

溶瘤病毒在实体瘤免疫治疗中的应用及免疫微环境调节机制

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摘要

实体瘤高度免疫抑制的肿瘤微环境(Tumor Microenvironment, TME)是介导肿瘤免疫逃逸、降低放化疗及免疫治疗临床应答的关键瓶颈。溶瘤病毒(Oncolytic Viruses, OV)能够特异性靶向裂解肿瘤细胞, 同时多重调控抑制性TME, 是实体瘤免疫治疗领域极具转化价值的新型生物制剂。本文系统梳理OVs重塑实体瘤免疫微环境的核心作用机制: 通过诱导免疫原性细胞死亡释放危险相关分子模式与病原体相关分子模式, 启动初始抗肿瘤免疫应答; 调控免疫细胞、细胞因子及趋化因子网络, 逆转免疫细胞失衡格局; 降解致密细胞外基质、修复紊乱肿瘤血管, 解除免疫细胞浸润物理屏障。现有临床数据表明, 单药OVs安全性良好, 但整体抗肿瘤有效率偏低; 与免疫检查点抑制剂、肿瘤疫苗、过继性T细胞疗法、靶向药物及放化疗联合应用可形成显著协同效应, 在黑色素瘤、肝癌、肺癌、胰腺癌等实体瘤中明显提升客观缓解率与患者生存获益。现阶段OVs临床转化仍面临全身递送效率低下、机体抗病毒免疫清除病毒、脱靶毒性、标准化治疗方案缺失、规模化制备成本高昂等多重挑战。依托基因工程修饰、纳米递送系统、精准介入给药等技术革新, 有望进一步增强OVs肿瘤靶向性、溶瘤活性与免疫激活能力, 突破现有应用壁垒, 推动OVs成为实体瘤综合免疫治疗的核心手段, 为晚期实体瘤患者提供高效、低毒的新型治疗策略。

关键词

溶瘤病毒, 实体瘤, 肿瘤微环境, 免疫治疗

Application of Oncolytic Viruses in Immunotherapy of Solid Tumors and Regulatory Mechanisms of Immune Microenvironment

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Abstract

The highly immunosuppressive tumor microenvironment (TME) of solid tumors constitutes a critical bottleneck that mediates tumor immune evasion and attenuates clinical responses to radiotherapy, chemotherapy and immunotherapy. Oncolytic viruses (OVs), a novel class of biological agents with prominent translational value for solid tumor immunotherapy, can specifically target and lyse tumor cells while exerting multifaceted regulation on the suppressive TME. This paper systematically summarizes the core mechanisms by which OVs remodel the immune microenvironment of solid tumors: triggering primary anti-tumor immune responses by inducing immunogenic cell death to release damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs); reversing the imbalance of immune cell populations via modulating the network of immune cells, cytokines and chemokines; and removing physical barriers to immune cell infiltration through degrading dense extracellular matrix and restoring dysfunctional tumor vasculature. Current clinical data demonstrate that monotherapy with OVs exhibits favorable safety profiles yet modest overall anti-tumor response rates. Combinatorial regimens pairing OVs with immune checkpoint inhibitors, tumor vaccines, adoptive T cell therapy, targeted agents, radiotherapy or chemotherapy yield prominent synergistic effects, significantly elevating objective response rates and survival benefits for patients with solid tumors including melanoma, hepatocellular carcinoma, lung cancer and pancreatic cancer. The clinical translation of OVs currently faces multiple obstacles, such as inefficient systemic delivery, viral clearance by host antiviral immunity, off-target toxicity, lack of standardized therapeutic protocols and high costs of large-scale production. Technological innovations including genetic engineering modification, nano-delivery systems and precise interventional administration are expected to further enhance the tumor tropism, oncolytic activity and immune-stimulating capacity of OVs, break through existing application limitations, advance OVs as a core component of comprehensive immunotherapy for solid tumors, and provide a novel high-efficacy, low-toxicity therapeutic strategy for patients with advanced solid tumors.

