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肝癌转化治疗抵抗机制的研究进展

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摘要　原发性肝癌是我国最常见的消化系统肿瘤之一。由于其发病隐匿、早期症状不典型, 大多数患者在确诊时处于中晚期, 失去手术切除的机会, 导致治疗效果差、生存期短。肝细胞癌转化治疗旨在通过介入治疗、靶向治疗和免疫治疗等手段, 将初诊为不可切除的肝癌降期转化为可切除, 提高整体生存率。然而, 多数患者都会出现原发性或继发性治疗抵抗, 严重影响转化治疗效

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果及患者预后。该综述聚焦于肝细胞癌转化治疗抵抗的部分分子机制, 涵盖信号通路异常、肿瘤微环境特征、肿瘤干细胞特性、遗传和表观遗传学改变等方面。深入探讨这些机制, 对于细分转化治疗获益人群, 开发有针对性的干预措施, 提高肝细胞癌整体治疗水平具有重要意义。

关键词 肝细胞癌; 转化治疗; 治疗抵抗

Mechanistic Insights into Resistance to Conversion Therapy in Hepatocellular Carcinoma

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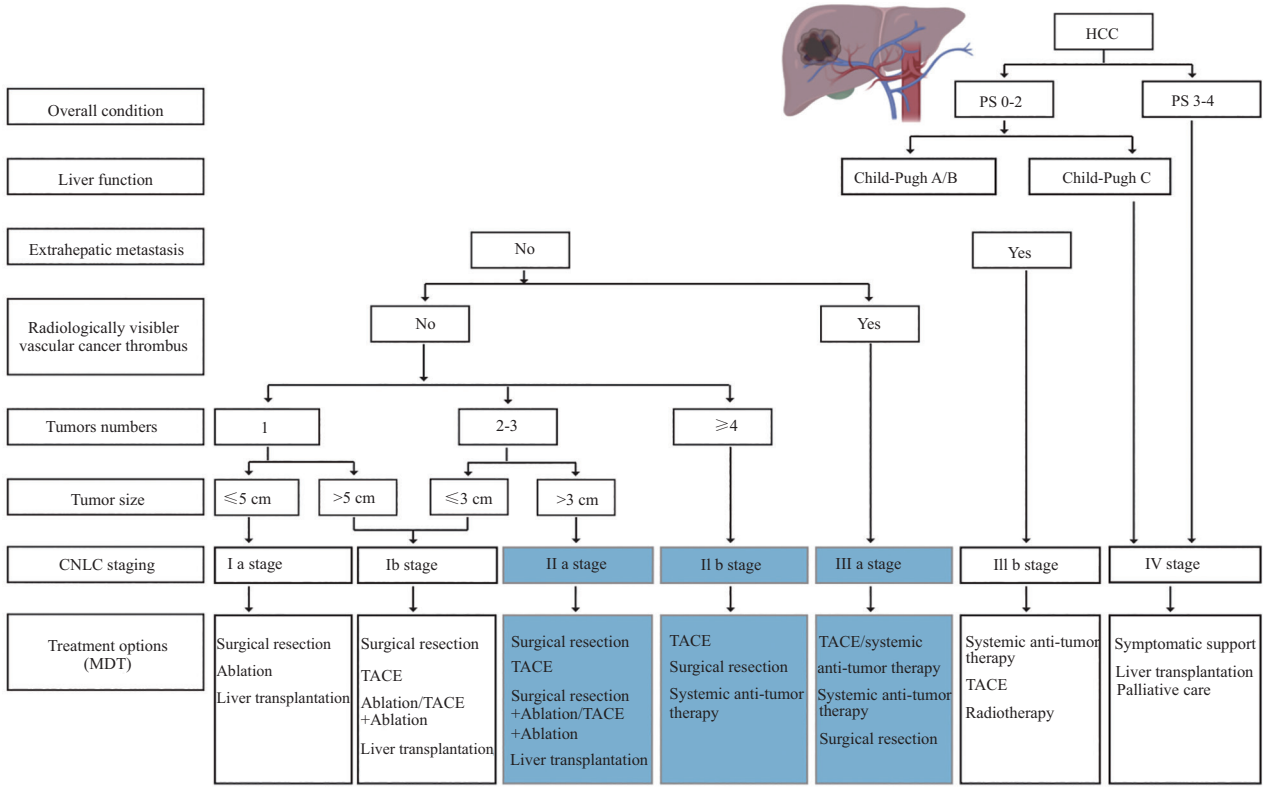
Abstract Primary liver cancer is one of the most common malignancies in China. Due to its atypical early symptoms, the majority of patients are diagnosed at an intermediate or advanced stage, resulting in unresectable disease and poor survival. Conversion therapy for HCC aims to downstage initially unresectable tumors to resectable disease through interventional therapy, targeted therapy, and immunotherapy, thereby offering a chance for cure and improving survival. However, there are still many patients developed primary or acquired resistance to treatment, which limits the efficacy of conversion therapy. This review focuses on the molecular mechanisms driving resistance to conversion therapy in HCC, including aberrant signaling pathways, tumor microenvironment dynamics, cancer stem cell characteristics, as well as genetic and epigenetic alterations. Further investigation of resistance mechanisms is critical for identifying patient subgroups most likely to benefit from conversion therapy, developing tailed therapeutic strategies, and enhancing the overall therapeutic efficacy in HCC.

