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·述评·

肝癌免疫微环境与免疫治疗：研究进展与发展趋势

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摘 要 肝癌微环境主要由肿瘤相关巨噬细胞、肿瘤相关中性粒细胞、骨髓源性抑制细胞、肿瘤相关成纤维细胞和肿瘤浸润性淋巴细胞等细胞组分，以及细胞外基质、细胞因子等非细胞组分组成。免疫微环境在肝癌进程、免疫逃逸和治疗抵抗中发挥重要作用。近期，以调变炎症免疫微环境为基础的免疫治疗取得突破性进展，免疫疗法的出现为肝癌治疗提供了全新的选择，但仍存在客观缓解率较低、不良反应多和耐药问题。因此，深入研究微环境在肝癌发生发展中的作用及探索免疫治疗的未来发展趋势可提高现有治疗手段的应答率，对肝癌精准诊断与治疗有重要的理论价值和临床意义。

关键词 癌，肝细胞；肿瘤微环境；免疫疗法；免疫检查点；过继转移；癌症疫苗
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Immune microenvironment and immunotherapy in hepatocellular carcinoma: research progress and development directions

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Abstract The tumor microenvironment in hepatocellular carcinoma (HCC) comprises a variety of cell types that include tumor-associated macrophages, tumor-associated neutrophils, myeloid-derived suppressor cells, cancer-associated fibroblasts and tumor infiltrating lymphocytes, etc., as well as extra-cellular components such as cytokines, growth factors, hormones, extracellular matrix. The immune microenvironment plays important roles in the progression, immune escape and therapeutic response of HCC. In recent years, dramatic advances have been achieved in immunotherapy based on inflammatory microenvironment modulation, and the emergence of immunotherapy provides a promising new strategy for the treatment of HCC. However, low objective response rate, and high adverse reaction and high resistance rates are still noted. Therefore, deep understanding of the role of the microenvironment in the progression of HCC and the exploration of the future development of immunotherapy will improve the response rates of the current treatment approaches, and be of great theoretical value and clinical significance for precise diagnosis and treatment of HCC.

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众所周知，肿瘤微环境是肿瘤发生、发展所处的内外环境，在肿瘤进程、免疫逃逸和治疗抵抗中发挥重要作用[1]。肿瘤微环境主要由肿瘤浸润的淋巴细胞、髓系来源细胞、成纤维细胞等细胞组分，以及分泌的炎症因子和趋化因子等非细胞成分组成[2]。肝细胞癌（hepatocellular carcinoma，HCC，简称肝癌）是典型的炎性相关性恶性肿瘤，其微环境中包含大量的巨噬细胞及一系列固有免疫和适应性免疫细胞，形成复杂的免疫耐受微环境[1, 3]。免疫治疗可通过增强机体免疫反应，激发肿瘤特异性免疫，打破免疫耐受，重新激活免疫细胞等途径使其识别并杀伤肿瘤细胞，进而达到延缓肿瘤进展的目的。目前已有多种免疫疗法应用于晚期肝癌治疗[4]。本文重点总结肝癌微环境的主要组分及其在肝癌发生发展中的作用、以及相关免疫治疗的最新进展。

1 肝癌的微环境

肝脏具有一定的特殊性，由于其经常暴露于肠源性抗原进而形成了免疫耐受的微环境，故被称为免疫特赦器官[5]。在我国，肝癌多发生在慢性乙型肝炎（以下简称“乙肝”）等基础上，在患者数十年的肝炎病程中，各种炎性细胞相互作用，形成了更为复杂的微环境，导致肝癌微环境常伴随慢性炎症[6]。肝癌的微环境主要由肿瘤相关巨噬细胞（tumor-associated macrophages，TAM）、肿瘤相关中性粒细胞（tumor-associated neutrophils，TAN）、骨髓源性抑制细胞（myeloid-derived suppressor cells，MDSC）、肿瘤相关成纤维细胞（cancer-associated fibroblasts，CAF）、肿瘤浸润淋巴细胞（tumor infiltrating lymphocytes，TIL）和树突状细胞（dendritic cells，DC）等细胞组分，以及细胞外基质（extracellular matrix，ECM）、细胞因子等非细胞组分组成。与其他肿瘤相比，肝癌免疫微环境表现为更强的免疫抑制作用，几乎所有细胞亚群和众多调控机制都有助于肝癌的进展。例如库普夫细胞是肝脏内的巨噬细胞，其通过产生抗炎分子转化生长因子β（TGF-β）、IL-10和前列腺素E2（PGE2），在抑制性微环境的形成的过程中发挥重要作用[7]。在病毒性肝炎介导肝癌的发生过程中，病毒感染可以通过驱动肝脏慢性炎症、分泌多种抑制性性因子促进肝癌发展和免疫逃逸[8]。此外，乙肝患者肝内调节性T细胞（regulatory T cells，Treg）的浸润频率与病毒载量相关，表明慢性病毒性肝炎感染肝脏中Treg的积累可能会阻止CD8+T细胞对病毒清除[9]。肝癌显著的免疫抑制微环境对有效的肝癌免疫治疗将是一个巨大的挑战。

