·脑胶质瘤免疫研究进展·

树突状细胞疫苗在恶性胶质瘤免疫治疗中的应用

刘鸿宇 沈少平 杨霖 余新光 陈凌

【摘要】 胶质母细胞瘤是成人最常见、最致命的原发性脑肿瘤，各种有希望的化疗方案、靶向治疗方案相关临床试验竞相开展，替莫唑胺仍是治疗胶质母细胞瘤的一线化疗药物。尽管采用最大限度手术切除辅助同步放化疗和替莫唑胺化疗的标准治疗方案，胶质母细胞瘤患者中位生存期仅14.6个月。树突状细胞是已知最强的抗原呈递细胞，在固有免疫系统和获得性免疫系统中均发挥重要作用，是多种肿瘤免疫治疗的主要载体。目前已开展多项树突状细胞疫苗治疗胶质母细胞瘤的临床试验，本文对其研究进展、应用前景和挑战进行综述。

【关键词】 神经胶质瘤； 树突细胞； 癌症疫苗； 免疫疗法； 综述

The application of dendritic cells vaccination in malignant glioma

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【Abstract】 Glioblastoma (GBM) is the most common and fatal primary adult brain tumor. To date, various promising chemotherapeutic regimens have been trialed for use in GBM; however, temozolomide (TMZ) therapy remains the only first-line chemotherapeutic option for newly diagnosed GBM. Despite maximal therapy with surgery and combined concurrent radiotherapy and chemotherapy, and adjuvant TMZ therapy, the median overall survival (OS) remains approximately 14.6 months. Given the failure of conventional chemotherapeutic strategies in GBM, there has been renewed interest in the role of immunotherapy in GBM. Dendritic cells (DC) are immune antigen-presenting cell (APC) that play a role in both the innate and adaptive immune system, thereby making them prime vehicles for immunotherapy via DC vaccinations in various cancers. There is great enthusiasm surrounding the use of vaccinations for GBM with multiple ongoing trials. In this review, we summarize the progress, prospects and challenges of DC vaccine in the treatment of GBM.

【Key words】 Glioma; Dendritic cells; Cancer vaccines; Immunotherapy; Review

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胶质瘤是中枢神经系统最为常见的恶性肿瘤，在中国人群中的年发病率为5~7/10万，且呈上升趋势。胶质瘤占全部中枢神经系统肿瘤的26%，占颅内恶性肿瘤的81%，其中恶性程度最高的类型为胶质母细胞瘤（WHOⅣ级），占全部胶质瘤的56.6%；中枢神经系统恶性肿瘤患者平均5年生存率为35%，而胶质母细胞瘤患者5年生存率低于6%[1]。胶质母细胞瘤发病率高、生存率低，是严重危及生命的重大疾病。目前标准治疗方案以手术切除为主辅以放射治疗和药物化疗等多种方式的综合治疗[2]，但复发率仍较高，其中位生存期仅为14.6个月[3]。胶质母细胞瘤的治疗困境促使临床医师和科研人员努力寻求新的治疗方法[4-6]。既往数十年，随着对免疫系统认识的不断深入，研究者对其在肿瘤发生发展中的作用产生了浓厚兴趣[7]，许多新的治