Keywords hepatocellular carcinoma; conversion therapy; treatment resistance

原发性肝癌主要包括肝细胞癌、肝内胆管癌、混合型肝细胞癌–胆管癌三种病理学类型, 其中肝细胞癌(hepatocellular carcinoma, 以下简称肝癌或HCC)占原发性肝癌的85%~90%, 发病率在全球癌症中居第六位, 死亡率居第四位[1]。我国是肝癌大国, 世界卫生组织数据显示, 仅2022年我国肝癌新发36.7万例(占全球新发病例42.4%)、死亡31.6万例(占全球死亡病例41.7%), 发病和死亡人数约占全球一半[1]。肝癌的外科切除在肝癌的综合治疗中扮演重要角色, 有望带来长期生存。然而, 由于肝癌起病隐匿、早期症状不典型, 70%~80%的患者就诊时已处中晚期, 错失手术时机, 导致治疗效果差、生存期短, 总体预后不甚理想。转化治疗是指对于因肿瘤体积过大、肿瘤分期中晚期等不可切除的肝癌患者, 采取一种或多种治疗手段使得肿瘤缩小或降期, 让部分患者重获根治性手术机会的治疗方式, 为中晚期肝癌患者带来新的希望。

肝癌转化治疗的干预手段多样, 主要包括局部治疗和系统治疗(图1)。肝癌局部治疗方法包括经肝动脉化疗栓塞(transarterial chemoembolization, TACE)、肝动脉灌注化疗(hepatic arterial infusion chemotherapy, HAIC)、经肝动脉放射栓塞(transarterial radioembolization, TARE)、立体定向放疗(stereotactic body radiation therapy, SBRT)等。系统治疗包括靶向治疗、免疫治疗和全身化疗等。随着相关技术的日益完善以及抗肿瘤药物的不断发展, 转化治疗使越来越多的肝癌患者获益。然而, 由于肿瘤的高度异质性及治疗手段伴随的潜在不良反应, 临床上往往面临患者原发性或继发性转化治疗抵抗的问题, 这严重影响肝癌患者整体预后(表1)。全面了解肝癌转化治疗抵抗的分子机制, 细分转化治疗获益人群, 开发有针对性的干预措施, 对提高肝癌整体治疗水平具有重要意义。

本文将结合本课题组围绕肝癌转化治疗抵抗的研究工作以及最近具有代表性的研究成果, 从现有肝癌转化治疗手段出发, 就近年来有关肝癌转化



HCC: 肝细胞癌; PS: 病人体能状态; CNLC: 中国肝癌分期; MDT: 多学科综合治疗协作组; TACE: 经肝动脉化疗栓塞。系统抗肿瘤治疗包括一线治疗: 阿替利珠单克隆抗体+贝伐珠单克隆抗体、信迪利单克隆抗体+贝伐珠单克隆抗体类似物、甲磺酸阿帕替尼+卡瑞利珠单克隆抗体、多纳非尼、仑伐替尼、替雷利珠单克隆抗体、索拉非尼、FOLFOX4。二线治疗: 瑞戈非尼、阿帕替尼、雷莫西尤单克隆抗体(血清甲胎蛋白水平≥400 μg/L)、帕博利珠单克隆抗体、卡瑞利珠单克降抗体、替雷利珠单克隆抗体。

