·综述·

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肝细胞癌基因治疗：现状及挑战

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摘要：肝细胞癌(HCC)作为全球常见的恶性肿瘤之一，多数病例确诊时已处于晚期阶段，因此预后较差且生存率低。传统治疗方法效果有限，而基因治疗作为一种新兴的治疗策略展现出巨大的潜力，同时面临着诸多挑战。本文主要介绍HCC基因治疗领域的最新进展，并分析该领域未来发展中亟待解决的关键问题。基因治疗凭借靶向性强、作用机制多样及个性化治疗的优点，已成为当前HCC的研究热点。虽然基因治疗在HCC治疗中仍处于探索阶段，但目前已取得一些初步研究成果。根据相关文献报道，基因治疗联合化学治疗、免疫治疗等其他治疗方法可提升疗效，并降低部分单药治疗的副作用。随着技术的不断进步，基因治疗有望为HCC患者带来新的希望。

关键词：癌，肝细胞；基因治疗；治疗学

Gene therapy for hepatocellular carcinoma: Current research status and challenges

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, and most patients are in the advanced stage at the time of diagnosis, leading to a poor prognosis and a low survival rate. Traditional treatment methods often have limited efficacy, while gene therapy, as an emerging therapeutic strategy, has shown great potential with numerous challenges. This article mainly introduces the latest advances in the field of gene therapy for HCC and analyzes the key issues that need to be addressed in the future development of this field. Gene therapy has become a research hotspot in HCC due to its advantages of strong targeting, diverse mechanisms of action, and individualized treatment. Although gene therapy is still in the exploratory stage in the treatment of HCC, some preliminary research findings have been achieved. According to the reports in the literature, the combination of gene therapy with other treatment methods, such as chemotherapy and immunotherapy, can improve treatment outcomes and reduce the side effects of monotherapy. With the continuous advances in technology, gene therapy is expected to bring new hope to HCC patients.

Key words: Carcinoma, Hepatocellular; Genetic Therapy; Therapeutics

肝细胞癌(hepatocellular carcinoma, HCC)占所有原发性肝癌的75%～85%[1]，其发病群体多为慢性肝病患者，尤其常见于因饮酒、慢性HBV/HCV感染或代谢功能障碍相关脂肪性肝炎引起的肝硬化患者[2]。作为全球癌症死亡的主要原因之一，HCC在亚洲和非洲地区发病率较高[3]。目前，HCC治疗主要以手术为主，而对于无法进行手术的晚期患者，治疗方案已从系统化疗逐渐向靶向治疗、免疫治疗、基因治疗及联合治疗过渡[4]。近年来，随着对HCC分子机制的不断深入研究，基于分子机制的基因治疗取得新的进展，为患者带来新的治疗选

择。本文主要围绕HCC基因治疗的研究进展及未来面临的挑战展开综述。

1 基因治疗的研究进展

1.1 RNA干扰（RNA interference，RNAi） RNAi由双链RNA诱发，可通过同源mRNA高效特异性降解，实现特定基因表达的下调。诱导特定基因降解并沉默特定基因表达的RNA被称为小干扰RNA（small interfering RNA，siRNA）。siRNA是外源基因入侵的天然防御机制，可抵御外源核酸的入侵并控制基因表达，凭借高效性、特异性的基因沉默特性，成为疾病治疗领域备受关注的研究方向[5]。基因沉默主要涉及miRNA（微小RNA）、shRNA（短发夹结构RNA）及siRNA 3类功能性RNA。当这些长度在18～25个核苷酸的合成RNA进入细胞后，会与细胞质中的特定蛋白（如Argonaute-2蛋白）结合，形成RNA介导的基因沉默复合体。该复合体能够识别并配对靶基因的mRNA，通过降解mRNA阻断相应蛋白质的合成，从而抑制基因的表达[6]。Zoheir等[7]利用RNAi技术沉默IQGAP1癌基因，通过在体内诱导肝癌模型，评估IQGAP1-shRNA和TRAIL（肿瘤坏死因子相关凋亡诱导配体）联合治疗效果，证实该疗法可有效抑制肿瘤的生长；另有研究开发静脉注射的多肽纳米颗粒，成功将特异性靶向TGF-β和Cox-2基因的siRNA递送至肝癌细胞，增强肿瘤抑制效果[8]。此外，具有双重功能的多肽载体研究显示，LHRH-MPG$^{\triangle NLS}$肽与siRNA组装形成的稳定纳米级多聚体，可显著提高对肝癌细胞的靶向性和基因沉默效率[9]。