1.1 TAM

TAM是肝癌微环境的重要组成部分，根据其功能特点，可分为两种类型：经典活化型巨噬细胞（classically activated macrophage，M1）和替代活化型巨噬细胞（alternatively activated macrophage，M2）[10]。既往认为巨噬细胞可以直接杀伤肿瘤、或者递呈抗原给T细胞，具有消灭肿瘤的能力，但越来越多的证据表明，TAM促进肿瘤的进展和转移[11]。近期，研究者们通过单细胞测序技术揭示肝癌免疫微环境的动态特征，发现肝癌肿瘤中的巨噬细胞呈现两种不同的状态：TAM-like和MDSC-like状态[12]。一般认为，TAM来源于外周血单核细胞，可被肿瘤微环境分泌的细胞因子如CCL2、CSF1等招募至肿瘤周围，肿瘤微环境将单核细胞“驯化”为M2型巨噬细胞，分泌抑炎性细胞因子如IL-8、IL-10、TGF-β等，促进血管生成、抗炎及基质重塑，诱导CD8+T淋巴细胞的凋亡，抑制Th1型免疫反应，重塑微环境，影响免疫稳态，从而促进肿瘤的生长、侵袭和转移[13-15]。目前，越来越多的研究[13, 16-18]证实，TAM影响包括肝癌在内多种肿瘤的血管生成、侵袭转移以及患者预后。我们课题组发现TAM与肝癌侵袭转移的关键调控基因骨桥蛋白（osteopontin，OPN）的表达密切相关，联合OPN及TAM可以预测肝癌患者预后，即使在甲胎蛋白（alpha fetoprotein，AFP）阴性的肝癌患者中，两者联合也具有很好的预测效能[15]。在此基础上，我们进一步发现OPN可通过PI3K-Akt-p65通路刺激巨噬细胞分泌CSF1，激活CSF1/CSF1R通路，进而促进巨噬细胞M2型极化，上调肝癌细胞PD-L1的表达，营造抑制性免疫微环境并诱导肝癌的免疫逃

逸[19]。因此，针对TAM设计抗肿瘤药物已成为肿瘤治疗的研究热点[20-22]。

1.2 TAN

TAN作为机体免疫系统的重要组成部分，在肿瘤进展与转移中扮演着多重角色。早在2009年，Fridlender等[23]将TAN划分为抑制肿瘤的N1和促肿瘤的N2亚型。N1表型具有细胞毒性和促炎活性，而N2表型具有较强的免疫抑制能力[24]。大量研究发现TAN能够分泌细胞因子、基质蛋白酶等促进肿瘤增殖、侵袭和转移；另一方面，中性粒细胞自身的细胞毒性对肿瘤也具有一定杀伤作用[25]。随着研究的深入，TAN在塑造转移前龛、捕获循环肿瘤细胞（circulating tumor cells，CTC）及免疫抑制方面的独特作用越来越受到关注，其在肝癌的进程中也发挥着重要作用。既往研究[26-27]发现中性粒细胞–淋巴细胞比值（neutrophil-lymphocyte ratio，NLR）可反映肝癌转移等进程。TAN通过招募TAM和Treg，促进肝癌的生长和血管形成[28]。此外，TAN可通过激活miR-301b-3p/LSAMP/CYLD通路，增强肝癌细胞的“干性”；同时，这些干细胞样肝癌细胞分泌趋化因子CXCL5，招募TAN瘤内浸润，从而构成TAN-干细胞样肝癌细胞环路，促进肝癌侵袭转移[29]。近年研究[30-31]证实TAN通过向胞外释放染色质结构形成胞外诱捕网（neutrophil extracellular traps，NET），通过炎症与免疫调控影响肿瘤进展。我们课题组发现肝癌患者中NET形成能力显著增强，并与肝癌转移密切相关。NET通过捕获CTC、并增加其迁移能力及血管新生最终促进肝癌转移[32]。