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疗方法聚焦于肿瘤免疫治疗[8-12]。

肿瘤免疫治疗的本质是肿瘤与免疫系统之间的博弈过程，这一过程早在2004年即由Dunn等[13]进行系统总结，提出“3Es假说”，即免疫细胞和肿瘤细胞在消灭（Elimination）、平衡（Equilibrium）和逃逸（Escape）中不断斗争，肿瘤细胞内源性或外源性因素参与其中，发挥对抗免疫系统的作用。但是对于恶性胶质瘤而言，肿瘤内源性抵抗和适应性抵抗均发挥较强作用，包括免疫抑制因子分泌和免疫检查点分子过表达[14-19]、人类白细胞抗原（HLA）水平降低[20]、调节性T细胞（Treg）数目增加[21-23]等，导致与其他肿瘤相比，免疫治疗难度更大。目前仅有不足10%的胶质瘤患者对免疫治疗产生反应。对胶质瘤而言，有效的免疫治疗不仅要打破免疫耐受，产生对肿瘤抗原的免疫应答，而且还要克服不断出现的一系列适应性和获得性免疫逃逸机制。免疫治疗通过免疫系统，特别是获得性免疫系统特异性攻击肿瘤，树突状细胞（DC）作为专职抗原呈递细胞（APC），在固有免疫和适应性免疫中均发挥重要作用，因此树突状细胞疫苗在免疫治疗中也占据一席之地，可以作为针对各种肿瘤的有希望的免疫治疗方法[9]，在胶质母细胞瘤及其他高级别胶质瘤的治疗中也受到越来越多的关注。

一、树突状细胞疫苗的作用原理

树突状细胞源于骨髓淋巴细胞，可定居在全身组织，对周围环境进行监视，并随时将捕获的信息传送至适应性免疫系统[T淋巴细胞（以下简称T细胞）和B淋巴细胞（以下简称B细胞）]，是表达主要组织相容性复合物（MHC）Ⅰ和Ⅱ类分子的专职抗原呈递细胞，是固有免疫和适应性免疫的关键关联纽带[24]。树突状细胞将从外周获取的抗原内化分解为短肽段，以肽段-MHC复合物形式表达于树突状细胞表面，这一过程也是树突状细胞成熟的过程，然后载有抗原肽的树突状细胞迁移至二级淋巴器官，在此激活T细胞[25]。与其他抗原呈递细胞相比，树突状细胞抗原提呈效率极高，且可诱导极少数T细胞应答，成为T细胞和B细胞反应最有效的内源性刺激[26-27]。

动物模型业已证实，肿瘤周围树突状细胞可以捕获肿瘤细胞释放的肿瘤抗原，这些抗原来源于死亡的肿瘤细胞或通过树突状细胞吞噬活的肿瘤细胞，再将这些抗原交叉提呈给肿瘤以引流淋巴结内T细胞，从而诱导肿瘤抗原特异性细胞毒性T细胞（CTL）的产生，杀伤肿瘤细胞[28-29]。在这一过程中，肿瘤细胞与树突状细胞相互制衡，一方面，死亡的肿瘤细胞释放信号如溶血磷脂酰胆碱（LPC）、1-磷酸鞘氨醇（S1P）等，使树突状细胞发现死亡的肿瘤细胞并促进其吞噬死亡细胞；同时，肿瘤细胞也释放一些信号，如CD47、乳铁蛋白等，阻碍树突状细胞对肿瘤的吞噬作用。上述因素均是影响树突状细胞疫苗的重要因素。

二、树突状细胞在恶性胶质瘤微环境中的地位

正常脑实质中通常不存在树突状细胞，而主要存在于富含血管部位，如脉络膜、脑膜等，提示外周循环中树突状细胞具备转移至中枢神经系统的潜力，但其在胶质瘤中的作用尚待进一步阐明。目前研究显示，在胶质瘤局部免疫微环境中，树突状细胞、小胶质细胞、巨噬细胞、T细胞和肿瘤细胞之间的相互作用十分复杂，已发现的可能作用机制是：树突状细胞在肿瘤局部捕获肿瘤抗原，并转移至颈深淋巴结，激活后续免疫应答，同时在肿瘤局部产生趋化因子如CC趋化因子配体9和10（CCL9和CCL10），以募集活化的淋巴细胞至肿瘤局部，最后在某些细胞因子如局部T细胞和自然杀伤（NK）细胞分泌的干扰素-γ（IFN-γ）作用下，树突状细胞可以产生细胞因子如白细胞介素-12（IL-12），进一步提升免疫细胞的抗肿瘤活性。然而在临床实践中，由于胶质瘤的整体免疫抑制大环境和肿瘤局部免疫微环境中多种细胞相互作用，使得树突状细胞无法顺利完成免疫应答，而且在肿瘤微环境中肿瘤细胞表达分泌的多种分子可以抑制树突状细胞活化并驱使树突状细胞向抑制型或调节型表型转化，抑制肿瘤的免疫应答。因此，尽管对树突状细胞的了解正在逐步完善，但其在胶质瘤微环境中的作用及其机制仍有待进一步探索。