HCC: hepatocellular carcinoma; PS: patient performance status; CNLC: China liver cancer staging; MDT: multidisciplinary team approach; TACE: transarterial chemoembolization. Systemic anti-tumor therapy includes first-line treatments: Atezolizumab+Bevacizumab, Sintilimab+Bevacizumab biosimilar, Apatinib Mesylate+Camrelizumab, Donafenib, Lenvatinib, Tislelizumab, Sorafenib, FOLFOX4 (combination chemotherapy regimen). Second-line treatments include: Regorafenib, Apatinib, Ramucirumab (for serum alpha-fetoprotein levels ⩾ 400 μg/L), Pembrolizumab, Camrelizumab, Tislelizumab.

图1　中国肝癌临床分期与治疗路线图[改自原发性肝癌诊疗指南(2024年版)]

Fig.1　Clinical staging and treatment roadmap for liver cancer in China [adapted from the Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2024 Edition)]

治疗抵抗相关机制的研究进展进行总结分析。

1　局部治疗

1.1　经肝动脉化疗栓塞(TACE)

TACE作为不可切除肝癌患者的经典治疗方法，广泛应用于临床中晚期肝癌患者的治疗，也是肝癌转化传统治疗手段之一。TACE治疗的原理主要是基于肝癌主要由动脉供血的特点，利用碘化油或微球等栓塞剂，选择性地阻断肝癌的动脉血供，使肝癌细胞缺血、缺氧坏死，同时动脉注射化疗药物，提高肿瘤组织局部药物浓度。相比于全身化疗，TACE具有疗效确切、可反复治疗等优势。尽管存在上述优点，但单纯TACE治疗缓解率有限。我们研究表明，TACE手术转化率约为10%，38.6%的患者存在疾病进展，提示TACE容易出现治疗抵抗[2]。

近年来，许多研究致力于阐明TACE治疗抵抗的分子机制。TACE引发的肿瘤缺氧环境被认为是推动肝癌进展的关键因素。TACE术后肿瘤细胞中缺氧诱导因子-1α(hypoxia inducible factor 1 subunit alpha, *HIF-1α*)、*TP53*(tumor protein P53)等基因异常表达，通过激活5'AMPK/mTOR(5' adenosine monophosphate-activated protein kinase/mammalian target of rapamycin)通路引发自噬，导致肝癌细胞对化疗产生耐药[3-5]。HIF-1α还通过上调Snail和Vimentin蛋白的表达，抑制促凋亡蛋白BAX/BAK(BCL2-associated X/BCL2 killer 1)的激活，减少BH3-only(BCL-2

表1 肝癌转化治疗转化率统计

Table 1 Conversion rate statistics of liver cancer

治疗方案 Treatment regimen	年份 Year	样本量 Sample size	患者分期 Patient staging	转化率 Conversion rate	客观缓解率 Objective response rate
TACE	2021[56]	42	BCLC A/B	9.5%	16.70%[a]
	2016[58]	831	BCLC B/C	10.0%	-
HAIC	2022[59]	130	BCLC B/C	12.3%	35.40%[a]
	2021[60]	159	BCLC A/B	16.0%	46.00%[b]
TACE+HAIC	2021[56]	41	BCLC A/B	48.8%	65.90%[a]
Sorafenib	2021[59]	132	BCLC B/C	-	5.30%[a]
	2019[61]	122	BCLC C	0.8%	2.46%[b]
Lenvatinib	2022[62]	9	BCLC B/C	88.0%	2.90%[a]
TKIs+anti PD-1 Ab	2023[63]	101	BCLC A/B/C	23.8%	32.70%[b]
	2022[64]	187	BCLC B/C	15.5%	37.40%[a]
T+A	2023[65]	156	BCLC B/C	10.9%	32.00%[b]
	2020[55]	336	BCLC A/B/C	-	33.20%[b]
HAIC+TKIs+anti PD-1 Ab	2021[66]	34	BCLC C	60.0%	96.00%[a]
TACE+HAIC+TKIs+anti PD-1 Ab	2023[57]	95	BCLC C	46.3%	53.7.0%[a]