1.3 MDSC

MDSC是具有显著异质性的抑制性免疫细胞，分布于骨髓、脾脏、外周血和肿瘤组织中，可分为单核MDSC（M-MDSC）和粒细胞或多形核MDSC（PMN-MDSC）两种类型[33]。近年来MDSC被认为是免疫抑制细胞的核心，具有多种促肿瘤作用。其可通过血管内皮生长因子促进肿瘤血管生成，同时破坏先天性和获得性抗肿瘤免疫[34]。另外，有大量文献报道MDSC可通过诱导Treg分化增殖、抑制DC、自然杀伤（natural killer，NK）细胞极化状态和巨噬细胞向M2表型转化、诱导氧化应激等途径发挥免疫抑制作用[35-37]。在肝癌中，已发现肝癌患者外周血MDSC可以预测患者预后。与肝炎或肝硬化患者及健康对照组相比，肝癌患者外周血MDSC的数量显著增加，而且外周血高密度的MDSC与肿瘤转移及不良预后有关[38-40]。肝癌细胞分泌的细胞因子如G-CSF、GM-CSF、VEGF、CCRK、IL-1β等可诱导MDSC浸润，靶向MDSC能增强索拉非尼或免疫检查点抑制剂的抗肿瘤作用[41-42]。

1.4 CAF

CAF是肿瘤微环境的重要组成部分，几乎存在于所有实体瘤中。肝癌组织中CAF特定的分子标志物如成纤维细胞激活蛋白（fibroblast activating protein，FAP）、α–平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）等高表达的患者，往往预后较差，易转移复发[43]。越来越多的研究[44-45]证实CAF可通过分泌多种生长因子和细胞因子促进肿瘤增殖、侵袭和转移。我们发现，CAF通过诱导肝癌细胞叉头框蛋白Q1（FOXQ1）的表达并激活调节基因1（NDRG1）促进肝癌干性特征。激活的肝癌细胞分泌C-C基趋化因子配体26（chemokine ligand 26，CCL26）从而招募更多的CAF促进肝癌进程[46]。在血管生成中，CAF通过CXCL12招募内皮祖细胞，并通过产生细胞外基质和分泌基质金属蛋白酶参与组织重塑，促进血管形成。而且，CAF可通过诱导肿瘤细胞上皮间质转化（epithelial-mesenchymal transition，EMT），增强其侵袭转移的能力[47]。近年来发现，CAF可通过分泌趋化因子等调节周围免疫细胞，在肿瘤免疫调控方面发挥重要作用。CAF可诱导TAN等髓系来源的免疫抑制性细胞介导免疫抑制的发生，参与肝癌免疫逃逸[48-50]。因此，靶向CAF的特异性分子标志物如FAP及靶向CAF特异基因抑制剂的治疗方案可能会成为一种有效的肝癌辅助治疗。

1.5 TIL

TIL是肝癌微环境的重要组成部分。早期临床数据表明，肝癌术后高水平淋巴细胞浸润，尤其是T细胞，可以减少复发，提高生存率[51]。TIL主要包括Treg、自然杀伤（natural killer，NK）细胞、细胞毒性T淋巴细胞（cytotoxic T lymphocyte，CTL）和B细胞等。Treg是一种CD4+T细胞的亚群，可通过多种方式抑制肿瘤免疫[52]。已发现肝癌组织中Treg细胞大量增加，且与门静脉癌栓形成、转移复发及不良预后相关[53]。Treg–细胞毒性T淋巴细胞（cytotoxic T lymphocyte，CTL）比值（Treg/CTL）反应肝癌局部免疫平衡状态，当CTL增多时，可以有效地对抗Treg对患者免疫系统的抑制作用，增强机体的免

疫力，有利于杀伤肿瘤细胞[54]。研究[53]发现肝癌中高密度的肿瘤浸润性CD4+CD25+Foxp3+Treg，预示不良预后。Lee等[55]发现肿瘤微环境中CD4+CD25+Treg的增加与肿瘤大小相关，且这些CD4+CD25+Treg抑制肝癌中DC的免疫应答。这些证据表明，抑制Treg可能是诱导肝癌免疫应答的重要途径。NK细胞和CTL是在肿瘤免疫监视和肿瘤细胞根除中起着不可或缺的作用的抗肿瘤免疫细胞。NK细胞介导固有免疫反应且能在不需要在致敏的情况下直接介导细胞毒副作用[56]。但在肿瘤内部NK细胞功能通常受到抑制。近期研究发现，肝癌高表达的miR-561-5p直接靶向降低CX3CL1的表达，减少微环境中CX3CR1+NK细胞亚型的浸润，促进癌细胞的存活并促进肺转移[57]。肝癌细胞外泌体来源的circUHRF可通过miR-449c-5p/TIM-3途径抑制NK细胞功能、促进肝癌的免疫逃逸和抗PD-1免疫疗法的耐药性[58]。CD8+T淋巴细胞是肝癌的主要CTL，研究发现CD8+T细胞Fas/FasL的表达与肝癌抗肿瘤免疫呈正相关[59]。然而，CTL介导的抗肿瘤免疫应答的有效性受到多种机制的限制，例如T细胞或肝癌细胞中大量免疫调节分子的高表达（如IL-10、Fas/FasL、CXCL17、VEGF、吲哚胺-2，3二氧合酶等），微环境改变（如乳酸过载、低pH、缺氧），与肿瘤细胞的“代谢竞争”以及缺乏CD4+T细胞的辅助等都可能是CTL功能受限的原因[59-61]。B细胞也是人体肿瘤组织中的一个重要免疫成分。目前，越来越多的证据表明B细胞浸润与肿瘤预后和免疫治疗疗效密切相关[62-63]。在晚期肝癌组织中，PD-1高表达的B细胞浸润水平与肝癌患者术后早期复发呈显著正相关，模式识别受体TLR4引起的Bcl-6上调是肝癌组织微环境引起PD-1高表达B细胞产生的重要机制且激活PD-1信号通路能够刺激该群细胞分泌IL-10从而抑制效应T细胞抗肿瘤免疫应答，促进肝癌生长[64]。此外，肝癌中B细胞的成熟及抗体分泌可显著影响甚至逆转表观遗传治疗的疗效，并提出基于体液免疫阻断以及表观遗传治疗的联合治疗方案为新型肿瘤免疫治疗策略提供理论依据[65]。2017年研究人员首次在单细胞水平上对肝癌微环境中T细胞进行系统分析，发现肝癌内存在大量肿瘤组织特异的克隆增生的耗竭性T细胞，而且在耗竭性CD8+T细胞亚群中发现了一类FOXP3+抑制性T细胞的存在，揭示了肝癌中T细胞的亚群分类、发展轨迹和分布[66]。

