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纳米材料在脑胶质瘤免疫治疗中的应用与发展

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摘　要

脑胶质瘤是一种起源于神经胶质细胞的肿瘤，是最常见的原发性颅内肿瘤。手术是治疗脑胶质瘤最有效的方法，但术后常常留下残余的肿瘤病灶，不可避免地导致其复发。复发性肿瘤经常出现放疗和/或化疗耐药，同时术后口服化疗药物难以避免出现的血液学副作用(包括恶心和呕吐)，剂量限制性药物毒性和骨髓抑制的副反应。面对脑胶质瘤患者低生存率，低手术成功率，生存质量差的困境，免疫治疗为脑胶质瘤病人的生存带来了改变和希望。但是由于其肿瘤微环境富集的免疫抑制因子和匮乏的细胞毒性的T淋巴细胞形成的“冷”肿瘤环境，制约了脑胶质瘤的免疫治疗效果。纳米材料因其具有高摄取率、高负载率、高响应性，成为免疫治疗的优选项，从而为治疗脑胶质瘤提供新的思路。

关键词

纳米材料，胶质瘤，术后耐药，免疫治疗

Application and Development of Nanomaterials in Immunotherapy of Gliomas of the Brain

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Abstract

Glioma, a tumour originating from glial cells, is the most common primary intracranial tumour. Surgery is the most effective treatment for gliomas, but it often leaves residual tumour lesions after

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surgery, which inevitably leads to their recurrence. Recurrent tumours are frequently radiotherapy and/or chemotherapy resistant, along with haematological side effects (including nausea and vomiting), dose-limiting drug toxicity and myelosuppressive side effects that are difficult to avoid with postoperative oral chemotherapeutic agents. Faced with the dilemma of low survival rate, low surgical success rate and poor quality of life of patients with glioma, immunotherapy has brought change and hope to the survival of patients with glioma. However, the "cold" tumour environment formed by the enrichment of immunosuppressive factors and the lack of cytotoxic T-lymphocytes in the tumour microenvironment restricts the effect of immunotherapy on glioma. Nanomaterials, due to their high uptake rate, high loading rate and high responsiveness, are preferred options for immunotherapy, thus providing new ideas for the treatment of gliomas.

Keywords

Nanomaterials, Glioma, Postoperative Drug Resistance, Immunotherapy

1. 简介

人类脑胶质瘤主要有两种类型：弥漫性胶质瘤和多形性胶质瘤[1]。弥漫性胶质瘤是最常见的原发性中枢神经系统(CNS)肿瘤，包括星形细胞瘤、少突胶质细胞瘤和少突星形胶质细胞瘤，可恶变并具有侵袭性。2016 年，世界卫生组织更新了脑肿瘤的分类方法，将组织学以及分子水平的特征纳入其中，从而制定了一个分级表[2] [3]。因此，弥漫性胶质瘤被划分为 II-IV 级，包括多形性胶质母细胞瘤(GBM)，一种 IV 级星形细胞瘤[4]，多形性胶质母细胞瘤被认为是恶性程度最高、侵袭性最强的人类脑肿瘤类型，也是成人脑肿瘤中最常见的一种。约 90%的胶质母细胞瘤为原发性胶质母细胞瘤，而少量的胶质母细胞瘤由低级别胶质瘤发展而来，也被称为继发性胶质母细胞瘤[5] [6]。在全球范围内，GBM 每年导致 10 多万人死亡，男性发病率高于女性[7]。