1.2 基因引入 通过基因引入技术重新激活HCC中下调的抑癌通路（即蛋白质替代疗法），其原理类似导入自杀基因或调控蛋白以干预细胞过程[10]。pDNA（质粒DNA）和mRNA（信使RNA）是常用的2种载体，其中mRNA具有制备工艺简单、包封率高等优势，且能在细胞质中直接发挥功能，无须经历核转运过程[11]。相关研究中，将含有TRAIL基因的pDNA导入HCC小鼠模型，成功诱导细胞凋亡转化为HCC并抑制肿瘤增殖，同时显著改善与HCC相关的肝纤维化程度[12]；向HCC递送编码共刺激剂OX40配体的mRNA，可通过诱导CTL（细胞毒性T淋巴细胞）活性激活抗癌免疫[13]；导入内皮抑素、PEDF（色素上皮衍生因子）、NK4等多种抗血管生成因子，可有效抑制肿瘤的生长和转移[14]。

1.3 基因组编辑 基因组编辑是一种可对特定基因进行敲入、敲除的治疗方法，通过ZFN（锌指核酸酶）、TALEN（转录激活因子样效应核酸酶）和带有CRISPR-Cas系统的CRISPR（成簇规则间隔短回文重复序列）等多种具有切割DNA能力的方式实现[10]。相较于其他基因治疗方法，基因组编辑更具优势，可实现可遗传的永久性治疗效果，从而避免重复治疗。Jennifer Doudna和Emmanuelle Charpentier因在CRISPR-Cas9技术开发中作出了突出贡献，被授予2020年诺贝尔化学奖[15]。目前，基因组编辑已经成为构建多样化基因敲除动物模型不可或缺的工具[16]。相关研究表明，CRISPR-Cas9敲除HCC细胞中的ALDOA（醛缩酶A）可抑制肿瘤细胞增殖和迁移，并通过耗竭乳酸诱导细胞周期停滞[17]；敲除CXCR2（CXC趋化因子受体2）基因可成功下调程序性死亡配体1表达，从而增强肿瘤对抗癌免疫的敏感性[18]；在小鼠HCC转移模型中，利用体内CRISPR文库筛选明确转移定植期间肿瘤免疫逃避的关键基因，证实血清和糖皮质激素调节激酶1缺失可通过增强肿瘤细胞的抗免疫反应促进HCC的转移[19]。综上所述，CRISPR-Cas9主要应用于精准编辑致癌基因、发现潜在治疗靶点以及构建新型疾病模型，以研究治疗肿瘤的最佳方案[20-22]。

1.4 病毒治疗 病毒治疗是一种募集细胞病变病毒以杀死靶细胞的方法。随着基因工程的发展，对病毒进行改造成为可能，改造后的病毒可单独复制到癌细胞中，因此这类病毒也被称为溶瘤病毒。其原理是通过在病毒复制关键基因中引入突变或插入肿瘤特异性启动子，使病毒仅在具有特定分子特征（如p53通路异常）的癌细胞中激活复制，从而实现肿瘤特异性病毒复制[14]。1996年被发现的ONYX-015是首个溶瘤病毒，其E1B 55K基因缺失的特点，有利于肿瘤特异性复制[23]。虽然在基础研究中表现显著，但该病毒作为单一疗法的Ⅱ期临床试验效果仍缺乏临床意义[24]。针对AFP阳性的HCC细胞，Takahashi等[25]开发了一种携带AFP启动子/增强子的腺病毒，可实现对该类细胞的特异性溶解。Han等[26]提出了一种新型抗HCC的方法，该方法基于腺病毒介导的Tetrahymena Ⅰ组反式剪接核酶，通过HCC特异性替代TERT（端粒酶逆转录酶）RNA，特异性诱导靶向自杀基因活性。该研究方法可有效抑制不同类型癌细胞的生长，由癌症特异性核酶介导的转录后调节RNA替代策略，为HCC治疗提供具有临床相关性、安全性和有效性的策略。一项临床研究评估了溶瘤腺病毒联合纳武利尤单抗治疗晚期HCC的效果与安全性，结果初步表明该研究方案具有一定疗效且对毒副作用耐受性良好，但仍需进一步验证[27]。