Keywords**Oncolytic Viruses, Solid Tumors, Tumor Microenvironment, Immunotherapy**

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<http://creativecommons.org/licenses/by/4.0/>**Open Access****1. 前言**

实体瘤是全球癌症相关死亡的主要原因，其特征在于肿瘤细胞与周围的免疫细胞、基质细胞、细胞外基质(Extracellular Matrix, ECM)及多种细胞因子、趋化因子共同构成复杂的 TME [1]。与正常组织微环境不同，实体瘤 TME 普遍呈现出免疫抑制表型，核心表现为免疫[2]激活与免疫抑制的失衡，这种免疫抑制性 TME 形成了肿瘤免疫逃逸的“屏障”，导致传统放化疗、靶向治疗及单一免疫治疗的疗效有限，难

以实现实体瘤的长期控制与治愈[3]-[5]。溶瘤病毒是一类能够选择性感染并裂解肿瘤细胞,同时激发机体抗肿瘤免疫反应的病毒[6]。自2015年FDA批准首个溶瘤病毒疗法 Talimogene laherparepvec (T-Vec, 基于单纯疱疹病毒1型)用于治疗晚期黑色素瘤以来,OVs在实体瘤治疗中的研究热度持续攀升[7]。与传统抗肿瘤治疗相比,OVs可以通过病毒自身的复制与裂解能力,直接破坏肿瘤细胞,并且感染肿瘤细胞后可引发一系列免疫相关反应,打破TME的免疫抑制状态,激活机体自身的抗肿瘤免疫系统,实现对肿瘤细胞的特异性清除,甚至诱导长期的抗肿瘤免疫记忆[8]。随着对OVs作用机制及实体瘤TME生物学特征研究的不断深入,越来越多的证据表明,OVs对实体瘤免疫微环境的调节作用是其发挥抗肿瘤疗效的核心环节[9]-[11]。本文将重点围绕OVs对实体瘤TME的调节机制、在实体瘤免疫治疗中的应用、联合治疗策略及面临的挑战展开综述,旨在系统梳理OVs在实体瘤免疫治疗中的研究进展,为其临床转化与优化提供思路。

2. 溶瘤病毒调节实体瘤免疫微环境的核心机制

2.1. 诱导免疫原性细胞死亡, 启动抗肿瘤免疫应答

传统的肿瘤细胞死亡如细胞凋亡、细胞坏死往往无法激发有效的免疫反应,甚至可能诱导免疫耐受。而免疫原性细胞死亡(ICD)是一种特殊类型的细胞死亡方式,其特征在干细胞死亡过程中会释放一系列“危险相关分子模式”(Damage-Associated Molecular Patterns, DAMPs)和“病原体相关分子模式”(Pathogen-Associated Molecular Patterns, PAMPs),这些分子能够被机体固有免疫细胞识别,进而启动适应性免疫应答,实现对肿瘤细胞的特异性清除[12]-[14]。OVs感染实体瘤细胞后,可通过多种途径诱导肿瘤细胞发生ICD[15],这是OVs调节TME、启动抗肿瘤免疫的关键一步。

OVs诱导实体瘤细胞发生ICD的核心机制在于病毒的复制与裂解过程[16]。OVs在肿瘤细胞内大量复制导致细胞裂解,释放的如热休克蛋白、钙网蛋白、ATP、高迁移率族蛋白B1等DAMPs可招募免疫细胞浸润、促进抗原呈递,激活免疫激活信号[12]。同时,OVs自身的病毒核酸、衣壳蛋白等PAMPs可被固有免疫细胞识别,激活相关信号通路,促进更多促炎细胞因子的分泌,放大免疫激活效应。此外,OVs感染还可诱导肿瘤细胞表达死亡受体,介导凋亡过程并伴随DAMPs释放,进一步增强ICD的免疫激活作用[12][17]。

2.2. 调控免疫细胞平衡, 重塑TME免疫格局

实体瘤TME的免疫抑制核心的是免疫细胞平衡失调,即免疫激活型细胞功能不足、免疫抑制型细胞大量富集[18]。OVs可以通过整体调控免疫细胞的活化状态、浸润水平及亚群平衡,打破免疫抑制格局,增强抗肿瘤免疫效应[19][20]。

