understanding the immunoenvironment of primary liver cancer: a histopathology perspective. J Hepatocell Carcinoma, 2022, 9: 1149-1169. doi: 10.2147/JHC.S382310.

[59] FENG H, ZHUO Y, ZHANG X, *et al*. Tumor microenvironment in hepatocellular carcinoma: key players for immunotherapy. J Hepatocell Carcinoma, 2022, 9: 1109-1125. doi: 10.2147/JHC.S381764.

[60] SEMENZA G L. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene, 2010, 29(5): 625-634. doi: 10.1038/onc.2009.441.

[61] LI H, GE C, ZHAO F, *et al*. Hypoxia-inducible factor 1 alpha-activated angiopoietin-like protein 4 contributes to tumor metastasis via vascular cell adhesion molecule-1/integrin β1 signaling in human hepatocellular carcinoma. Hepatology, 2011, 54(3): 910-919. doi: 10.1002/hep.24479.

[62] MARSCHALL Z V, CRAMER T, HOECKER M, *et al*. Dual mechanism of vascular endothelial growth factor upregulation by hypoxia in human hepatocellular carcinoma. Gastroenterology, 2001, 118(1): A562-A562. doi: 10.1136/gut.48.1.87.

[63] SEMENZA G L. The hypoxic tumor microenvironment: a driving force for breast cancer progression. Biochim Biophys Acta, 2016, 1863(3): 382-391. doi: 10.1016/j.bbamcr.2015.05.036.

[64] De BOCK K, MAZZONE M, CARMELIET P. Antiangiogenic therapy, hypoxia, and metastasis: risky liaisons, or not? Nat Rev Clin Oncol, 2011, 8(7): 393-404. doi:10.1038/nrclinonc.2011.83.

[65] BONNANS C, CHOU J, WERB Z. Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol, 2014, 15(12): 786-801. doi: 10.1038/nrm3904.

[66] KAI A K L, CHAN L K, LO R C L, *et al*. Down-regulation of TIMP2 by HIF-1α/miR-210/HIF-3α regulatory feedback circuit enhances cancer metastasis in hepatocellular carcinoma. Hepatology, 2016, 64(2): 473-487. doi: 10.1002/hep.28577.

[67] ZHANG J, GU C, SONG Q, *et al*. Identifying cancer-associated fibroblasts as emerging targets for hepatocellular carcinoma. Cell Biosci, 2020, 10(1): 127. doi: 10.1186/s13578-020-00488-y.

[68] MANFREDI G F, CELSA C, JOHN C, *et al*. Mechanisms of resistance to immunotherapy in hepatocellular carcinoma. J Hepatocell Carcinoma, 2023, 10: 1955-1971. doi: 10.2147/JHC.S291553.

[69] ZOU B, LIU X, ZHANG B, *et al*. The expression of FAP in hepatocellular carcinoma cells is induced by hypoxia and correlates with poor clinical outcomes. J Cancer, 2018, 9(18): 3278-3286. doi: 10.7150/jca.25775.

[70] ANKOMA-SEY V, WANG Y, DAI Z. Hypoxic stimulation of vascular endothelial growth factor expression in activated rat hepatic stellate cells. Hepatology, 2000, 31(1): 141-148. doi: 10.1002/hep.510310122.

[71] WANG H, YUNG M M H, NGAN H Y S, *et al*. The impact of the tumor microenvironment on macrophage polarization in cancer metastatic progression. Int J Mol Sci, 2021, 22(12): 6560. doi:10.3390/ijms22126560.

[72] COLEGIO O R, CHU N Q, SZABO A L, *et al*. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature, 2014, 513(7519): 559-563. doi: 10.1038/nature13490.

[73] WU Q, ZHOU W, YIN S, *et al*. Blocking triggering receptor expressed on myeloid cells-1-positive tumor-associated macrophages induced by hypoxia reverses immunosuppression and anti-programmed cell death ligand 1 resistance in liver cancer. Hepatology, 2019, 70(1): 198-214. doi: 10.1002/hep.30593.

[74] ZHANG J, ZHANG Q, LOU Y, *et al*. Hypoxia-inducible factor-1α/interleukin-1β signaling enhances hepatoma epithelial-mesenchymal transition through macrophages in a hypoxic-inflammatory microenvironment. Hepatology, 2018, 67(5): 1872-1889. doi: 10.1002/hep.29681.

[75] ZHANG Q, HE Y, LUO N, *et al*. Landscape and dynamics of single immune cells in hepatocellular carcinoma. Cell, 2019, 179(4): 829-845.e20. doi:10.1016/j.cell.2019.10.003.