TACE: 经肝动脉化疗栓塞; HAIC: 肝动脉灌注化疗; TKIs: 酪氨酸激酶抑制剂; PD-1: 程序性死亡(蛋白)-1; T: 阿替利珠单抗; A: 贝伐珠单抗; [a]基于改良实体瘤疗效评估标准(mRECIST)评估; [b]基于实体瘤疗效评估标准(RECIST)评估; BCLC为巴塞罗那临床肝癌分期。-: 未见报道。

TACE: transarterial chemoembolization; HAIC: hepatic arterial infusion chemotherapy; TKIs: tyrosine kinase inhibitors; PD-1: programmed death protein-1; T: Atezolizumab; A: Bevacizumab; [a]assessed based on the mRECIST (modified Response Evaluation Criteria in Solid Tumors); [b]assessed based on the RECIST (Response Evaluation Criteria in Solid Tumors); BCLC refers to the Barcelona Clinic Liver Cancer staging system. -: unreported.

homology domain 3)蛋白的表达, 抑制肿瘤细胞凋亡, 最终推动肝癌进展。同时, 肿瘤细胞在急性缺氧条件下发生的线粒体网络重编程, 对TACE术后肝癌的进展至关重要[6-7]。本课题组通过对人体组织标本、裸鼠缺血模型及细胞内CRISPR-Cas9进行筛选, 鉴定出S100A9(S100 calcium binding protein A9)可能是介导肝癌TACE治疗抵抗的关键驱动因子。功能实验进一步表明, S100A9能够促进线粒体分裂, 增加细胞内活性氧的产生, 从而促进肝癌细胞的生长和转移。机制上, S100A9通过募集线粒体功能调控蛋白PGAM5(phosphoglycerate mutase family member 5)和USP10(ubiquitin specific peptidase 10)形成三聚体, 进而加速线粒体分裂, 最终导致肝癌的转移与TACE治疗抵抗[8]。另外, 缺氧对肿瘤微环境的重塑, 也是引起TACE治疗抵抗的重要一环。研究表明, 缺氧可促进肝癌细胞分泌细胞外信号调节激酶1/2(extracellular signal-regulatory kinase 1/2, ERK1/2)和SMAD3(SMAD family member 3), 从而促进肝星状细胞(hepatic stellate cells, HSCs)的增殖和活化[9]。活化的HSCs通过增加胶原和纤维连接蛋白的积累, 形成刚性的细胞外基质, 促进肿瘤进展[10-11]。

除了缺氧引发的肿瘤恶性特征之外, 肝癌患者肿瘤免疫微环境的改变也与TACE治疗抵抗密切相关。研究表明, 对TACE治疗响应较差的患者肿瘤组织中PD-L1和PD-1蛋白的表达水平显著升高, 而TACE治疗本身也会进一步上调肿瘤组织中PD-1和PD-L1的表达[12]。此外, 肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)来源的IL-6(interleukin-6)通过STAT3(signal transducer and activator of transcription 3)转导信号诱导HCC细胞表达CD47, 从而增强HCC细胞的抗吞噬作用, 降低TACE疗效[13]。

1.2 肝动脉灌注化疗(HAIC)

同样基于肝癌主要由动脉供血的特点, HAIC是经肝动脉插管对肿瘤供血动脉直接灌注化疗药物, 提高局部病灶内药物浓度的同时完全舍弃栓塞剂, 减少因栓塞引起的各种不良反应。随着对肝癌认识的不断进步, HAIC的用药方案也在不断改进。现我国常用化疗方案为以奥沙利铂为基础的FOLFOX方案, 我中心研究数据显示, 较之于TACE, FOLFOX-HAIC治疗明显提高了晚期肝癌的肿瘤客观缓解率和延长了患者无病生存时间[14]。因此, HAIC在中晚期肝癌的治疗中越来越受重视。我们也留意到, 有研究提示, 约20%的患者接受HAIC治疗后出现疾病进展, 而在HAIC治疗抵抗的分子机制方面, 研究重点集中于肝癌患者对奥沙利铂的原发或继发性耐药上。