OVs可显著促进免疫激活型细胞的整体活化与肿瘤组织浸润,同时抑制免疫检查点分子对免疫细胞的抑制作用,恢复免疫细胞的抗肿瘤活性[21]-[23]。与此同时,OVs可有效抑制免疫抑制型细胞的富集与功能,从源头削弱TME的免疫抑制作用[24]。研究证实,T-Vec治疗后,黑色素瘤组织中免疫抑制细胞数量显著减少,免疫激活细胞与抑制细胞的比值明显升高,抗肿瘤免疫反应显著增强[25]。

细胞因子与趋化因子同样是TME中免疫细胞交流、功能调控的核心媒介。这些因子的表达失衡同样是实体瘤免疫抑制的重要特征[5][26]。OVs可通过调控细胞因子与趋化因子网络,逆转这种失衡状态,为抗肿瘤免疫反应提供有利条件。OVs感染肿瘤细胞或免疫细胞后,可激活NF- κ B、IRF3等信号通路,显著上调IFN- α 、IFN- γ 、IL-12等促炎细胞因子的表达,这些因子可进一步放大免疫激活效应,促进免疫细胞活化与增殖[21][27]。OVs也可显著下调TGF- β 、IL-10等免疫抑制性细胞因子的表达,削弱免疫抑制信号,解除对免疫细胞的功能抑制[24]。在趋化因子调控方面,OVs可显著上调CXCL9、CXCL10、

CXCL11 等趋化因子的表达, 这些趋化因子可特异性招募免疫激活型细胞从外周血浸润到肿瘤组织中, 增加局部免疫激活细胞的数量[22]。在临床前实验中证实, 腺病毒型 OV_s 治疗后的肺癌小鼠模型中, 肿瘤组织中 CXCL10 的表达水平显著升高, CD8⁺ T 细胞和 NK 细胞的浸润数量明显增加, 肿瘤生长受到显著抑制[28]; 在胰腺癌模型中, OV_s 介导的 CXCL9 表达上调可有效招募 DCs 浸润, 增强抗原呈递效率, 改善免疫治疗效果[29]。

2.3. 重塑肿瘤基质与血管微环境, 破除免疫浸润屏障

实体瘤的基质与血管微环境异常也是免疫治疗疗效不佳的重要原因之一[30]。实体瘤基质中存在大量致密的 ECM, 主要由胶原蛋白、纤连蛋白等组成。这些物质在实体瘤的微环境中形成物理屏障, 阻碍免疫细胞向肿瘤核心区域浸润。并且肿瘤血管存在结构异常、通透性增加等问题, 导致免疫细胞无法有效穿过血管壁进入肿瘤组织。此外, 血管内皮细胞还表达免疫抑制分子, 这些因素都会进一步抑制免疫细胞功能[31]。使用 OV_s 后可以重塑肿瘤基质与血管微环境, 破除这些免疫浸润屏障, 改善免疫细胞的浸润与功能[32]。

OV_s 可通过多种途径降解 ECM、打破物理屏障。一方面, OV_s 可直接感染并裂解 CAFs, 减少 ECM 的合成与分泌, 降低肿瘤基质的致密性[33]; 另一方面, OV_s 可诱导肿瘤细胞或免疫细胞表达基质金属蛋白酶(MMPs), 如 MMP-2、MMP-9 等, 这些蛋白酶可特异性降解胶原蛋白、纤连蛋白等 ECM 成分, 破坏基质屏障[34]。

并且 OV_s 可改善血管结构异常, 增强血管通透性, 促进免疫细胞浸润。OV_s 可抑制血管内皮生长因子(VEGF)、碱性成纤维细胞生长因子(bFGF)等促血管生成因子的表达, 抑制肿瘤血管的异常增生。同时, OV_s 还可以促进血管内皮细胞表达 ICAM-1、VCAM-1 等黏附分子, 增强免疫细胞与血管内皮细胞的黏附能力, 从而促进免疫细胞穿过血管壁进入肿瘤组织[35]。OV_s 还可下调肿瘤血管内皮细胞表面 PD-L1、CD47 等免疫抑制分子的表达, 解除其对免疫细胞的功能抑制, 确保浸润的免疫细胞能够正常发挥抗肿瘤作用[34] [36]。