随着肿瘤的不断生长，侵袭性也会加剧，由于生长位置的不同，临床表现上也会不一样的出现头痛、呕吐、局灶性或进行性神经功能缺损、癫痫发作、视力障碍和频繁晕厥的临床症状[8]。目前治疗脑胶质瘤的治疗方法主要有手术治疗，放化疗[9]。手术治疗目前仍是治疗中最优先的选择方式，但是由于存在肿瘤大小、肿瘤切除不充分、肿瘤位置以及患者的病情(年龄、性别或合并症)等各种问题，手术的有效性存在局限[10] [11]，术后放化疗能在一定程度上延长患者的生存周期，但是存在术后患者耐药及不良的生物学反应(如恶心、呕吐)，也在一定程度上剥夺了患者的生存质量[12] [13]。目前也有倾向探索靶向治疗脑胶质瘤的方法，有临床实验把贝伐珠单抗用于联合化疗药物治疗，获得了一些有效数据，但由于有效性的支持量存在争议[14]，仍没有大范围地用于临床。而随着进一步了解脑胶质瘤的治疗效果，免疫治疗成为目前关注脑胶质瘤的焦点。

2. 免疫治疗在脑胶质瘤细胞中的应用

在早期研究中一直将大脑视作为免疫抑制环境，免疫治疗不能为胶质瘤患者带来明显的收益。而现在大脑免疫豁免的理念被推翻，有研究证实脑内是存在淋巴系统的，并且 T 细胞是能够进入大脑的目前在胶质母细胞瘤中开展的免疫治疗(图 1)大致分为肿瘤溶瘤病毒治疗、嵌合抗原受体 T 细胞治疗(CAR-T)、免疫检查点阻断治疗及疫苗治疗[15]。溶瘤病毒治疗可以用各种方式来对抗胶质母细胞瘤。癌细胞病毒通

常具有复制能力，并被设计为选择性地诱导肿瘤细胞的细胞毒性。这种方法旨在引发免疫反应，从而刺激抗肿瘤免疫力[16] [17]。病毒的局部递送提高了效率，并限制了病毒量的系统性传播。许多病毒疗法已经被在胶质母细胞瘤患者中进行了研究，病毒可以通过病原体相关的分子模式和模式识别受体激活免疫系统。此外，病毒经常通过受体，如 TLRs82 来激活巨噬细胞。作为次要效应，被激活的骨髓细胞可以改善 T 细胞对肿瘤的浸润，促进炎症微环境的形成。因此，病毒疗法是克服胶质母细胞瘤免疫抑制的一个非常有趣的方法。虽然最初的策略是使用无复制能力的病毒来避免脑炎的并发症[18]，但当代的溶瘤病毒治疗方法越来越多地利用有复制能力的病毒，如逆转录病毒、腺病毒、单纯疱疹病毒(HSVs)、脊髓灰质炎病毒和麻疹病毒[19] [20]。但是目前抗病毒治疗效果与剂量毒性并不能获得正向反馈，许多溶瘤病毒疗法的安全性可以得到，然而，总生存期的中位数只有 6.2 个月其免疫治疗效果也需要进一步探究[21]。

但是目前胶质瘤免疫治疗自身无法规避的弊端即是免疫毒性和自身免疫[22]，最近的临床研究结果表明，“热肿瘤”高密度分泌干扰素(IFN-γ)的细胞毒性 T 淋巴细胞是治疗成功的关键标志，T 细胞的表型及其在肿瘤微环境中的定位，可能会影响免疫疗法的疗效[23]。迄今为止，最引人注目的例子是阻断抑制性免疫检查点蛋白细毒性 T 淋巴细胞抗原 4 (CTLA4)和 PD1 的抗体。大多数免疫治疗机制也集中在 CTLA-4 和 PD-1 通路上[24]-[26]。T 细胞通常表达 CTLA-4 和 PD-1 等抑制性蛋白及其他免疫抑制标记物，这些分子在抗肿瘤起的作用非常有效，CTLA-4 和 PD-1/轴调节生理性免疫平衡，下调炎症反应，并推定促进癌细胞的免疫逃避，在胶质瘤中 CD4+和 CD8+ T 细胞上的 PD-1 表达量逐渐增加，而 PD-1 在肿瘤浸润 T 细胞上高表达，反而加剧 T 细胞的凋亡，但是 GL261 肿瘤中分泌 IFN-γ 的却能减少 PD-1 的表达[27]。所以目前大量的研究文章侧重于促进 IFN-γ 分泌调节 CTLA-4 和 PD-1 轴，实现抗肿瘤最大的效果，也有相应的临床实验去进一步探索其治疗效果至于获得进一步收益仍需要更长久的数据支持[28] [29]。