铜的内流和外排转运蛋白在铂类药物蓄积中的作用已被证实[15]。肿瘤细胞内的两种ATP酶，ATP7A和ATP7B(ATPase copper transporting alpha and beta)，负责铜的隔离和排出，它们能够将奥沙利铂隔离到亚细胞区室，从而限制其细胞毒性。有机阳离子转运蛋白2(organic cation transporter 2, OCT2)与奥沙利铂的摄取和细胞毒性之间存在明确的关联。此外，谷胱甘肽(glutathione, GSH)通过促进细胞内铂类药物(包括奥沙利铂)外排，引起肿瘤细胞耐药[16]。

表观遗传学修饰在肝癌对奥沙利铂耐药的过程中起到了关键作用。本课题组通过奥沙利铂耐药的肝癌组织标本及代谢功能障碍相关的脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)相关肝癌标本进行检测，筛选出候选长链非编码RNA lnc-OXAR，进一步研究发现m^6A甲基化修饰通过调控lnc-OXAR表达，促进DNA损伤修复蛋白KU70(X-ray repair cross complementing protein 6, XRCC6)稳定，进而引起肝癌细胞奥沙利铂耐药[17]。

此外，借助CRISPR-Cas9全基因组激活文库高通量筛选结合组织标本测序，本课题组首次发现精氨酸甲基转移酶3(protein arginine methyltransferase 3, PRMT3)是介导肝癌奥沙利铂耐药的关键分子。PRMT3高表达的肝癌患者对HAIC治疗的客观缓解率显著低于PRMT3低表达的患者。体内外功能实验证实PRMT3高表达促进肝癌对奥沙利铂耐药。机制上发现PRMT3通过甲基化修饰IGF2BP1 452位精氨酸促进其稳定，进而促进其结合并稳定*HEG1*(heart development protein with EGF like domains 1)的mRNA，最终介导奥沙利铂耐药[18]。

最后，另有研究表明，DNA损伤的核苷酸切除修复(nucleotide excision repair, NER)系统修复、细胞凋亡、调控性坏死、自噬、衰老等细胞死亡途径都与肝癌奥沙利铂耐药密切相关。尽管关于肝癌奥沙利铂耐药的研究多有报道，但我们必须承认，奥沙利铂耐药并不完全等同于HAIC治疗抵抗，是否还有其他影响因素的存在需要研究工作者进一步的挖掘与探索。

2 系统抗肿瘤治疗

2.1 靶向治疗

分子靶向治疗是指利用瘤细胞和正常细胞分子生物学上的差异，针对可能导致细胞癌变环节，以细胞受体、关键基因和调控分子为靶点，设计相应治疗药物，选择针对性阻断、干预与肿瘤发生密切相关的信号转导通路，从而特异性抑制肿瘤生长和转移，是肝癌转化治疗的重要组成部分。目前肝癌靶向治疗药物主要包括血管生成抑制剂和多激酶抑制剂(tyrosine kinase inhibitors, TKIs)等。血管生成抑制剂有贝伐珠单抗、雷莫西尤单抗等，TKIs主要包括仑伐替尼、索拉非尼、瑞戈非尼等。尽管靶向药物的发展使晚期肝癌患者有更多的临床获益，但容易发生治疗抵抗，因此探究靶向药物耐药的相关机制也成为克服肝癌转化治疗抵抗的重要方向。

首先，表皮生长因子受体(epidermal growth factor receptor, EGFR)信号通路在靶向治疗抵抗中扮演重要角色。EGFR突变激活了多个下游致癌通路，包括丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、磷脂酰肌醇-3-激酶–蛋白激酶B(phosphatidylinositol 3-kinase-AKT murine thymoma viral oncogene homolog, PI3K-AKT)和酪氨酸激酶(Janus kinase, JAK)等，导致多激酶抑制剂未能显著改善患者生存率[19]。抑制EGFR的表达可增强HCC细胞对仑伐替尼的敏感性。联合EGFR抑制剂可阻止仑伐替尼对EGFR高表达细胞株中的EGFR信号通路的激活，并抑制下游靶点的磷酸化[20]。此外，本课题组研究发现，分泌蛋白Elafin可以结合EGFR并诱导其二聚体化，进而激活下游的AKT信号通路，促进肝癌转移以及抗EGFR治疗耐药[21]。