三、树突状细胞疫苗在恶性胶质瘤中的临床试验

鉴于树突状细胞在固有免疫和适应性免疫中的关键作用，以及临床前研究结果显示的树突状细胞疫苗可以成功诱导抗肿瘤免疫反应，相关临床试验正逐步开展并初见成效。2010年，美国食品与药品管理局（FDA）批准首个树突状细胞疫苗Provenge用于治疗难治性前列腺癌[30]；此后，相继在乳腺癌、膀胱癌、肾癌、结肠癌和直肠癌、肺癌、黑色素瘤的治疗中取得一定疗效[31]。上述这些在临床所取得的初步成果，目前均为高级别胶质瘤树突状细胞疫

苗临床试验的基础[32-64]。

最早应用树突状细胞疫苗治疗高级别胶质瘤的两项临床试验发表于2001年。Kikuchi等[32]将手术切除的肿瘤组织先行处理，获得自体胶质瘤细胞后用X线照射，然后将经过处理的自体胶质瘤细胞作为抗原致敏树突状细胞，回输至8例复发高级别胶质瘤患者体内，其中2例达到部分缓解，但该项研究并未报道其生存期。Yu等[33]对9例新发高级别胶质瘤患者（新发胶质母细胞瘤7例、间变性星形胶质瘤2例）接种以自体肿瘤细胞表面肽为抗原的树突状细胞疫苗，同时选择42例同期接受相同手术的高级别胶质瘤患者作为对照，结果显示，疫苗接种组患者外周循环和肿瘤局部均产生大量细胞毒性物质，生存分析提示，与对照组相比，疫苗接种组患者中位总生存期（OS）从257天增至455天。初步试验的良好疗效促使一系列树突状细胞疫苗治疗高级别胶质瘤的Ⅰ期试验不断涌现[34-47]，以评价其有效性和安全性。Rutkowski等[37]以12例经标准方案治疗后复发的胶质母细胞瘤患者作为观察对象，每2～4周接种1次树突状细胞疫苗，平均治疗5次（2～7次）后评价治疗的有效性和安全性，仅1例注射疫苗前有明显残留肿瘤的患者治疗过程中反复出现治疗相关瘤周水肿，4例出现轻微不良反应，无一例发生严重不良反应；在肿瘤部分切除患者中，1例病情稳定、1例肿瘤体积缩小50%，肿瘤全切除患者中2例生存期分别为35和36个月。Yamanaka等[34]的临床试验显示，经树突状细胞疫苗治疗的胶质瘤患者部分瘤内淋巴细胞浸润增多。Liau等[39]采用树突状细胞疫苗共治疗12例胶质母细胞瘤患者，治疗后肿瘤局部$CD3^+$T细胞数目均明显增加，1例影像学检查显示肿瘤体积明显缩小，6例外周血抗肿瘤CTL细胞数目明显增加，余未见明显免疫应答，但外周血效应性T细胞（Teff）数目增加与生存期并无显著关联性；其中8例经历再次手术，4例瘤内CTL细胞数目增加，而瘤内Teff细胞数目增加与生存期呈正相关。Yamanaka等[40]完成的Ⅰ期/Ⅱ期试验是迄今纳入病例数最多的初期临床试验，24例高级别胶质瘤患者（WHOⅢ级6例、WHOⅣ级18例）均对现有标准治疗方案耐药，皮下注射或皮下联合瘤内注射树突状细胞疫苗，仅出现注射部位红肿，未见其他不良反应；中位总生存期增至480天，进一步研究显示，T细胞活性与总生存期延长呈正相关。