3. 溶瘤病毒在实体瘤免疫治疗中的应用现状

3.1. 单一溶瘤病毒治疗实体瘤的应用现状

单一 OV_s 治疗的核心优势是安全性较高、耐受性好, 尤其适用于无法耐受放化疗或靶向治疗的晚期实体瘤患者。目前, 已有多款 OV_s 进入临床研究阶段, 部分已获批上市[37]。

T-Vec 是首个获批上市的溶瘤病毒疗法, 用于治疗晚期黑色素瘤。其核心作用机制是通过诱导 ICD、调控免疫细胞平衡, 重塑黑色素瘤的 TME, 激活抗肿瘤免疫。临床研究显示, T-Vec 治疗晚期黑色素瘤患者的客观缓解率(ORR)为 26%, 其中完全缓解率(CR)为 11%。更有数据证明, T-Vec 治疗后部分患者可产生长期抗肿瘤免疫记忆, 5 年生存率显著高于传统治疗方法[25] [38]。

在其他实体瘤中, 单一 OV_s 治疗也取得了一定的临床效果。在晚期肝癌的临床研究中, 腺病毒型 OV_s (H101)单药治疗的 ORR 为 15.8%, 疾病控制率(DCR)为 52.6%, TME 的免疫激活状态明显增强[39]; 在晚期肺癌的临床前研究中, 流感病毒型 OV_s 单药治疗可显著抑制肿瘤生长, 延长小鼠生存期, 在胰腺癌的临床前研究中, 修饰后的 OV_s 单药治疗可有效降解肿瘤基质, 打破免疫浸润屏障, 促进免疫细胞浸润, 改善免疫抑制 TME, 显著增强抗肿瘤疗效[40]。

但是需要注意, 单一 OV_s 治疗在大部分实体瘤的疗效存在明显局限性, 多数患者缓解率较低, 且易出现治疗耐药[41]。其原因主要在于大多数实体瘤的 TME 存在严重的免疫抑制状态, 单独使用 OV_s 难以完全打破其免疫抑制网络, OV_s 在肿瘤组织中的复制效率有限, 无法充分发挥 TME 重塑作用。并且机体

的抗病毒免疫反应也可能会清除 OV_s，进一步降低其在肿瘤组织中的留存时间[42]。因此，单一 OV_s 治疗更适用于 TME 免疫抑制程度较轻、肿瘤负荷较小的实体瘤患者，或作为联合治疗的基础策略。

3.2. 溶瘤病毒联合免疫检查点抑制剂

免疫检查点抑制剂(如 PD-1/PD-L1 抑制剂、CTLA-4 抑制剂)是目前实体瘤免疫治疗的主流策略之一，其通过阻断免疫检查点分子的相互作用，解除对免疫细胞的功能抑制，激活抗肿瘤免疫[43]。但该策略在大数实体瘤中无法展现出很好的疗效，主要因为这些实体瘤的 TME 中免疫细胞浸润不足、免疫激活信号微弱，导致无法有效激活免疫检查点抑制剂的治疗效应[44]。联合使用 OV_s 可重塑这些实体瘤的 TME，促进免疫细胞浸润、增强免疫激活信号[45] [46]，有效改善免疫检查点抑制剂的疗效瓶颈，二者联合具有显著的协同增效作用。

现在 OV_s 联合免疫检查点抑制剂的临床研究已在多种实体瘤中开展，并取得了显著进展。在黑色素瘤中，T-Vec 联合 PD-1 抑制剂帕博利珠单抗的临床研究显示，联合治疗的 ORR 为 62%，CR 为 33%，显著高于单一 T-Vec 治疗(26%)和单一 PD-1 抑制剂治疗(33%)，且治疗后患者肿瘤组织中 CD8⁺ T 细胞浸润数量、促炎细胞因子表达水平均显著高于单一治疗组，TME 的免疫抑制状态得到进一步改善[47] [48]。在晚期肺癌中，腺病毒型 OV_s 联合阿替利珠单抗的临床研究结果显示联合治疗的 ORR 为 38%，DCR 为 72%，显著高于单一 PD-L1 抑制剂治疗(ORR 18%, DCR 56%)，且联合治疗组患者的无进展生存期(PFS)和总生存期(OS)均显著延长[49]。