其次，肿瘤细胞上皮–间充质转化(epithelial-mesenchymal transition, EMT)可显著促进肝癌靶向治疗抵抗。文献报道，由M2型肿瘤相关巨噬细胞分泌的肝细胞生长因子(hepatocyte growth factor, HGF)，通过激活肿瘤细胞中的HGF/肝细胞生长因子受体(cellular-mesenchymal to epithelial transition factor, c-Met)、ERK1/2-MAPK和PI3K-AKT通路，促进HCC细胞的EMT，维持肿瘤生长和转移，从而赋予HCC对索拉非尼或仑伐替尼的耐药性。成纤维细胞生长因子19(fibroblast growth factor 19, FGF19)通过下调E-钙黏蛋白阻止活性氧的生成并促进EMT，影响肝癌细胞对索拉非尼的敏感性[22]。αB-晶状体蛋白和14-3-3ζ蛋白过表达诱导的EMT组成性地激活ERK通路，而这可减弱索拉非尼在HCC中的治疗作

用[23]。

再次, 肿瘤干细胞促使肝癌发生、去分化、进展和耐药。肝癌干细胞含多个癌细胞亚群, 每个克隆亚群对靶向药物的敏感性不同[24]。多种细胞亚群标志物被认为与治疗耐药性相关, 如肿瘤细胞CD133和CD90的过表达与索拉非尼治疗反应低响应相关。Wnt/β-连环蛋白、ERK、转化生长因子-β(transforming growth factor, TGF-β)、AKT等多条信号通路在肝癌肝细胞中表达异常, 促进患者TKIs治疗耐药。HCC细胞中过表达腺苷甲硫氨酸脱羧酶1(adenosylmethionine decarboxylase 1, AMD1)可显著上调包括NANOG(Nanog homeobox)、*SOX2*(SRY-box transcription factor 2)、*KLF4*(KLF transcription factor 4)和*OCT4*(octamer-binding transcription factor 4)在内的多个干性基因表达, 进而降低HCC细胞对索拉非尼的敏感性[25]。

另外, 包括微小RNA(microRNA)在内的表观遗传学改变也是导致肿瘤细胞对靶向治疗耐药的重要因素之一。有研究显示miR-221、miR-128-3p分别通过调控PI3K-AKT-mTOR通路以及c-Met的表达影响HCC对治疗的敏感性。针对肝癌的抗血管靶向治疗, 本课题组研究发现肝癌中miR-130b-3p下调HOXA5(Homeobox A5)表达, 从而促进肝癌的血管生成, 引起治疗抵抗, 靶向干预HOXA5可显著抑制肝癌血管异常增殖[26]。

研究还表明, 肿瘤微环境的改变、缺氧信号通路的激活以及药物转运通路的失衡等方面都会造成肝癌靶向治疗的失能[27]。

2.2 免疫治疗

随着免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)包括PD-1(programmed death-1)抑制剂和PD-L1(programmed death-ligand 1)抑制剂在临床上的普及, 肝癌正式进入免疫治疗时代。免疫治疗的目标为患者的免疫系统及肿瘤微环境, 并非直接杀死或干扰肿瘤细胞, 而是通过激活体内免疫效应细胞杀死肿瘤细胞的, 或通过激活机体内抗肿瘤免疫应答抑制肿瘤细胞的发生发展, 从而延长患者生存时间。免疫治疗的迅速发展为肝癌治疗提供了全新的治疗理念及方法, 但免疫治疗也并非全人群获益, 仍存在治疗抵抗等问题。临床研究结果显示只有少数肝癌患者对抑制免疫检查点通路治疗有响应, 其中抗PD-1单抗治疗在肝癌患者中的客观缓解率约为20%, 抗CTLA-4(cytotoxic T lymphocyte-associated antigen 4)单抗则仅为17%[28-29]。大量研究致力于探索引起肝癌免疫治疗抵抗的分子机制, 其中包括肿瘤内源性通路异常、微环境适应性改变、抗药物抗体的产生等, 以下就相关机制进行总结。