嵌合抗原受体 T 细胞治疗(CAR-T)是基于基因工程技术使 T 细胞表达针对特定抗原的嵌合抗原受体(CARs)，当 CAR 蛋白与其相关抗原结合后，会促进 T 细胞活化与增殖，同时 T 细胞释放大量的细胞因子、颗粒酶，发挥杀伤肿瘤细胞的作用[30]。针对颅内脑胶质瘤的治疗，关于 CAR-T 细胞的临床实验逐年增多，主要集中在针对人表皮生长因子受体 2 (HER2)、EGFRvIII 和白细胞介素-13 受体 α2 (IL-13rα2)，但脑胶质瘤免疫抑制的肿瘤微环境仍然限制其发挥作用[31]。免疫检查点是指免疫细胞表面上存在的一种抑制性蛋白或者信号通路，目前最受关注的治疗包括抗 PD-L1 及抗 CTLA-4 等药物[32]。T 细胞表面的 PD-L1 与肿瘤细胞表面 PD-L1 的结合，导致下游 PI3K/AKT 信号通路的抑制进而下调 Bd-2 家族基因的表达，一方面致使细胞毒性 T 细胞(CTL)的凋亡，另一方面抑制 CTL 分泌抑癌性的细胞因子，如干扰素、肿瘤坏死因子-α 和白介素-2。CTLA-4 通过与配体 CD86 和 CD80 的结合，竞争性地抑制 CD28 的激活，导致 T 细胞活性的抑制，进而抑制其抗癌作用，但在文献报道其作用临床实验上收效甚微[33]-[35]。

疫苗治疗在脑胶质瘤治疗中已经进入临床试验阶段[36] [37]。有文献报道回输负载肿瘤抗原的自体树突状细胞(dendretic cell, DC)的 DC 疫苗提高了胶质母细胞瘤患者的五年生存率。个性化肿瘤疫苗(personalized cancer vaccines, PCV)已经用于脑胶质瘤的抗肿瘤治疗，其原理是经颅外免疫激活、扩增胶质瘤特异性 T 淋巴细胞，从而使 T 淋巴细胞移行入颅内抑制、杀伤胶质瘤细胞，因而延缓、抑制手术后胶质瘤的复发、延长患者的生存期[38] [39]。肿瘤裂解物疫苗(tumor lysate vaccines, TLVs)是采用经手术或活检获取的肿瘤制备的裂解物为抗原的 PCV，已有临床研究证实胶质瘤裂解物装载自体疫苗能够在术后延长患者的生存期[40]。但是由于其缺乏强烈的免疫原性，不能激发有效的抗肿瘤免疫应答，故需要相应的免疫佐剂，增强其免疫治疗效果。但是目前在临床应用中缺乏有效的生物标志物是目前治疗胶质母细胞瘤患者的挑战之一，为实现个体化疫苗治疗设置了杠杆[41]。核磁共振成像仍然是确定疾病负担的金标准方法，个体化疫苗在临床开展过程中仍然受限。

纳米材料由于本身具备高摄取率、高负载率、高响应性，使其具备克服血脑屏障的作用到达肿瘤部位，目前大量纳米材料的研发集中在功能化纳米载体，借助纳米载药后达到精准靶向治疗[42]，从而实现大量分泌抑制肿瘤因子促进其抑制胶质瘤生长效果。因此目前脑胶质瘤免疫治疗也在大量利用各种纳米材料实现免疫治疗在胶质瘤治疗的最大作用。