1.6 DC

DC是人体最重要的抗原呈递细胞，通过向淋巴组织中没有接触过抗原的T细胞以抗原肽–主要组织相容性复合体（major histocompatibility complex，MHC）复合体的形式呈递捕获的抗原并激发免疫反应并诱导MHC Ⅱ和共刺激因子CD80/86的表达，迁移到区域淋巴结，并与T细胞相互作用并激活适应性免疫应答[67]。研究[68]发现肝癌组织内浆细胞样DC是原发性肝癌切除术后的不良预后因素，瘤内浸润的DC可能通过诱导由调节性T细胞和IL-17产生免疫致炎性肿瘤微环境，与肝癌患者不良预后密切相关。单细胞测序发现在肝癌中富集cDC1、cDC2和LAMP3+DC 3个DC亚群，LAMP3+DC是从肿瘤迁移到淋巴结的更成熟的DC形式，可通过CCL19-CCR7、CCL22-CCR4和CD86-CD28等多条信号途径发挥作用，提示LAMP3+DC与T细胞功能障碍有关[12]。此外，有研究[69]提示CD14+DC表达高水平的CTLA-4，并通过诱导IL-10和吲哚胺-2，3–双加氧酶（indoleamine 2，3-dioxygenase，IDO）表达抑制T细胞效应。当前以DC 为基础的免疫治疗是肿瘤生物免疫治疗中最有前景和最有价值的治疗方法之一，因此，如何调控DC的免疫功能使其发挥抗肿瘤作用将是未来研究的方向。

1.7 肝癌微环境的非细胞组分

肝癌微环境中各种细胞分泌的炎性因子、趋化因子以及ECM等非细胞组分均参与肝癌的增殖、侵袭、转移等不同过程[70-71]。我们与美国国立卫生研究院（NIH）合作，通过分析伴有与不伴转移肝癌的癌周肝组织基因表达谱差异，发现其中最重要的是细胞免疫、炎症应答相关基因，而且伴转移的癌周肝组织存在明显细胞因子应答和炎症反应失衡（Th1/Th2 shift）。利用17个癌周肝组织炎症免疫因子的转移及免疫分子预测标签可以很好的预测肝癌患者的生存和转移复发[72]。在此基础上，我们进一步经过临床大样本验证，证实癌旁肝组织中IL-2和IL-15、M-CSF表达与肝癌进展、复发相关，其表达水平可预测早期肝癌术后转移复发和生存[73-74]。此外发现，炎症因子IL-6可通过OPN调控肝癌干性、促进转移[75]。近年来研究发现趋化因子CXCL12及其受体CXCR7、CXCR4可促进肝癌的侵袭和转移，与肝癌进程、新生血管形成、EMT及不良预后等密切相关[76-77]，CCL2在肝癌患者中表达水平可作为肝癌患者预后预测