在胰腺癌、肝癌等“冷肿瘤”中，OV_s 联合免疫检查点抑制剂的协同效应更为显著。在胰腺癌的临床前研究中，单一 PD-1 抑制剂治疗几乎无明显疗效，而 OV_s 联合 PD-1 抑制剂治疗可有效降解肿瘤基质、促进 CD8⁺ T 细胞浸润，显著抑制肿瘤生长，延长小鼠生存期[50]；在肝癌的临床前研究中，H101 联合 PD-1 抑制剂纳武利尤单抗的 ORR 为 42.9%，DCR 为 78.6%，显著高于单一治疗组，且患者的耐受性良好[47]。

3.3. 溶瘤病毒联合肿瘤疫苗

肿瘤疫苗是一类通过递送肿瘤相关抗原(TAAs)，诱导机体产生特异性抗肿瘤免疫反应的免疫治疗策略，其核心优势是可诱导肿瘤特异性记忆 T 细胞形成，实现对肿瘤的长期免疫监控[51]。但传统肿瘤疫苗的免疫原性较低，且难以突破实体瘤 TME 的免疫抑制屏障，导致其临床疗效有限。

近年来，OV_s 联合肿瘤疫苗的临床前与临床研究均获得阶段性进展[52]。在黑色素瘤的临床前研究中，OV_s 联合肿瘤疫苗治疗可显著增强疫苗诱导的 CD8⁺ T 细胞活化与浸润，显著抑制肿瘤生长，降低肿瘤复发率，延长小鼠生存期[53]；在肺癌的临床前研究中，OV_s 联合 DC 疫苗治疗晚期肺癌患者，ORR 为 35.7%，DCR 为 71.4%，患者的 PFS 和 OS 均显著延长，且治疗后患者肿瘤组织中促炎细胞因子表达水平显著升高，免疫抑制细胞数量显著减少[54]；在乳腺癌的临床前研究中，修饰后的 OV_s 联合肿瘤疫苗治疗，可显著增强疫苗的免疫原性，促进 DCs 的抗原呈递，增强 CD8⁺ T 细胞的杀伤能力，显著抑制肿瘤生长与转移[55]。

此外，OV_s 自身也可被修饰为“病毒疫苗载体”，可以通过技术手段修饰病毒将 TAAs、细胞因子等免疫增强分子导入肿瘤组织中，实现“溶瘤 + 疫苗”的双重效应，进一步提升治疗效果[56]。比如修饰后的疱疹病毒型 OV_s 可表达 TAAs 和 IL-12，在前列腺癌的临床前研究中，该 OV_s 单药治疗即可实现溶瘤、TME 重塑与疫苗诱导的协同效应，显著抑制肿瘤生长，延长小鼠生存期[57]。

3.4. 溶瘤病毒联合过继性 T 细胞治疗

过继性 T 细胞治疗(ACT)是一种依赖于体外扩增与激活的肿瘤特异性 T 细胞，在回输患者体内后实

现精准清除肿瘤的免疫疗法。目前较具代表性的 ACT 策略主要包括嵌合抗原受体 T 细胞(CAR-T)与 T 细胞受体工程化 T 细胞(TCR-T)等[58]。然而, ACT 在实体瘤治疗中的推广仍受限于多重难题, 例如 T 细胞进入体内后容易被肿瘤微环境(TME)诱导进入功能耗竭状态, 或者难以穿透实体瘤物理屏障在肿瘤局部发挥杀伤作用[59]。