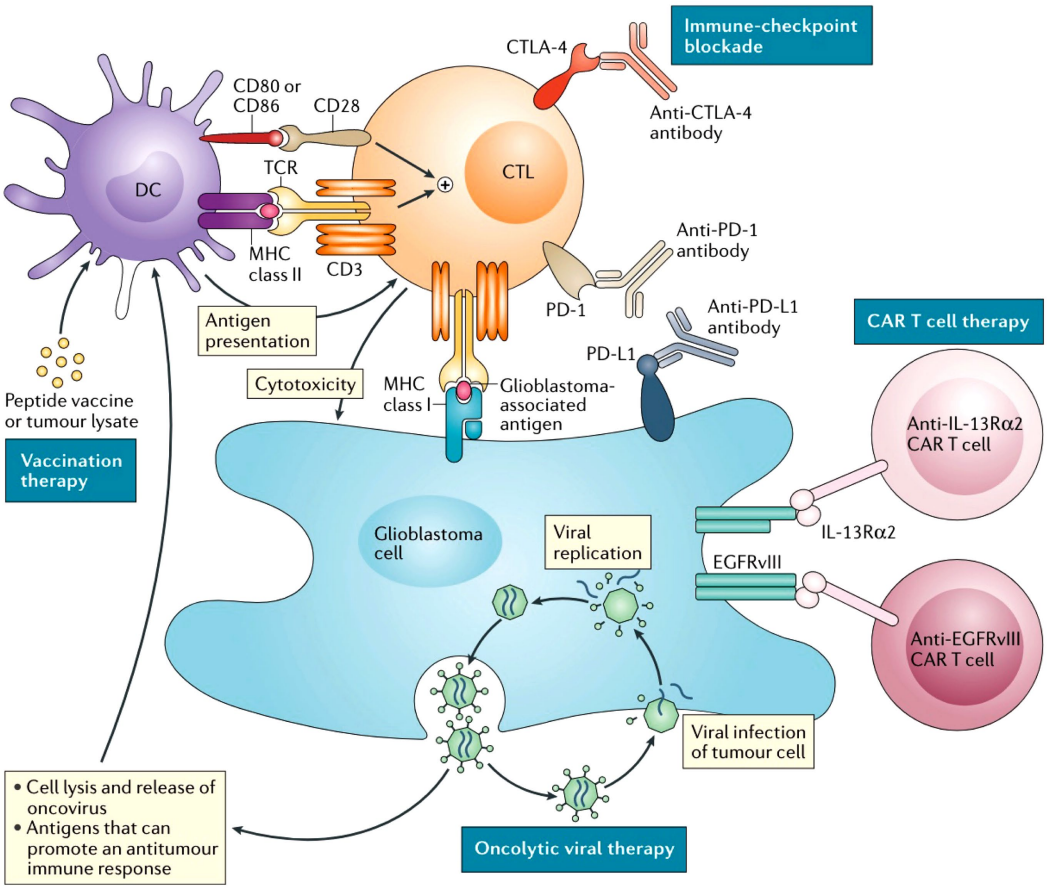

Figure 1. Current immunotherapy modalities for the treatment of glioblastoma
图 1. 目前治疗胶质细胞瘤的免疫疗法模式

3. 纳米材料在脑胶质瘤免疫治疗中的应用

纳米材料，特别是纳米颗粒，正在作为潜在的方法进行研究，以加强对 GBM 患者的杀瘤药物递送[43]。直径从 1 纳米到 1000 纳米不等的纳米颗粒可用于药物递送以外的不同用途，包括基因递送和诊断。目前存在多种类型纳米颗粒，它们的形状、大小、电荷、成分和功能各不相同；可以使用一系列技术制造它们，包括纳米沉淀法、双乳液溶剂蒸发法或光刻法。使用纳米沉淀法，可利用可生物降解、生物相容性好的聚酯均聚物合成纳米颗粒，如聚乳酸(PLA)、聚乳酸－共－乙醇酸(PLGA)和聚己内酯(PCL)，这些均聚物可诱导/吸附药物化合物，在适当的功能化处理后，可改善疏水性或亲水性小药物分子向特定靶点的递送[44] [45]。从而合成水凝胶，流体明胶，纳米贴片等材料从而发挥其最大的作用，纳米颗粒可以减少某些药物化合物的副作用，提高溶解度和渗透性，保护药物免受酶和化学降解。