因子[77]。而且趋化因子也可通过招募免疫细胞影响免疫应答，如CCR4可招募中性粒细胞参与转移前龛的形成、进而促进肝癌转移[78]；CCR6-CCL20可通过招募Treg促进肝癌进展和不良预后[79]。另外，ECM在肿瘤发生发展中也发挥重要作用，肿瘤细胞表达多种ECM蛋白成分使得肿瘤组织结构改变进而影响肿瘤进程[80]。利用瞬时弹性成像技术检测肝组织硬度，发现肝癌患者中肝组织硬度明显增加，而且肝组织硬度与肝癌进展相关[81]。同时基质支撑可为肿瘤起始细胞提供有利壁龛，促进肝癌增殖、化疗抗性和去分化[82]。而且在肝癌转移前壁龛的形成过程中，ECM还可为免疫抑制细胞浸润提供机械支撑[83]。因此阻断肝癌细胞炎症因子、趋化因子相关的信号通路，可有效抑制肝癌进程。

2　肝癌免疫治疗策略

近年，以免疫检查点抑制剂为代表的肿瘤免疫治疗取得突破性进展[84]，为肿瘤的治疗带来了新的曙光。免疫疗法的出现为肝癌治疗提供了新的选择，包括免疫检查点抑制剂、过继细胞疗法（adoptive cell transfer，ACT）、肿瘤疫苗以及细胞因子治疗等。

2.1　免疫检查点抑制剂

免疫检查点抑制剂通过逆转T细胞功能的耗竭，恢复免疫识别和免疫攻击，从而增强抗肿瘤免疫反应。目前，免疫检查点抑制剂靶点主要包括程序性细胞死亡配体1（programmed death ligand 1，PD-L1）及其受体PD-1（programmed cell death protein 1）、细胞毒性T淋巴细胞相关抗原4（cytotoxic T lymphocyte antigen 4，CTLA-4）[85]。PD-1是CD28家族的一员，表达于大多免疫细胞表面，主要在CD8+T细胞上表达。其可与配体PD-L1和PD-L2结合导致抑制性信号传递到T细胞并诱导耐受[86]。PD-L1在多种肿瘤包括肝癌中异常表达，肿瘤细胞可通过异常表达PD-L1或PD-L2获得免疫逃逸[87]。2017年9月23日，美国食品药品监督管理局（FDA）批准了纳武单抗（nivolumab，PD-1单抗）在晚期肝癌中的二线治疗[88]。截止目前，免疫检查点抑制剂已经在肝癌领域进行了多项探索性研究。随着CheckMate 040、KEYNOTE-240、KEYNOTE-224和SHR-1210等研究结果陆续发布，派姆单抗（pembrolizumab，PD-1单抗）、阿特利珠单抗（atezolizumab，PD-L1单抗）已相继被国内外多个指南纳入并推荐作为肝癌的临床治疗选择。作为我国自主研发的PD-1抑制剂——卡瑞利珠单抗（艾瑞卡®）是我国首个获批肝癌适应证的PD-1抑制剂。今年中国临床肿瘤学会（CSCO）指南的二线治疗更是将nivolumab、pembrolizumab、卡瑞利珠单抗3种PD-1抑制剂，共同提升到了I级推荐（2A级证据）。CTLA-4是CD28家族的另一个成员，主要在活化的T细胞和树突状细胞上表达，与B7分子结合后参与免疫反应的负性调节[64]。伊匹单抗（ipilimumab）和替西木单抗（tremelimumab）均为CTLA-4抑制剂，其中ipilimumab是首个获FDA批准，最早应用于临床的免疫检查点抑制剂。2013年临床试验表明tremelimumab可以有效发挥抗肝癌作用[89]。随着对CTLA-4抗体药物的作用机制的深入研究，有学者认为CTLA-4抗体药物的作用机理并不是免疫检查点假说，而是通过靶向清除肿瘤内Treg发挥治疗效果[90-91]。目前临床试验结果显示单用免疫检查点抑制剂的患者应答率较低，因此免疫检查点抑制剂与其他治疗方式的联合应用将是未来方向。

2.2　过继细胞疗法（ACT）

ACT是一种以利用肿瘤患者自身免疫细胞为基础的免疫治疗。分离肿瘤患者体内免疫活性细胞，通过细胞因子刺激、体外培养或肿瘤抗原负载，在体外进行大量扩增和功能鉴定，再回输至患者体内，增强免疫功能，达到杀伤肿瘤的目的。与抗体或其他靶向药物相比，ACT可以在体内激活和增殖，具有持久抗肿瘤作用，因此ACT又被称为是一种“活”的治疗方法[92]。对于肝癌来说，细胞因子诱导的杀伤细胞（cytokines induced killer cells，CIKs）和嵌合抗原受体T细胞（chimeric antigen receptor T-cell，CAR-T）是主要的治疗策略。CIKs是人的外周血单核细胞（peripheral blood mononuclear cell，PBMC）在IL-2、IFN-γ和抗CD3单抗存在条件下体外扩增产生的异质性免疫细胞群[93]，由自然杀伤T（natural killer T，NKT）细胞、NK细胞和CTL组成，对肿瘤细胞具有较强的细胞溶解活性，与MHC限制性无关。CIKs可清除残余癌细胞，预防肿瘤的复发和转移，用于放化疗无效的患者。肝癌的多项临床试验表明，CIKs治疗可提高患者的总生存率（overall survival，OS）和无瘤生存率（disease