尽管Ⅰ期临床试验结果令人鼓舞，但是由于大部分研究所纳入的病例数较少，临床疗效的可靠证据并不强，仅能说明树突状细胞疫苗安全可行，有初步效果。在此基础上，大样本的Ⅱ期/Ⅲ期临床试验逐渐开展。2008年，De Vleeschouwer等[42]率先完成早期较大规模的Ⅱ期临床试验，共纳入56例复发胶质母细胞瘤患者，以肿瘤细胞裂解物致敏树突状细胞疫苗辅助注射肿瘤细胞裂解物，并根据治疗频率进行分组，虽然生存率未见明显提高，但亚组分析提示，每周接种疫苗的患者可获得生存期延长。2018年，Liau等[64]公布以自体肿瘤细胞裂解物致敏树突状细胞疫苗DCVax-L联合替莫唑胺化疗治疗新发胶质母细胞瘤的Ⅲ期临床试验的中期结果，331例患者均随访至肿瘤复发，所有患者均予DCVax-L治疗，中位总生存期为术后23.1个月，其中223例术后总生存期＞30个月、182例术后总生存期＞36个月；进一步根据O^6-甲基鸟嘌呤-DNA甲基转移酶（*MGMT*）突变进行分层分析显示，*MGMT*突变患者（131例）中位总生存期为34.7个月，其中100例达40.5个月，但未探究预后相关影响因素；仅2.11%（7/331）患者出现3或4级不良事件[美国国立癌症研究所（NCI）通用毒性标准（CTC）]，包括脑水肿3例、癫痫发作2例、恶心1例、淋巴结感染1例，推测可能与接种疫苗有关。该项研究的Ⅲ期试验结果显示出良好的应用前景，表明树突状细胞疫苗可使患者获得显著的生存获益。2019年，Wen等[65]报告其最新树突状细胞疫苗ICT-107治疗新发胶质瘤母细胞瘤的Ⅱ期临床试验结果，并评价其有效性和安全性以及对生存获益和诱导免疫反应的影响。ICT-107是靶向6个特异性抗原的自体树突状细胞疫苗，分别为人类白细胞抗原A1（HLA-A1）限制性MAGE-1、AIM-2以及HLA-A2限制性人表皮生长因子受体2（HER2）、TRP-2、gp100、IL-I3Rα2，上述6个抗原在83%肿瘤细胞中全部表达。疫苗接种组纳入81例胶质母细胞瘤患者，对照组纳入43例胶质母细胞瘤患者，疫苗接种方案为放化疗后4周为诱导期（注射疫苗1次/周），随后为维持期（替莫唑胺治疗第1、3、6、10个疗程的第21天注射疫苗1次，以及药物化疗结束后每6个月注射1次，直至试验结束）。结果显示，疫苗接种组患者最常见的不良事件为乏力、呕吐、眩晕，与对照组相比无显著差异；生存分析提示，两组患者总生存期差异无统计学意义（17个月对15个月，$P=0.580$），而疫苗接种组无进展生存期（PFS）优于对照组（11.2个月对9个月，

$P=0.011$）；亚组分析显示，仅在HLA-A1阳性伴*MGMT*启动子区甲基化患者中，疫苗接种组总生存期优于对照组（47.6个月对25.8个月，$P=0.049$），表明该多靶点疫苗既可改善胶质母细胞瘤免疫抑制微环境，又能在一定程度上克服肿瘤异质性。