研究表明，聚乙二醇化可减少蛋白吸附，从而减少网状内皮系统(RES)的摄取，从而延长聚乙二醇化 NPs 的循环半衰期。在 Zhao 等人的研究中，他们使用了一种 GBM 小鼠模型来证明 PEG 化聚氨基胺

(PAMAM)第五代树枝状聚合物纳米颗粒与 CREKA 肽共轭。他们的研究表明，与未包被的纳米颗粒相比，这些 PEG 化的纳米颗粒延长了体内循环时间，降低了 PAMAM 的固有毒性，并能深入穿透 GBM 组织[46]。

纳米材料用于胶质瘤免疫治疗的文献近几年也在疯狂增长。山东大学 Jing Zhang 等人利用开发一种自制的低聚肽水凝胶作为药物库，以共同传递 CXCL10 和 THINR 纳米颗粒，引起小鼠体内产生免疫原性细胞死亡，对于术后脑胶质瘤治疗效果明显[47]，Chen 等人利用特异性嵌合抗原受体(CAR)巨噬细胞/小胶质细胞包裹于复合纳米颗粒来进行脑肿瘤治疗，利用巨噬细胞极化效果发挥肿瘤体内的抗炎作用，实现抑制胶质瘤复发[48]。Feihu Wang 团队利用一种自组装紫杉醇(PTX)长丝(PF)纳米水凝胶，它能刺激巨噬细胞介导的免疫反应，用于复发性胶质母细胞瘤的局部治疗[49]。Jing Kuang 等人利用 iRGD 修饰纳米粒子 DOX@MSN-SS-iRGD&1MT，用于将化疗药物(阿霉素，DOX)和免疫检查点抑制剂(1-甲基色氨酸，1MT)同时递送到原位胶质瘤中，实现脑胶质瘤原位激活细胞毒性 CD8+ T 淋巴细胞使抗肿瘤细胞因子 IFNα/β、IFN-γ、TNF、IL-17、STING 和 GrzB 的表达上调，抑制胶质瘤生长效果显著[50]，Wang 制备肽(Pep-1)修饰的 PTX 纳米粒子(PNP PTX)和甘露醇修饰的 CpG 纳米粒子(MNPCPG)，将其包埋于 PLGA 1750-PEG 1500-PLGA 1750 温敏水凝胶框架中，建立 PNP PTX &MNP CpG @Gel 缓释药物递送系统，从而实现抑制肿瘤生长效果研究[51]。现在仍有大量研究来拓展免疫治疗的效果，同时也不断有新的尝试把免疫治疗与其他研究结合起来，增强其抗肿瘤效果，为之后的研究拓展思路。

4. 总结

与身体其他部位的肿瘤相比，GBM 等恶性脑肿瘤由于受血脑屏障的影响，治疗难度更大。为了克服这一难题以及与脑肿瘤相关的其他难题，人们设计、合成并评估了各种新型给药系统(如用于 GBM 的纳米材料)，与可溶性治疗剂相比，这些系统在临床前研究中延长了中位生存时间。与可溶性药物相比，更能实现精准靶向治疗。同时随着大脑免疫治疗的研究进展，越来越多的文献研究旨在把纳米材料和免疫治疗相结合，实现其抗肿瘤的最大效应，从本文所述的结果来看，把纳米材料和胶质瘤脑部疾病的免疫材料结合，是一个充满希望的新时代有望到来。

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