　

free survival，DFS），具有相当的疗效[94-96]。但由于CIKs细胞因子相关的不良反应以及存在免疫逃逸机制和缺乏特定肿瘤抗原，该疗法仍未广泛应用于临床[97]。CAR-T免疫疗法是一种利用基因工程技术修饰患者T细胞使其能够表达嵌合抗原受体CAR以特异性识别并杀死癌细胞发挥抗肿瘤作用，是目前ACT治疗的研究热点。CAR-T细胞疗法已在血液系统肿瘤中获得成功，靶向CD19的CAR-T细胞已获FDA批准应用于急性B淋巴细胞白血病及某些B细胞淋巴瘤的治疗[98]。但由于实体瘤缺乏特异性靶点且易受肿瘤微环境的影响，关于肝癌的CAR-T疗法仍处于研究阶段[99]。目前，主要以磷脂酰肌醇聚糖（glypican-3，GPC3）为靶点的CAR-T细胞已证实能清除GPC3高表达的肝癌[100]。近日，全球首个靶向GPC3的CAR-T细胞治疗晚期肝癌的I期临床研究结果公布，治疗的安全性和有效性均获得了令人期待的结果。接受该治疗后患者耐受性良好、安全基本可控，罕见严重毒副反应，并初步显示出较好的临床获益[101]。

2.3 治疗性肿瘤疫苗

肿瘤疫苗是将肿瘤抗原以多种形式导入患者体内，克服免疫抑制状态，增强免疫原性，进而激活患者自身免疫系统来治疗肿瘤的免疫疗法。2010年，provenge（普列威）成为首款被FDA批准上市的前列腺癌抗肿瘤疫苗。目前，用于肝癌的肿瘤疫苗主要包括多肽疫苗、DC疫苗和溶瘤病毒疫苗。目前多肽疫苗报道较多的是AFP多肽疫苗和GPC3多肽疫苗。AFP是一种被广泛用作肝癌患者的血清标志物[102]，因在肝癌细胞中的高表达使其成为基于疫苗治疗的一个有前途的靶点[103]。早期用肝癌-AFP多肽疫苗进行的临床研究体现较好的抗肿瘤活性[103-105]。一项肝癌的I期临床试验发现GPC3肽疫苗具有良好的耐受性，可检测到显著的免疫应答和抗肿瘤作用，并延长患者总体生存时间[106]。目前在肝癌中发现了大量的肿瘤抗原，但仅针对AFP、GPC-3和MRP3的疫苗表现出良好的耐受性和安全性，这些疫苗的特异性T细胞应答率超过70%。相比之下，针对NY ESO-1、SSX-2、MAGE-A和TERT肽疫苗的T细胞应答率低于40%[107]。在一些回顾性研究以及I、II期临床研究中，DC疫苗被应用于晚期肝癌患者并在部分患者中体现出对于肿瘤的免疫应答[108-109]。JX-594是目前临床试验中与肝癌相关的主要溶瘤病毒，来源于痘苗病毒疫苗株，在癌细胞中优先复制并裂解，临床试验结果显示它是安全的[110]。目前，有两项与JX-594相关的晚期肝癌的III期临床实验正在进行中（NCT02562755，NCT03071094）。尽管肝癌治疗性肿瘤疫苗显示良好的临床应用前景，但其临床应用仍需更多的临床实验进一步验证其疗效及安全性。

2.4 干扰素和其他细胞因子治疗

目前，一些具有免疫细胞激活功能的细胞因子在肿瘤中被广泛研究，以发展潜在的免疫激活剂和抗肿瘤药物。干扰素α（IFN-α）是FDA批准第一个应用于肿瘤免疫治疗的药物[111]，能抑制病毒诱导的肿瘤生长，具有抗增殖、免疫调节和抗病毒的特性[112]。近年不少研究发现IFNs有预防病毒性肝炎相关肝癌发生及肝癌术后复发、转移的作用。本课题组通过对照研究发现，根治性切除的肝癌患者术后长期使用长效干扰素能够有效延长患者生存，推迟复发[113]。一项Meta分析显示，干扰素辅助治疗可提高肝癌患者治疗性肿瘤疫苗术后总生存率，同时可降低部分治疗患者术后复发率[114]。目前研究及报道较多的是干扰素联合化疗栓塞治疗预防肝癌术后复发，研究发现肝癌患者术后给予干扰素联合化疗栓塞较单纯化疗栓塞组术后复发率明显降低。尽管干扰素作为抗肿瘤药物的一线地位逐渐被取代，但在肝癌领域，IFN-α的新型制剂长效聚乙二醇化IFN-α（PEG-IFN-α）则继续扮演着重要的辅助用药角色。临床前研究发现干扰素β（IFN-β）除了抗病毒作用外，也可通过JAK-STAT信号途径和p53蛋白两条途径发挥抗肿瘤活性[115]。此外，IL-2对免疫系统也具有多效性作用，可以增强T细胞的增殖并激活其抗肿瘤作用。对于无法手术的肝癌患者，经IL-2治疗后，患者的生存率有所提高[116]。这些结果提示肝癌中干扰素和其他细胞因子治疗具有良好的免疫治疗应用前景。