[76] RUF B, HEINRICH B, GRETEN T F. Immunobiology and immunotherapy of HCC: spotlight on innate and innate-like immune cells. Cell Mol Immunol, 2021, 18(1): 112-127. doi: 10.1038/s41423-020-00572-w.

[77] LI Z, ZHANG Z, FANG L, *et al*. Tumor microenvironment composition and related therapy in hepatocellular carcinoma. J Hepatocell Carcinoma, 2023, 10: 2083-2099. doi: 10.2147/JHC.S436962.

[78] SUTHEN S, LIM C J, NGUYEN P H D, *et al*. Hypoxia-driven immunosuppression by Treg and type-2 conventional dendritic cells in HCC. Hepatology, 2022, 76(5): 1329-1344. doi: 10.1002/hep.32419.

[79] HOECHST B, VOIGTLAENDER T, ORMANDY L, *et al*. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology, 2009, 50(3): 799-807. doi: 10.1002/hep.23054.

[80] CHIU D K C, TSE A P W, XU I M J, *et al*. Hypoxia inducible factor HIF-1 promotes myeloid-derived suppressor cells accumulation through ENTPD2/CD39L1 in hepatocellular carcinoma. Nat Commun, 2017, 8(1): 517. doi: 10.1038/s41467-017-00530-7.

[81] ZHOU S L, ZHOU Z J, HU Z Q, *et al*. Tumor-associated neutrophils recruit macrophages and t-regulatory cells to promote progression of hepatocellular carcinoma and resistance to sorafenib. Gastroenterology, 2016, 150(7): 1646-1658.e17. doi:10.1053/j.gastro.2016.02.040.

[82] CHEN Y, RAMJIAWAN R R, REIBERGER T, *et al*. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. Hepatology, 2015, 61(5): 1591-1602. doi: 10.1002/hep.27665.

[83] PRIETO J, MELERO I, SANGRO B. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol, 2015, 12(12): 681-700. doi: 10.1038/nrgastro.2015.173.

[84] LIU L, LI S, WANG G, *et al*. Dynamic toxicity landscape of immunotherapy for solid tumors across treatment lines. J Natl Cancer Cent, 2023, 3(3): 186-196. doi: 10.1016/j.jncc.2023.07.002.

[85] NOMAN M Z, DESANTIS G, JANJI B, *et al*. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med, 2014, 211(5): 781-790. doi: 10.1084/jem.20131916.

[86] CHEN Z Q, ZUO X L, CAI J, *et al*. Hypoxia-associated circPRDM4 promotes immune escape via HIF-1α regulation of PD-L1 in hepatocellular carcinoma. Exp Hematol Oncol, 2023, 12(1): 17. doi: 10.1186/s40164-023-00378-2.

[87] CHEU J W S, CHIU D K C, KWAN K K L, *et al*. Hypoxia-inducible factor orchestrates adenosine metabolism to promote liver cancer development. Sci Adv, 2023, 9(18): eade5111. doi: 10.1126/sciadv.ade5111.

[88] SHANNON A H, RUFF S M, PAWLIK T M. Expert insights on current treatments for hepatocellular carcinoma: clinical and molecular approaches and bottlenecks to progress. J Hepatocell Carcinoma, 2022, 9: 1247-1261. doi: 10.2147/JHC.S383922.

[89] XU Y, LI Y, LU Y, *et al*. Liver regeneration-related genes of nontumor liver tissues predict the prognosis of patients with hepatocellular carcinoma. J Hepatocell Carcinoma, 2023, 10: 2197-2209. doi: 10.2147/JHC.S433688.

[90] LUO L, HE Y, ZHU G, *et al*. Hepatectomy after conversion therapy for initially unresectable HCC: What is the difference? J Hepatocell Carcinoma, 2022, 9: 1353-1368. doi:10.2147/JHC.S388965.

[91] CHEN B, DA W, BASANGDUNZHU, *et al*. The speed of liver regeneration in ALPPS may be influenced by hypoxia at high altitudes: a case report. Asian J Surg, 2024, 47(5): 2527-2528. doi: 10.1016/j.asjsur.

2024.02.001.

[92] STOLZ D B, MARS W M, PETERSEN B E, *et al*. Growth factor signal transduction immediately after two-thirds partial hepatectomy in the rat. Cancer Res, 1999, 59(16): 3954-3960.

[93] PARANJPE S, BOWEN W C, MARS W M, *et al*. Combined systemic elimination of MET and epidermal growth factor receptor signaling completely abolishes liver regeneration and leads to liver decompensation. Hepatology, 2016, 64(5): 1711-1724. doi: 10.1002/hep.28721.

