·脑胶质瘤免疫研究进展·

靶向胶质瘤干细胞及其微环境的免疫治疗进展

王海洋　董军

【摘要】 胶质瘤是中枢神经系统最常见的原发性恶性肿瘤，胶质瘤干细胞及其微环境是支持胶质瘤发生、恶性进展的根本原因，将其作为包括免疫治疗在内的各项治疗策略的靶点有望提高疗效。单克隆抗体可通过特异性识别胶质瘤干细胞标志物，靶向并抑制其生物学活性；胶质瘤干细胞中肿瘤相关基因变异，使溶瘤病毒选择性复制，裂解胶质瘤干细胞，抑制肿瘤生长；过继转移的嵌合抗原受体T细胞经体外激活、回输后可直接靶向胶质瘤干细胞相关抗原，发挥抗肿瘤作用；树突状细胞疫苗通过胶质瘤干细胞mRNA致敏，发挥靶向激活抗胶质瘤干细胞免疫反应的作用。胶质瘤干细胞活化性配体表达水平升高且低表达主要组织相容性复合物Ⅰ类分子，针对此特点，自然杀伤细胞可以较好地发挥抗肿瘤作用。胶质瘤干细胞微环境中免疫检查点抑制在免疫逃逸过程中起关键作用，对这些免疫检查点进行干预成为肿瘤免疫治疗的重要靶点。靶向胶质瘤干细胞的免疫治疗策略虽在不同程度上显示出一定疗效，但远未成熟，尚待持续深入探究。

【关键词】 神经胶质瘤；　肿瘤干细胞；　肿瘤微环境；　免疫疗法；　综述

Immunotherapy targeting glioma stem cells and its microenvironment

WANG Hai-yang, DONG Jun

Department of Neurosurgery, the Second Affiliated Hospital of Soochow University, Suzhou 215000, Jiangsu, China

Corresponding author: DONG Jun (Email: djdongjun@163.com)

【Abstract】 Glioma is the most prevailing primary malignant tumor in the central nervous system. Given that glioma stem cells (GSCs) and its microenvironment are pivotal for the occurrence and progression of glioma, various targeted therapy including immunotherapy is promising to improve prognosis of glioma. Monoclonal antibodies could inhibit GSCs biological activity through specifically recognizing GSCs markers. GSCs tumor-related gene mutations lead to selective replication of oncolytic viruses in GSCs, which inhibits proliferation of GSCs. The chimeric antigen receptor T cells (CAR-T) are activated in vitro, transferred back, and set off targeted immune cascade towards GSCs. Because of the high expression of activated ligand and low expression of major histocompatibility complex Ⅰ (MHC-Ⅰ) in GSCs, Natural killer (NK) cells have a promising anti-tumor performance. Furthermore, the inhibition of immune checkpoints in GSCs microenvironment plays a vital role in process of immune escape. So intervention of these immune checkpoints has be a heated topic in tumor immunotherapy. Although the immunotherapy strategy targeting GSCs shows a certain effect to varying degrees, it is far from mature and needs to be further explored.

【Key words】 Glioma; Neoplastic stem cells; Tumor microenvironment; Immunotherapy; Review

This study was supported by Research and Practice Innovation Program for Postgraduates in Jiangsu Province, China (No. KYCX19_1982) and Science and Technology Program of Health and Family Planning Commission in Suzhou, Jiangsu Province, China (No. LCZX201807).

Conflicts of interest: none declared

高级别胶质瘤是中枢神经系统最常见的原发性肿瘤，具有广泛性浸润生长、强大的新生血管形成能力和对现有治疗方法高耐受等生物学特点，患者生存期短、预后不良[1-2]。目前，针对胶质瘤的规范化治疗方案（手术最大限度安全切除肿瘤辅以术后同步放化疗或辅助化疗），以及在体部恶性肿瘤治疗中已取得显著疗效的的分子靶向治疗、免疫治疗、肿瘤治疗电场（TTF）等方法仅能在有限程度上