3 肝癌免疫治疗面临的挑战与展望

近年来免疫治疗在肿瘤治疗领域取得重大突破，其在肝癌中的应用越来越受到关注，但目前仍面临着疗效不确定性、客观缓解率低、不良反应多、甚至患者获益之后仍可出现耐药抵抗等问题。因此，如何改善肿瘤免疫微环境，调节机体免疫反应，基于分子分型指导肝癌免疫治疗方案的选择及联合治疗等有效提高免疫治疗疗效，让

更多的肝癌患者从中获益，是肝癌精准治疗亟待解决的问题和未来发展方向。

3.1 肝癌免疫治疗面临的挑战

尽管免疫疗法经取得令人欣喜的成果且已批准用于肝癌的治疗选择。然而，单用PD-1/PD-L1抗体的客观反应率很少超过40%，而且nivolumab与pembrolizumab在肝癌中的客观反应率也未超过20%[117]。目前认为免疫治疗客观缓解率低的主要原因在于耐药的产生[118]。免疫治疗的耐药是一个复杂、多机制相互依赖的动态过程，包括肿瘤内免疫浸润受损、T细胞耗竭、免疫抑制细胞（Treg、MDSC）募集、表观遗传改变等原因。此外，免疫相关不良反应也是影响免疫治疗广泛应用的重要原因[119]。如免疫检查点抑制剂可引起炎症性不良反应，包括垂体炎、甲状腺功能障碍和糖尿病。靶向CTLA4免疫治疗的患者对垂体炎的易感性增加，而靶向PD1与原发性甲状腺功能不全有关，少数病例表现为I型糖尿病[120]。而CAR-T治疗的重大缺陷是副作用，如细胞因子释放综合征、神经毒性等，而且有7%~9%的患者由于CAR-T细胞生产失败而不能接受CAR-T治疗。另外，免疫治疗特异性靶点的选择、如何保证ACT细胞更有效的到达肿瘤部位以及如何抵抗肿瘤微环境的免疫抑制等也是肝癌等实体瘤的免疫治疗过程中面临的挑战[4]。因此，免疫治疗的安全性、疗效及选择合适的靶抗原是肝癌免疫治疗成功的关键，也是肝癌免疫治疗应用于临床之前必须解决的问题。

3.2 以肝癌免疫治疗为基础的联合治疗

肝癌处于复杂的免疫微环境中，目前单一免疫疗法具有较低的缓解率和生存率，特别是Checkmate-459 III期临床试验结果表明nivolumb对不可切除肝癌的治疗效果并未优于索拉非尼，免疫治疗冲击肝癌一线治疗药物的首次尝试宣告失败（NCT02576509）[121]。因此，针对肝癌免疫治疗研究的重点也逐渐转向多靶点联合治疗。近期，临床III期试验IMbrave150相关研究数据表明atezolizumab联合抗血管生成药贝伐珠单抗（bevacizumab）显著降低晚期不可手术切除的肝癌患者的死亡风险，且明显改善患者生存质量，成为首个不可切除的晚期肝癌的一线联合治疗方案[122]。该“T+A”免疫联合疗法是目前全球公认的一线治疗方案，也是CSCO指南推荐的唯一一个一线首选（Ⅰ级专家推荐）免疫治疗方案。另一项临床试验KEYNOTE-524旨在评价肝癌靶向治疗一线药物仑伐替尼（lenvatinib）联合帕博利珠单抗（pembrolizumab）治疗不可切除的肝癌，今年ASCO最新数据显示，该联合方案对肝癌的客观缓解率高达46%，但其临床应用还有待于III期临床实验数据的进一步证实。此外，肝癌靶向治疗药物卡博替尼联合Atezolizumab的COSMIC-312 III期临床研究也在进行中。目前，双肿瘤免疫疗法相关的临床研究也在不断开展，CheckMate040是评估nivolumab联合ipilimumab的治疗效果，提示针对不同靶点的免疫检查点抑制剂的联合使用可能会产生协同效应（NCT01658878），目前该双免疫疗法已正式获FDA批准用于既往接受过索拉非尼治疗的肝癌的患者。PD-L1单抗德瓦鲁单抗（durvaluamb）联合tremelimumab一线治疗晚期肝癌的临床研究也正在进行中（NCT03298451）。同样，免疫治疗与局部治疗如消融、放疗、栓塞、化疗栓塞或放射性栓塞的联合应用也可促进抗肿瘤免疫治疗疗效。研究[123]发现，接受射频消融治疗的晚期肝癌患者使用tremelimumab治疗后肿瘤内CD8+T细胞的积聚增加且中位生存期提高至13个月。射频消融术联合序贯细胞免疫治疗可提高肝癌患者无进展生存期[124]。另外，卡瑞利珠单抗联合化疗方案FOLFOX4的III期临床试验正在进行中。目前，多项免疫治疗与局部治疗联合的临床实验也已启动以评估其安全性、耐受性和疗效（NCT03143270、NCT02837029、NCT02821754、NCT01853618），有待进一步研究结果。因此，针对免疫治疗开展的联合干预有助于探索新型的有效治疗策略，给肝癌患者带来更加持久的生存获益，可能成为未来肿瘤治疗的发展方向。