但并非所有的临床试验均显示树突状细胞疫苗可使胶质母细胞瘤患者生存获益。Walker等[43]的Ⅰ期临床试验纳入9例胶质母细胞瘤患者和4例间变性星形细胞瘤患者，予树突状细胞疫苗联合胶质瘤标准治疗，再次手术后肿瘤标本中T细胞浸润增多，但总生存期并无明显延长。因此，可能尚有其他因素影响治疗效果，这些均需积累更多的数据或探索更优的治疗方案以达到更稳定的疗效。

四、树突状细胞疫苗在胶质瘤治疗中的前景展望

树突状细胞疫苗的疗效和相对安全性引起了研究者对这种新疗法的极大兴趣。目前已发表的11项树突状细胞疫苗治疗新发高级别胶质瘤的临床试验中7项表现出生存获益，但是评价树突状细胞疫苗治疗复发高级别胶质瘤效果的临床试验中仅有不足20%的患者生存获益，究其原因是所纳入的病例数较少而无法得出明确结论。临床应用树突状细胞疫苗存在诸多困境与挑战，如疫苗来源、疫苗抗原和佐剂选择、疫苗靶向优化、迁移性限制、联合治疗等，均有待进一步深入研究。

1.疫苗来源　目前，体外制备可应用于临床的树突状细胞疫苗大多通过自体血分离$CD14^+$单核细胞诱导而来，但存在制备时间长、细胞数目有限、制备过程繁琐、费用高昂等问题。由此可见，解决疫苗来源是最根本问题。晚近有研究者通过诱导型多能干细胞（iPSCs）、增殖型髓系细胞等诱导抗原呈递细胞，可以制备大量树突状细胞样细胞，与骨髓来源树突状细胞功能、表型等一致，可能有望解决树突状细胞疫苗来源的问题。

2.疫苗抗原和佐剂的选择　目前，构建树突状细胞疫苗的抗原多为肿瘤相关抗原（TAA）或肿瘤细胞裂解物，其优点是制备简便且有一定疗效；此外，肿瘤细胞来源外泌体作为肿瘤抗原也备受关注。外泌体是细胞分泌至细胞外环境的一种小囊泡，含有许多抗原提呈所必需的分子，如特异性抗原、MHC Ⅰ和Ⅱ、共刺激分子和细胞间黏附分子（ICAM）[66]。肿瘤细胞来源外泌体显示出许多优于传统抗原的特性，包括对肿瘤免疫微环境的抵抗、强大的抗原提呈表型、将抗原从专业抗原呈递细胞转移至其他抗原呈递细胞的能力，并能够长期保存。2017年，Liu等[66]在胶质瘤小鼠模型中发现，以外泌体致敏的树突状细胞疫苗具有更强的抗肿瘤细胞毒性作用。除优化疫苗抗原外，联合佐剂治疗也可以增强疗效，不仅可以激活树突状细胞，还可以激活免疫系统的多个分支，从而对抗肿瘤的免疫逃逸机制，增强树突状细胞介导的免疫治疗。临床前研究证实有一种细胞佐剂有较好的应用前景，即自然杀伤T细胞（NKT）。NKT细胞不仅具有直接攻击肿瘤细胞的能力，而且可通过分泌辅助性T细胞1和2（Th1和Th2）调节T细胞活性，通过CD40L/CD40介导的相互作用促进树突状细胞成熟[67-69]。其另一个优势在于对胶质母细胞瘤微环境的抗肿瘤免疫调节作用，包括激活免疫细胞（如B细胞、T细胞和树突状细胞），以及下调和杀伤肿瘤相关巨噬细胞（TAMs）和骨髓来源抑制细胞（MDSC）[66,70-72]。此外，NKT细胞与树突状细胞之间的协同作用可以增强$CD4^+$和$CD8^+$T细胞活性，在诱导强而持久的免疫应答中非常有效[70]。Liu等[66]通过肿瘤细胞来源外泌体联合恒定自然杀伤T细胞（iNKT）佐剂构建的树突状细胞疫苗在小鼠原位胶质瘤模型中验证了这一点，经治疗后小鼠存活期明显延长，表明组合疗法可以导致针对胶质瘤的协同细胞毒性抗肿瘤效应。