doi:10.3969/j.issn.1672-6731.2020.02.004

基金项目：江苏省研究生科研创新计划项目（项目编号：KYCX19_1982）；江苏省苏州市卫生计生委科技项目（项目编号：LCZX201807）

作者单位：215000 苏州大学附属第二医院神经外科

通讯作者：董军，Email：djdongjun@163.com

缓解病情，对总生存率并无明显改善。对于高度异质性胶质瘤，针对何种治疗靶点才能真正提高疗效，是当前临床治疗所关注的焦点问题。近年对胶质瘤起源的研究显示，胶质瘤干细胞（GSCs）在胶质瘤发生、恶性进展、治疗抵抗和复发过程中发挥关键作用[3-4]，但此类细胞是起源于室管膜下区恶性转化的神经干细胞（NSCs）还是由脑胶质瘤细胞分化而来，尚无定论。在胶质瘤微环境中，胶质瘤干细胞不仅可使微环境中相关细胞发生有利于其组织重构的重编程，而且具有高度抑制免疫细胞的抗肿瘤活性作用。近年来，肿瘤免疫治疗方法和临床疗效已取得巨大进步[5]，但有关靶向胶质瘤干细胞免疫治疗的研究鲜有文献报道。胶质瘤干细胞不仅可以作为靶向治疗的理想靶点，而且有望成为免疫治疗的首选靶点，有可能从根本上改善胶质瘤的治疗前景。

一、胶质瘤干细胞概述

早在20世纪70年代，Hamburger等学者即已提出导致肿瘤发生、发展、复发的肿瘤干细胞理论，迄今已获得大量研究证据的支持[6]。肿瘤干细胞占肿瘤细胞的比例较小，具有自我更新、多系分化潜能和耐受常规治疗的生物学特性。胶质瘤干细胞是胶质瘤中具有肿瘤起始作用的细胞[3,7]，存在异质性，即使起源于同一肿瘤，其生物学特性亦不完全相同[8-9]。胶质瘤干细胞具有诱导肿瘤血管生成、促进肿瘤侵袭播散和对放化疗高度耐受等特性，并可在常规治疗压力下迅速重建肿瘤，导致胶质瘤快速复发[10]。越来越多的研究聚焦于与上述生物学特征相关的重要分子调控通路，以期获取高效、可靠的治疗靶点。

胶质瘤干细胞表面可表达不同的蛋白质，与维持其自身稳态息息相关，这些细胞表面蛋白质是筛选和靶向胶质瘤干细胞的理想标志物，其中以CD133最为经典。体外实验显示，胶质瘤细胞中的$CD133^+$细胞亚群具有较强的自我更新和增殖能力，且可在脑组织内启动肿瘤细胞之生物学活性[3]。与此同时，CD15、CD36、CD44、SOX2、巢蛋白（Nes）和ATP结合盒转运子G2（ABCG2）等亚群也为较受关注的胶质瘤干细胞标志物，早期研究多通过制备针对上述标志物的特异性单克隆抗体靶向胶质瘤干细胞。然而，正常神经干细胞也可表达上述标志物，而且某些胶质瘤细胞亚群存在类胶质瘤干细胞样生物学行为，但并不表达胶质瘤干细胞标志物，例如，$CD133^-$胶质瘤细胞也可表现出较强的组织重构等胶质瘤干细胞表型[11-12]。有多条关键信号转导通路与胶质瘤干细胞生物学特性相关，其中研究最多的通路是Notch、Sonic Hedgehog、Wnt/β-连环蛋白（β-catenin）、磷脂酰肌醇3-激酶（PI3K）/丝氨酸/苏氨酸激酶（AKT）、信号传导与转录激活因子3（STAT3）通路。然而，通过上述信号转导通路靶向胶质瘤干细胞仍面临较大困难，这是由于上述通路并非胶质瘤干细胞所特有，亦同时存在于正常神经干细胞和部分肿瘤细胞中。体外研究显示，胶质瘤细胞过表达*POU3F2*、*SOX2*、*OLIG2*、*SALL2*基因，可使胶质瘤细胞去分化为胶质瘤干细胞样细胞[13]，提示关键促瘤基因可决定胶质瘤干细胞分化与否，并进一步调控胶质瘤之进展。胚胎发育中的功能转录因子，如双螺旋丝蛋白20（PHF20）、SOX2、SOX9和鸟氨酸氨基甲酰转移酶4（OCT4）等兼具促肿瘤效应，其中PHF20被鉴定为胶质瘤特异性抗原，但临床研究显示，接受抗PHF20抗体治疗的胶质瘤患者并未获得优于对照组的疗效[14]。PHF20高表达于神经源性肿瘤，通过显著上调SOX2和OCT4表达水平以增强神经母细胞瘤自我更新和肿瘤启动能力，在肿瘤发生中具有重要作用[15]；SOX2和SOX9则高表达于胶质瘤干细胞，发挥维持胶质瘤干细胞功能稳态的重要作用[16-17]；SOX2、SOX9和OCT4表达缺失可抑制胶质瘤干细胞活性并延缓肿瘤启动[18-19]。上述研究均提示，PHF20-SOX2-SOX9-OCT4轴对维持胶质瘤干细胞生物学表型具有重要作用，探究上述特定肿瘤干细胞相关基因之间的相互作用，有助于明确胶质瘤起源，从而为靶向胶质瘤干细胞的免疫治疗提供新的靶点。