3.3 肝癌分子分型与免疫治疗

异质性是影响实体肿瘤疗效的根本原因[125]，肝癌被认为是异质性最强的实体瘤之一[126]，因此，不同的肝癌人群对免疫治疗疗效存在显著差异。大量研究[127-128]提示PD-L1表达水平、TIL丰度、肿瘤突变负荷（tumor mutational burden，TMB）和微卫星不稳定（microsatellite instability，MSI）等可以预测免疫检查点抑制剂疗效。另外，有研究[129]发现基于肿瘤中心和边缘T细胞浸润频率和分布模式以及相关免疫基因的表达水平可建立肝癌微环境评分系统，对免疫治疗具有一定的指导意

义。例如基于肿瘤微环境评分可将肝癌分为免疫激活型、免疫耗竭型和免疫豁免型。对于免疫激活型，因肿瘤中心部位有一定量的特异性T细胞，利用免疫检查点抑制剂可有效恢复T细胞的杀伤活性并取得显著的抗肿瘤疗效；免疫豁免型因缺乏特异性T细胞，需要通过放疗、ACT、溶瘤病毒等方法促进T细胞浸润；免疫耗竭型则主要通过诱导T细胞归巢、打破T细胞浸润屏障的治疗策略提升抗肿瘤免疫反应[130]。近期基于中国人群中肝癌的蛋白组学的分析结果显示，肝癌患者中常携带的马兜铃酸的突变“指纹”与TMB、肿瘤新抗原、微环境免疫耐受（如CD8+T细胞浸润、PD-L1等免疫检查点丰度）显著相关，提示该类患者可能从免疫治疗中获益[131]。因此切实有效的肝癌分子分型是指导精准治疗的基础。

3.4 肝癌“免疫正常化”疗法

一直以来，癌症免疫治疗的基本策略是利用抗肿瘤免疫反应，人们主要致力于激活和增强免疫反应以消除肿瘤，包括癌症疫苗、细胞因子、CAR-T等治疗方法。但这种“免疫增强”的治疗策略常常导致一系列副作用——免疫相关不良事件（immune-related adverse events，irAEs）。目前针对PD-1/PD-L1途径的癌症免疫疗法取得了较高的客观疗效且irAEs较少见，这种方法基于免疫逃逸的机制，使得抗肿瘤免疫反应失而复得，故称之为“免疫正常化”疗法[132]。该治疗手段强调了在肿瘤进展过程中识别免疫反应的特定缺陷或功能障碍并据此纠正这些缺陷且恢复天然的抗肿瘤免疫能力的重要性。由于肝癌是高度免疫抑制性肿瘤，故“免疫正常化”疗法在肝癌治疗中前景广阔。目前除靶向PD-1/PD-L1外，靶向微环境中的免疫抑制细胞相关的通路或靶点如：CSF1/CSF1R、IDO、T淋巴细胞免疫球蛋白黏蛋白3（T lymphocyte immunoglobulin mucin 3，TIM-3）、淋巴细胞活化基因3（lymphocyte activation gene 3，LAG-3）等途径也可纠正肝癌诱导的免疫缺陷，促使免疫正常化[19, 133-134]。但目前上述相关靶点仍处于相应的临床前研究阶段。

4 结 语

尽管目前针对肝癌的免疫治疗已取得一定成果，但仍面临着客观缓解率低和治疗不良反应等挑战。因此，从基因突变、基因表达、细胞因子/趋化因子和肿瘤浸润细胞等方面进行综合分析，为肝癌患者制定个性化的精准免疫治疗方案，有效评估和预测免疫治疗的疗效及采取联合治疗策略等，是在精准医学时代背景下亟需回答的问题，也是肝癌免疫治疗研究的未来趋势。

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