1.5 抗肿瘤疫苗 抗肿瘤疫苗属于一种免疫疗法，其原理为将编码某种新抗原的mRNA/DNA递送至抗原呈递细胞并激活T细胞的免疫反应能力，从而靶向杀伤癌细

胞。研究表明,GNOS-PV02疫苗联合PD-1(程序性死亡受体1)单抗治疗晚期肝癌时,客观缓解率达30.6%,显著提升疗效[28]。随着mRNA肿瘤疫苗的问世,肿瘤学领域取得重大进展,该疫苗凭借安全性高的独特优势得到广泛应用。由于mRNA对递送系统具有高需求性,当前采用的脂质纳米颗粒递送系统可提高mRNA疫苗的靶向性,减少副作用[29]。现阶段,mRNA疫苗仅能预防与癌症相关的病毒感染,而针对癌症相关病毒的疫苗仍主要处于临床前阶段,未来应用前景广阔。树突状细胞疫苗的制备过程如下:利用患者自体细胞在体外诱导或构建可特异性识别肿瘤的树突状细胞,负载相应肿瘤抗原后回输至肿瘤患者体内,以激活T细胞对肿瘤的免疫反应。研究人员设计的基于HCC新抗原的纳米疫苗,通过纳米颗粒递送至树突状细胞,再由基因编辑重塑肿瘤相关中性粒细胞,可提升树突状细胞疫苗的疗效和抗肿瘤能力[30]。一项Ⅱ期临床试验结果显示,基于新生抗原的树突状细胞疫苗联合T细胞治疗可降低HCC的复发率[31]。此外,基于AFP靶点的疫苗通过表达AFP蛋白或其衍生肽段来激活免疫反应,研究构建的Ad-hAFPm病毒载体可表达AFP/热休克蛋白70融合蛋白和粒细胞-巨噬细胞集落刺激因子,在过表达AFP的移植瘤模型中展现出良好的肿瘤抑制效果和免疫细胞浸润能力[32]。

1.6 *基因工程细胞疗法* 基因工程技术的发展使人类细胞修饰成为可能,通过体外修饰增强肿瘤识别能力或抗癌特性的过程被称为过继细胞转移[33]。嵌合抗原受体T细胞治疗(chimeric antigen receptor T cell theropy,CAR-T细胞治疗)是一种典型的细胞治疗模型,其原理是在体内利用CAR(嵌合抗原受体)转染人类CTL,以增强其肿瘤识别能力并进行扩增,将改造后的细胞回输患者体内后即可发挥抗肿瘤作用。GPC3(磷脂酰肌醇蛋白聚糖-3)在HCC中高表达,而在正常肝组织中几乎不表达,因此被视为理想的免疫治疗靶点,相关研究中2例晚期HCC患者在接受局部治疗联合GPC3 CAR-T细胞治疗后,无瘤生存期均超过5年[34]。然而,CAR-T细胞输注通常会造成脱靶毒性、细胞因子释放综合征和神经毒性等不良事件[35],研究证实基因组编辑有助于增强CAR-T细胞的安全性[36]。此外,一种新型T细胞疗法通过将靶向AFP的T细胞受体基因转导至自体T细胞中,使其能够特异性识别并杀伤表达AFP的肿瘤细胞,该疗法目前处于Ⅰ期临床试验阶段[37]。肿瘤相关成纤维细胞(cancer-associated fibroblast,CAF)在HCC的发生和发展中发挥重要作用,是免疫抑制微环境的关键组成部分。研究人员通过单细胞测序技术发现,肝祖细胞在炎性细胞因子刺激下,由MAPK(丝裂原活化蛋白激酶)信号通路和下游转录因子ERG(ETS相关基因)通过TLR(Toll样受体)4受体激活介导,可异常分化为PDGFRα^{+}CAF。该研究证实,下调肝祖细胞中ERG的表达可显著减少PDGFRα+CAF的数量及HCC中肿瘤相关巨噬细胞的浸润,从而抑制肝癌发生[38-39]。