针对肿瘤内源性通路的异常, 研究表明Wnt/β-连环蛋白信号通路在HCC中的异常激活与肿瘤进展、干细胞特性、转移以及耐药性密切相关。*CTNNB1*(Catenin beta 1)基因突变或Wnt/β-连环蛋白通路的激活会通过下调趋化因子CCL5(C-C motif chemokine ligand 5)的表达抑制树突状细胞(dendritic cells, DCs)的招募, 进而促进免疫逃逸, 并导致HCC对ICIs的耐药[30]。此外, Wnt信号通路的激活还会降低蛋白酪氨酸激酶2(protein tyrosine kinase 2, PTK2)的甲基化水平, 增强HCC干细胞的特性, 从而增加耐药性和复发风险[31]。干扰素-γ(interferon-γ, IFN-γ)信号通路的异常同样是肿瘤内源性耐药的重要机制之一。文献报道IFN-γ通路中*JAK1/2*基因突变, 或信号相关基因的丢失与抑制基因的扩增, 已在对抗CTLA-4和PD-1治疗无反应的患者中被发现, 这进一步揭示了IFN-γ信号通路中断在ICIs耐药中的关键作用[32]。IFN-γ信号通路的损伤还可能导致肿瘤细胞对IFN-γ的反应不敏感, 减少MHC I(major histocompatibility complex class I)类抗原的呈递作用, 从而帮助肿瘤细胞逃避免疫监视[33]。此外, *TP53*基因在HCC的免疫逃逸中也发挥了重要作用。一项包含240例HCC样本的研究发现, 在具有免疫浸润减少和免疫抑制微环境特征的患者中, *TP53*突变率显著增加[34]。本课题组研究结果显示, PRMT3在免疫治疗抵抗肝癌患者肿瘤细胞中表达上调, 上调PRMT3通过对热休克蛋白60(heat shock protein 60, HSP60)的446位精氨酸进行非对称双甲基化修饰, 促进其多聚化, 维持其作为线粒体稳态调节蛋白的功能, 抑制线粒体DNA释放, 进而抑制cGAS/STING(cyclic GMP-AMP synthase/stimulator of interferon genes)信号通路及免疫激活[35]。

肿瘤免疫微环境改变也是影响肝癌免疫治疗疗效的重要因素[36]。癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)具有促进肝癌发生的能力, 它们与肿瘤免疫微环境交互作用, 招募负责抑制免疫应答的树突状细胞和单核细胞, 并通过上调PD-1的表达引起免疫治疗抵抗[37]。CAFs与巨噬

细胞的相互作用促进了肿瘤免疫屏障的构建，而这与ICIs的疗效相关[38]。活化的HSCs在肝癌中扮演着多重角色，初期HSCs通过分泌TGF-β抑制肿瘤生长，但随着疾病进展，TGF-β信号通路激活可能导致PD-1表达上调，从而诱导T细胞耗竭，使肿瘤对PD-1阻断疗法产生耐药性[39]。激活的HSCs还能将成熟的外周血单核细胞转化为髓源性抑制细胞诱导T细胞凋亡及Treg细胞在肝内发生聚集[40-41]。TREM-1(triggering receptor expressed on myeloid cells-1)是髓系细胞触发受体TREMs中的一员，阻断TREM-1阳性的TAMs可以逆转免疫抑制和提高对PD-L1治疗的敏感性[42]。另外有文献报道，肝癌癌旁肝细胞通过分泌血清淀粉样蛋白A，活化中性粒细胞糖酵解途径，激活其LDHA/STAT3通路，进而上调PD-L1的表达；同时，血清淀粉样蛋白A还能促进中性粒细胞分泌肿瘤抑制素M(oncostatin M, OSM)，从而共同抑制$CD8^+$ T细胞的细胞毒功能，最终引起肝癌免疫治疗抵抗[43]。肿瘤浸润性B细胞在肝癌中具有高度的异质性，研究发现，IgG^+浆细胞和巨噬细胞的浸润程度增加与肝癌患者更差的生存相关，机制上肿瘤相关巨噬细胞通过CXCR3-CXCL10轴募集IgG浆细胞，反过来，这些IgG浆细胞主要促进致瘤性巨噬细胞的形成，进而引起免疫抑制微环境的形成[44]。此外，非细胞微环境组分如乳酸[45]、果糖[46]等对肝癌免疫抑制微环境的形成也发挥重要的促进作用。