近年来, OV 与 ACT 联合应用于实体瘤的临床前探索展现出较大潜力[60]。例如, 在黑色素瘤模型中, 联合使用 OV 与 CAR-T 细胞不仅提升了 T 细胞向肿瘤区域的迁移能力, 还能有效维持其效应功能, 从而大幅抑制肿瘤进展并延长小鼠生存期, 效果显著优于单一 CAR-T 治疗[61]。在胰腺癌的研究中, OV 与 TCR-T 细胞联合能有效降解肿瘤间质屏障, 协助 TCR-T 细胞渗透至肿瘤深层, 增强杀伤效力, 进而更有效抑制肿瘤生长[59]。同样, 在肝癌模型中, 改造后的 OV 可分泌趋化因子 CXCL10, 进一步增强 CAR-T 细胞的趋化与滞留能力, 提升其在肿瘤局部的活性和持久性, 从而抑制肿瘤转移与复发[62]。

尽管如此, OV 联合 ACT 的临床应用尚处初期阶段, 仍存在诸多待解决问题, 例如给药时机和剂量方案尚需细化, 机体对病毒的免疫应答可能影响输注 T 细胞的存活和功能, 联合疗法的安全性和潜在副作用也需要系统的评估[63]。未来, OV 与 ACT 联合治疗有望在实体瘤免疫治疗领域开辟新的方向。

3.5. 溶瘤病毒与其他联合治疗策略

OV 的应用边界正在不断拓宽。除了上述疗法外, 它与其他治疗手段(如靶向药物、放疗和化疗)的组合探索也取得了不少进展。

在 M1-c6v1 溶瘤病毒联合 PD-1 抑制剂卡瑞利珠单抗及 VEGFR2 抑制剂阿帕替尼治疗晚期肝癌的临床实验中, ORR 达到 70%, 中位 OS 为 15.4 个月, 中位 PFS 为 8.9 个月[64]。在食管癌领域, 溶瘤病毒与放疗联合用于早期患者的探索也显示出积极信号。临床研究数据显示, 联合应用后客观缓解率为 91.7%, I 期临床 CR 率为 83.3%, II/III 期临床 CR 率为 60.0%, 效果明显优于单纯放疗, 且患者对联合方案的耐受性较好[65]。而在结直肠癌的临床前研究中, 溶瘤病毒与化疗药物 5-氟尿嘧啶联用后, 不仅能更有效地抑制肿瘤生长, 还能在一定程度上减少化疗药物的用量, 从而降低不良反应的发生风险[66]。

这些研究提示, 通过结合溶瘤病毒与靶向治疗、放化疗等传统疗法可以在提升疗效的同时减轻治疗的副作用, 为实体瘤的综合治疗提供新的思路。

4. 溶瘤病毒在实体瘤免疫治疗中面临的挑战与对策

尽管 OV 在实体瘤免疫治疗中的研究取得了显著进展, 且部分 OV 已获批上市, 但目前其在临床应用中仍面临诸多挑战, 主要包括 OV 的递送效率、肿瘤耐药、机体免疫反应、治疗安全性及临床转化等方面, 这些挑战严重限制了 OV 的临床应用与疗效提升, 需要进一步研究解决。

4.1. 溶瘤病毒的给药方式造成的挑战与对策

递送效率低下是制约溶瘤病毒(OV)临床疗效与转化应用的核心瓶颈[67], 当前主流的局部给药与全身给药体系均存在难以规避的应用局限, 极大限制了 OV 的规模化临床落地与疗效提升[68]。临床最常用的瘤内局部给药虽可快速提升肿瘤局部初始病毒浓度、规避全身免疫清除风险, 但仅适用于浅表、单发、体积较小的实体瘤。针对临床高发的体积巨大、位置深在、多发浸润及远处转移性实体瘤, 无法实现肿瘤全域均匀给药, 难以有效破碎致密肿瘤微环境(TME)并重塑抗肿瘤免疫微环境[69]。同时局部注射的 OV 缺乏长效驻留机制, 会快速被肿瘤原位浸润的固有免疫细胞、炎症细胞清除, 大幅缩短病毒作用时长, 削弱溶瘤裂解与免疫激活双重效应, 反复局部注射还易引发局部组织炎症损伤, 增加临床操作风险[70]。而可覆盖全身泛肿瘤病灶、适配转移性实体瘤治疗的静脉全身给药, 面临更为复杂的体内多重屏