3.迁移限制　树突状细胞疫苗应用过程中面临的另一棘手问题是疫苗迁移。研究显示，仅不足5%的树突状细胞疫苗可迁移至淋巴结[73]，因此，改善树突状细胞淋巴结归巢是提高肿瘤抗原特异性树突状细胞疗效的重要方法[60]。Mitchell等[60]将Td类毒素作为一种有效抗原，对胶质母细胞瘤患者的疫苗接种点进行预处理，使树突状细胞迁移增强，生存率显著提高。体内靶向树突状细胞的研究也显示出克服树突状细胞迁移能力较差的缺点[74]。树突状细胞疫苗的体内接种方法主要是单克隆抗体靶向特异性细胞表面受体。CD205是介导抗原摄取和提呈的新受体，对黑色素瘤小鼠模型的观察显示，注射抗CD205抗体耦联的肿瘤抗原可以刺激小鼠体内$CD4^+$和$CD8^+$T细胞的增殖活化，延缓肿瘤生长[75]。Dhodapkar等[76]的人抗CD205抗体与肿瘤抗原NY-ESO-1相结合致敏树突状细胞疫苗的研究也证实人体内治疗的可行性。涉及单克隆抗体介导的胶质母细胞瘤抗原向树突状细胞传递的体内靶

向方法尚待进一步研究，值得期待。

4. 联合治疗 为提高树突状细胞疫苗的疗效，多种免疫治疗方法的联合应用不失为更有效的策略。免疫检查点抑制剂在改善恶性肿瘤患者预后方面业已取得瞩目成就[77-80]。尽管单纯免疫检查点抑制剂治疗恶性胶质瘤的研究结果并不乐观，已有Ⅲ期临床试验（CheckMate-143）证实其延长生存期的作用并不优于贝伐单抗，但与树突状细胞疫苗联合应用的疗效可能有所不同，树突状细胞疫苗可以增加肿瘤局部浸润T细胞数目，免疫检查点抑制剂可以减少肿瘤局部T细胞耗竭，二者结合使治疗效果更佳。Keskin等[81]研究发现，个体化树突状细胞疫苗可以增强胶质母细胞瘤新抗原特异性$CD4^+$和$CD8^+$T细胞免疫应答，使肿瘤局部浸润的肿瘤浸润淋巴细胞（TIL）数目增加。Garris等[82]的研究也证实免疫检查点抑制剂发挥作用需肿瘤局部树突状细胞与T细胞相互作用。关于二者联合应用的临床试验目前正在进行中，国内也有研究团队开展了这一联合治疗方法的临床试验（试验编号：ChiCTR1900025835）。

通过优化树突状细胞的靶向和抗原负载、克服迁移性限制、结合其他免疫治疗方法等以改善肿瘤免疫抑制微环境，有助于提高树突状细胞疫苗治疗胶质母细胞瘤的疗效，有可能在Ⅲ期临床试验中取得有希望的结果，成为重要的临床治疗方法。

五、小结

树突状细胞在固有免疫和获得性免疫系统中发挥重要作用，在胶质母细胞瘤微环境中具有复杂的免疫功能。临床前研究和临床试验业已显示出树突状细胞疫苗可以增强免疫应答并延长患者总生存期。各种协同佐剂的组合旨在克服胶质瘤诱导的免疫抑制，树突状细胞疫苗治疗新发胶质母细胞瘤患者的Ⅲ期临床试验中期结果证实其有效性、安全性和可行性。尚待进一步探讨基于此免疫疗法的最佳组合，从而使患者有最大获益。随着对胶质母细胞瘤免疫基因组学和肿瘤逃逸途径的不断了解，使基于树突状细胞疫苗的免疫疗法不断完善，有助于使基于主动免疫的特异性肿瘤治疗成为可能。

利益冲突 无

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