[94] CORPECHOT C, BARBU V, WENDUM D, *et al*. Hepatocyte growth factor and c-Met inhibition by hepatic cell hypoxia: a potential mechanism for liver regeneration failure in experimental cirrhosis. Am J Pathol, 2002, 160(2): 613-620. doi: 10.1016/S0002-9440(10)64881-X.

[95] SCHADDE E, TSATSARIS C, SWIDERSKA-SYN M, *et al*. Hypoxia of the growing liver accelerates regeneration. Surgery, 2017, 161(3): 666-679. doi: 10.1016/j.surg.2016.05.018.

[96] MAENO H, ONO T, DHAR D K, *et al*. Expression of hypoxia inducible factor-1alpha during liver regeneration induced by partial hepatectomy in rats. Liver Int, 2005, 25(5): 1002-1009. doi: 10.1111/j.1478-3231.2005.01144.x.

[97] TAJIMA T, GODA N, FUJIKI N, *et al*. HIF-1alpha is necessary to support gluconeogenesis during liver regeneration. Biochem Biophys Res Commun, 2009, 387(4): 789-794. doi: 10.1016/j.bbrc.2009.07.115.

[98] HUANG H, DU J, MENG X, *et al*. Growing research and development of targeted anticancer drugs in China. J Natl Cancer Cent, 2023, 3(2): 129-134. doi: 10.1016/j.jncc.2023.02.004.

[99] SALMAN S, MEYERS D J, WICKS E E, *et al*. HIF inhibitor 32-134D eradicates murine hepatocellular carcinoma in combination with anti-PD1 therapy. J Clin Invest, 2022, 132(9): e156774. doi:10.1172/JCI156774.

[100] WU J, CONTRATTO M, SHANBHOGUE K P, *et al*. Evaluation of a locked nucleic acid form of antisense oligo targeting HIF-1α in advanced hepatocellular carcinoma. World J Clin Oncol, 2019, 10(3): 149-160. doi: 10.5306/wjco.v10.i3.149.

[101] MCGINN O, GUPTA V K, DAUER P, *et al*. Inhibition of hypoxic response decreases stemness and reduces tumorigenic signaling due to impaired assembly of HIF1 transcription complex in pancreatic cancer. Sci Rep, 2017, 7(1): 7872. doi: 10.1038/s41598-017-08447-3.

[102] SKORUPAN N, AHMAD M I, STEINBERG S M, *et al*. A phase Ⅱ trial of the super-enhancer inhibitor Minnelide™ in advanced refractory adenosquamous carcinoma of the pancreas. Future Oncol, 2022, 18(20): 2475-2481. doi: 10.2217/fon-2021-1609.

（2024－08－05收稿，2024－10－28修回）

编辑　刘　华

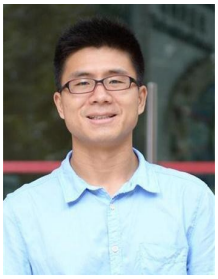
开放获取　本文使用遵循知识共享署名—非商业性使用4.0国际许可协议（CC BY-NC 4.0），详细信息请访问 https://creativecommons.org/licenses/by/4.0/。

OPEN ACCESS　This article is licensed for use under Creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0). For more information, visit https://creativecommons.org/licenses/by/4.0/.

© 2024《四川大学学报(医学版)》编辑部

Editorial Office of *Journal of Sichuan University (Medical Sciences)*

作者简介



陈勇彬，研究员，现任中科院昆明动物研究所肿瘤信号转导研究组负责人。研究方向：肿瘤发生机制；干细胞多能性维持；抗肿瘤及提高干细胞功能新药筛选。2005年在中科院上海生化与细胞研究所获理学博士学位。2005−2012年在美国德州西南医学中心先后作为博士后和研究助理从事肿瘤与干细胞信号转导通路研究工作。2012年回中科院昆明动物研究所，成立肿瘤信号转导研究课题组。曾获云南省科技进步（特等奖、一等奖）等奖励，第七届云南省青年科技奖。在国际主流杂志发表论著20余篇。已获国家自然科学基金委优秀青年科学基金、国家自然科学基金面上项目、国家重点基础研究发展计划（973计划）项目（课题骨干1项）等多个项目资助。兼任中国抗癌协会肿瘤标志物专委会青年副主委，中国抗癌协会、细胞生物学会、病理生理学会和遗传学会常务青年委员（理事），云南省骨肉瘤专业委员会副主任委员等。