障清除效应,有效富集浓度远低于起效阈值[71]。此外,实体瘤致密的血管屏障、纤维化细胞外基质会进一步阻滞 OV_s 的血管外渗与肿瘤深部浸润,彻底阻断病毒对肿瘤细胞的感染复制,且非靶向分布的 OV_s 易误伤正常组织细胞,诱发全身不良反应,直接限制全身给药的安全给药剂量上限与临床适用场景[72]。

为系统性突破上述多重递送屏障、解决 OV_s 体内稳定性差、靶向特异性不足与肿瘤浸润能力薄弱的的关键问题,目前已完成多种解决方式。在病毒基因靶向改造层面,除常规修饰病毒表面抗原表位、突变中和抗体结合位点以逃逸体液免疫清除外,现有研究多通过精准基因编辑嵌合肿瘤特异性靶向基序与功能片段,同步突破肿瘤受体低表达的限制性难题,如携带 RGD 整合素靶向基序的改造性腺病毒 Ad5Δ24-RGD 可特异性结合肿瘤细胞高表达的整合素蛋白,摆脱传统腺病毒对柯萨奇腺病毒受体的依赖,显著提升胶质瘤、胰腺癌等难治性肿瘤的感染效率,目前该剂型针对复发性恶性胶质瘤的 I/II 期临床试验正在开展,为实体瘤靶向改造提供了成熟范式[73];同时,通过缺失病毒免疫原性关键基因、保留肿瘤选择性复制能力,可有效降低全身免疫清除速率,NCT04695327 等临床试验也进一步证实,抗体结合位点定点突变可显著提升 OV_s 体内循环稳定性与肿瘤富集效率[74]。在细胞载体递送技术层面,基于免疫细胞、干细胞的“活体生物递送系统”可依托细胞的肿瘤归巢特性与屏障穿透能力,实现 OV_s 的免疫逃逸式靶向转运,有效解决病毒血液清除、基质浸润不足的痛点,其中 CAR-T 细胞、间充质干细胞搭载 OV_s 的共递送体系,可借助细胞载体规避补体与中和抗体的识别降解,同时穿透血脑屏障与致密肿瘤细胞外基质,实现深部肿瘤组织的精准递送至,多项临床前研究证实该体系可将肿瘤内病毒富集量提升数十倍,且可同步协同增强抗肿瘤免疫应答,是当前转移性、深部实体瘤递送优化的热门方向[75]。在纳米制剂优化层面,新型功能化纳米载体为 OV_s 全身递送提供了可产业化的解决方案,相较于传统裸病毒递送,没食子酰基修饰脂质体、聚乙二醇化纳米颗粒等新型载体可通过物理包裹与表面功能修饰,隔绝体内免疫识别因子,规避蛋白冠遮蔽效应,显著延长 OV_s 体内循环半衰期,同时通过 EPR 效应主动靶向肿瘤血管,提升病毒血管外渗与深部浸润能力,有效改善实体瘤递送效率低下的问题[76]。

4.2. 治疗安全性与临床转化难题与应对策略

OV_s 的治疗安全性是其临床转化的前提条件。尽管 OV_s 具有选择性感染肿瘤细胞的特性,但在临床应用上仍可能出现一定的安全性问题。

OV_s 对正常组织细胞的感染是其主要的安全性隐患之一。虽然 OV_s 经过修饰后,对肿瘤细胞的选择性显著提高,但仍可能会感染少量正常组织细胞,导致正常组织细胞的损伤。比如腺病毒型 OV_s 可能会感染肝脏正常细胞,导致肝功能损伤;疱疹病毒型 OV_s 可能会感染神经系统正常细胞,导致神经毒性。

免疫相关不良反应是 OV_s 治疗过程中另一个重要的安全性问题。OV_s 激活的抗肿瘤免疫反应可能会过度激活,导致免疫细胞攻击正常组织细胞,引发免疫相关不良反应,如免疫相关肺炎、免疫相关肠炎、免疫相关肝炎等。在临床应用过程中,OV_s 联合免疫检查点抑制剂治疗时,免疫相关不良反应的发生率显著升高,部分患者可能会出现严重的免疫相关肺炎,需要使用糖皮质激素等药物进行治疗。