免疫治疗抵抗的另一个潜在原因是抗药抗体(anti-drug antibodies, ADAs)的产生。大多数单克隆抗体在与宿主免疫相互作用后能够诱导ADAs的形成，部分ADAs可改变药物的清除和中和药物的活性。IMBrave150试验的探索性分析表明，ADA检测结果阳性的患者阿替利珠单抗全身暴露减少，且疗效差于ADA阴性患者[47]。有研究指出高ADAs水平患者的血清阿替利珠单抗浓度降低，$CD8^+$ T细胞增殖受损，$CD8^+$ T细胞产生的IFN-γ和TNF-α(tumor necrosis factor-alpha)水平减少[48]。此外，ADAs可分为中和性和非中和性[49]，中和性ADAs可与单克隆抗体的可变区结合，防止药物被靶向，降低其治疗活性[50]。然而，也有分析指出并非所有ADAs都与药物疗效丧失相关。目前ADAs在免疫治疗中的意义尚未完全明确，需要进一步探索。

另外，有研究报道，肠道微生物组通过与肠道黏膜的免疫细胞相互作用调节免疫反应[51]，然而这种说法在科学界存在争议，有待进一步研究。

3 靶向和免疫联合治疗

如前文所述，单一的治疗方式并不能完全消除肿瘤，且通常存在治疗抵抗的问题，因此近年来肿瘤治疗已经从单一治疗逐渐向联合治疗发展，力求达到“1+1>2”的治疗效果。其中阿替利珠单抗(Atezolizumab)联合贝伐珠单抗(Bevacizumab)(以下简称为T+A方案)被推荐为晚期肝癌治疗的一线用药，与单一治疗方式相比能够显著提高肝癌患者临床完全缓解(complete remission, CR)率，改善患者预后。IMBrave150临床试验数据表明，T+A方案的客观应答率为33.2%，疾病控制率为72.3%[52]。仍有部分患者对T+A方案存在治疗抵抗。GO30140和IMbrave150两项研究中，对患者组织样本开展全转录组测序以及基因富集分析，结果显示，T+A方案响应的患者显著富集抗肿瘤免疫反应相关分子通路，包括IFN-α/γ通路等；而治疗抵抗的患者主要富集血管生成、胆固醇稳态、胆汁酸代谢和Notch信号通路基因[53]。*CXCR2P1*(C-X-C motif chemokine receptor 2 pseudogene 1)、诱导性共刺激分子基因*ICOS*(inducible T cell costimulator)、*TIMD4*(T cell immunoglobulin and mucin domain containing 4)等显著差异基因可作为T+A治疗临床响应潜在分子标志物。同时，初步免疫浸润分析表明，$CD8^+$ T细胞、$CD4^+$ T细胞、Tregs、B细胞、DC细胞均参与T+A治疗调控[53]。

联合治疗方面，本课题组提出强化化疗的TACE联合HAIC策略。研究结果发现，相较于传统的TACE治疗，TACE-HAIC可大幅度提高肝癌手术转化成功率，改善肝癌总体预后[2]。TACE-HAIC组手术转化率为48.8%，而TACE组为9.5%。同时，TACE-HAIC未增加严重不良反应，可行性高，这在一定程度上缓解了单一TACE/HACI治疗抵抗压力。此外，团队探讨了TACE-HAIC联合靶向免疫的新治疗模式对肝癌合并门静脉癌栓患者的疗效。相较于传统的TACE治疗方式，新治疗模式可显著提高该类患者转化手术率和改善预后[2]。联合组患者ORR为53.7%，而单纯TACE组仅7.8%(mRECIST)，联合组中位无进展生存期为14.8个月，显著长于TACE组的2.3个月[54]。尽管联合治疗模式可有效提高肝癌患者转化治疗疗效，但仍存在治疗抵抗的情况，其分子机制是否与单一治疗相同或者存在新的机制，还需要进一步探究。

4 结语

经过多年探索, 转化治疗已成为肝癌临床治疗的重要组成部分, 克服患者转化治疗抵抗也成为临床以及科研工作者面临的巨大挑战。目前, 针对已发现的耐药靶点、新的小分子抑制剂、蛋白降解靶向嵌合分子(PROTAC)以及CAT-T治疗等逆转手段的研究也在不断涌现, 并逐步应用于临床。未来的研究重点将继续聚焦于新的分子标记物和逆转耐药靶点的发掘, 同时推动联合用药新药研发, 从而为患者提供更精准、高效的治疗方案, 延长肝癌患者整体生存期, 并显著提升患者的生活质量。

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