1.7 *其他疗法* 最新研究表明,髓样细胞触发受体2巨噬细胞通过抑制CD8^{+}T细胞浸润及促进肿瘤细胞糖酵解,在HCC进展中发挥驱动作用,为HCC提供新的治疗靶点[40]。最近报道的一种新型人工纳米仿酶P-Por-Os,该技术整合超声波激发和基因治疗,不仅破坏HCC细胞内的氧化还原平衡,还在极低浓度下实现精确和受控的肿瘤消融,并创新性地提出CDT+SDT+PGT(化学动力治疗+声动力治疗+精准基因治疗)的三联治疗策略。这种联合疗法能够有效杀伤肿瘤细胞,同时减少对正常组织的损伤[41]。研究人员结合三萜类化合物模板自组装纳米系统和CRISPR-Cas9基因编辑技术,通过TLR2和免疫检查点阻断的协同作用,显著提升HCC的免疫治疗效果[42]。一项研究利用CRISPR-Cas9基因编辑技术敲除CT10调控激酶样调节因子,在原位小鼠模型和患者来源的器官型肿瘤球体模型中有效恢复抗PD-1疗法的功效,证实CT10调控激酶样调节因子抑制剂与免疫制剂联合可用于治疗HCC[43]。有研究团队开发了一种混合纳米系统,通过介导化学治疗联合基因治疗向靶细胞递送药物,在提升治疗效果的同时减少与治疗药物相关的副作用[44]。Rong等[45]采用乳糖酸修饰的脂质纳米粒,将化疗药喜树碱和miR-145共转染表达去唾液酸糖蛋白受体的肝癌细胞,研究显示化疗-基因联合疗法可对抗耐药性并提升癌细胞对细胞毒剂的敏感性。综上所述,基因治疗联合免疫治疗或化学治疗能够增强抗肿瘤的效果,并在一定程度上减轻药物的副作用。

2 小结与展望

近年来,HCC的基因治疗取得了显著进展。腺相关病毒载体因其高效转导、低致病性和免疫原性等优势,成为基因递送的重要工具并被广泛应用于临床[46]。创新性的三联治疗策略(CDT+SDT+PGT)利用基因治疗增强肿瘤细胞对活性氧的敏感性,展现出良好的应用前景[41]。多组学技术的引入进一步推动HCC精准诊疗的发展,为揭示疾病机制、开发新的靶点和生物标志物提供了有力支持[47]。然而,HCC的基因治疗仍面临诸多挑战。mRNA固有的不稳定性、对高效和靶向递送系统的需求、免疫耐受风险及肿瘤细胞的逃避是当前的研究重

点[29]。CRISPR-Cas9技术展现出巨大的潜力,但仍面临脱靶效应、递送效率低和细胞毒性等挑战。近年来,研究人员通过多种策略对CRISPR-Cas9系统进行升级,例如以mRNA形式递送Cas9基因,而非借助病毒载体递送gRNA[48],以及开发脂质纳米颗粒和聚合物载体等非病毒递送系统以提高体内稳定性和靶向性[49]。现有研究表明,病毒载体能有效递送CRISPR-Cas9系统实现基因编辑,但腺相关病毒载体的安全性和有效性仍需进一步评估,尤其是潜在的致癌风险;同时,基因编辑技术的脱靶效应和效率问题尚未完全解决[46]。非病毒载体具有靶向性强、载量高、免疫毒性低等特点,比病毒载体更适合治疗肿瘤[50]。为提高非病毒递送的效率和安全性,研究人员提出通过脂质体、聚合物或纳米颗粒等载体,增强递送系统的稳定性和靶向性,并在载体表面引入抗体和肽段等肿瘤特异性配体,进一步提高靶向递送的精准性[51]。肿瘤异质性导致不同细胞对基因治疗的反应差异明显,增加治疗难度[52-53];HCC基因治疗的临床试验数量有限,缺乏大规模数据支持,且个性化治疗的复杂性要求未来开发更精准的生物标志物以预测治疗反应[54];同时,临床前模型难以完全模拟人体的病理特征,从而影响疗效预测准确性,这些因素均影响临床转化进程。未来研究应聚焦于开发高效、安全的靶向递送系统以提升药物的精准性,设计个体化方案解决肿瘤的异质性问题,联合基因治疗与免疫治疗进一步延长患者的生存时间,最终实现从基础研究到临床应用的系统性突破。

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