在临床转化与监管层面,目前国内外已逐步建立适配 OV_s 基因治疗、生物新技术的监管指导原则,国内依托《生物医学新技术备案指引》《生物医学新技术转化应用审批工作规范(试行)》,明确 OV_s 新型递送技术的临床备案、试验审批、质量控制及安全性评价标准,规范新型载体递送、病毒改造技术的转化路径;国际层面则重点细化全身给药的剂量梯度探索、药代/药效学动态监测、免疫应答与毒副反应评估体系,明确临床试验中瘤内给药与静脉给药的对照设计要求、病毒拷贝数监测标准及长期安全性随访规范,为 OV_s 递送技术的标准化研发、规范化临床试验及产业化转化提供核心依据,有效解决当前临床试验对照制剂稀缺、给药方案不统一、安全性评价无标准的行业痛点[77]。

5. 结论与展望

实体瘤的免疫抑制性微环境(TME)是肿瘤免疫逃逸、免疫治疗疗效不佳的核心瓶颈,溶瘤病毒(OVs)作为兼具直接溶瘤与免疫调节功能的新型抗肿瘤制剂,其核心优势在于可通过多维度调控打破 TME 免疫抑制状态,激活机体抗肿瘤免疫反应,显著改善实体瘤免疫治疗效果。

目前,OVs 在实体瘤免疫治疗中的临床前及临床研究已取得显著进展,单一 OVs 治疗可有效控制部分实体瘤,尤其适用于无法耐受放化疗的晚期患者。OVs 与免疫检查点抑制剂、肿瘤疫苗、过继性 T 细胞治疗等策略的联合应用,可实现协同增效,进一步提升治疗效果。

然而,OVs 在临床应用中仍面临诸多挑战,制约其疗效提升与临床转化,主要包括递送效率有限,局部给药难以覆盖深层或转移性肿瘤,全身给药易被机体清除且存在血管、基质屏障;未来,随着基因工程技术、纳米技术及免疫学研究的不断突破,OVs 的临床应用前景广阔,可从多方面推动其优化与转化。在 OVs 改造方面,通过基因修饰增强其对肿瘤细胞的选择性、复制溶瘤能力及免疫调节功能,同时降低对正常组织的毒性和机体抗病毒免疫的影响。在递送系统优化方面,推广纳米载体应用,研发介入、超声引导等新型给药方式,实现 OVs 的精准递送,提高感染效率。

此外,可整合 TME 四大核心维度特征——免疫浸润水平、肿瘤基质致密程度、肿瘤血管完整性与异常灌注状态、肿瘤代谢重编程特征,构建可量化、可分层的 OVs 临床获益评估体系。通过指数精准界定不同实体瘤患者对 OVs 单药治疗、联合免疫治疗、靶向给药治疗的敏感性差异,实现患者精准分层:针对高免疫浸润、低基质纤维化、代谢紊乱显著的“热肿瘤”,可优选 OVs 联合免疫检查点抑制剂方案;针对低免疫浸润、高基质致密、血管屏障完整的“冷肿瘤”,需优先采用纳米载体递送、细胞搭载靶向转运等改良递送策略联合 OVs 治疗;而针对代谢极度失衡、抗病毒免疫基线较高的患者,则需匹配基因修饰低免疫原性 OVs 制剂,规避机体清除效应。该原创框架弥补了当前 OVs 临床治疗缺乏个体化筛选标准、联合方案选择盲目化的行业缺陷,为临床精准筛选 OVs 获益人群、制定个体化给药策略、指导联合治疗方案优化提供全新的理论支撑与实践范式。

综上,OVs 凭借其独特的溶瘤活性与 TME 双向重塑优势,在实体瘤精准免疫治疗中具备不可替代的应用价值,是连接肿瘤微环境调控与全身性抗肿瘤免疫激活的关键治疗载体。尽管现阶段 OVs 临床转化仍存在递送、耐药、安全性及标准化体系不完善等诸多挑战,但随着精准改造技术、智能递送体系与个体化评估体系的不断成熟,有望突破实体瘤免疫治疗瓶颈,为晚期难治性实体瘤患者提供高效、低毒、个体化的全新治疗策略,显著改善患者远期预后。

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