二、靶向胶质瘤干细胞的免疫治疗

目前一直在探寻疗效确切的胶质瘤免疫治疗方案，主要包括被动免疫治疗、过继免疫治疗和主动免疫治疗。被动免疫治疗是利用抗体或毒素等免疫效应分子，在不直接激活免疫系统的情况下靶向杀伤肿瘤细胞；过继免疫治疗是通过过继性T细胞转移和应用嵌合抗原受体T细胞（CAR-T），在体外以肿瘤抗原激活T细胞，然后再将这种可特异性识别肿瘤的活化T细胞输入患者体内，达到免疫治疗目的。主动免疫治疗通常称为疫苗接种，通过各种来源的肿瘤相关抗原（TAA），如肿瘤裂解物、肿瘤细胞、mRNA或多肽，直接激活患者免疫系统，实现抗肿瘤之目的。

1.靶向胶质瘤干细胞的单克隆抗体　由单克隆抗体介导的靶向肿瘤抗原的免疫治疗已逾30年，由于单克隆抗体的直接细胞杀伤和免疫调节作用而在肿瘤免疫治疗中曾占据重要地位[20]，随着各种胶质瘤干细胞标志物陆续得到鉴定，各类人源化小分子多功能单克隆抗体被寄予厚望。表皮生长因子受体(*EGFR*)基因扩增和突变是胶质瘤干细胞的重要遗传学特征[21]，直接靶向EGFR的单克隆抗体已用于胶质瘤的治疗，其中研究最多、应用最广泛的是西妥昔单抗，通过干扰配体结合和EGFR细胞外二聚体形成，阻断EGFR介导的信号转导通路而发挥功能[22]。转化生长因子-β(TGF-β)信号转导通路参与胶质瘤发生和恶性进展的多个环节，恶性胶质瘤患者血清TGF-β表达变化与肿瘤分级和预后呈正相关[23]，TGF-β信号转导通路主要通过调控干细胞相关基因如*SOX4*、*SOX2*、*LIF*，实现胶质瘤干细胞的自我更新并抑制其分化[23-24]。临床研究显示，靶向TGF-β的免疫治疗无明显不良反应，复发胶质瘤患者的肿瘤细胞可被抗TGF-β抗体GC1008靶向结合，并在治疗早期即显示出良好的肿瘤抑制作用，但并不能阻止治疗后期临床和影像学出现的肿瘤进展，故而未能实现长期临床获益[25]。贝伐单抗是另一用于治疗胶质瘤的单克隆抗体，是美国食品与药品管理局(FDA)批准用于治疗高级别胶质瘤的人源血管内皮生成因子(VEGF)单克隆抗体，具有显著的抗肿瘤血管生成作用，且可干扰胶质瘤干细胞小生境中的血管状态，导致胶质瘤干细胞易受其他治疗方法的损伤[26-27]，但在多项临床试验中并未观察到明显的生存获益，仅可在一定时间内控制瘤周水肿以改善临床症状，以及在放射治疗所致假性进展方面有确切疗效[28]。

2.靶向胶质瘤干细胞的溶瘤病毒　溶瘤病毒(OVs)是经过设计的具有选择性在肿瘤细胞中繁殖并杀伤肿瘤细胞的治疗药物。其重要设计原则是减弱或删除病毒毒力因子，使溶瘤病毒无法在正常组织中复制，但仍保留在肿瘤细胞内复制并杀伤肿瘤细胞的能力[29]。目前已证实肿瘤特异性基因，如RAS、TP53、RB1、同源性磷酸酶-张力蛋白(PTEN)和Wnt信号转导通路中的编码基因及其他肿瘤相关基因，可增加肿瘤细胞对病毒的易感性[30]，这是由于促肿瘤与抗病毒的信号转导通路之间形成干扰，从而为病毒复制提供适宜的环境。此外，哺乳动物细胞抗病毒过程中的关键环节是由干扰素(IFN)介导的，而肿瘤细胞中IFN信号转导通路缺陷，不具有较强的抗病毒能力[31]。肿瘤干细胞同样具有肿瘤特异性基因突变和IFN信号转导通路缺陷的特点，故溶瘤病毒可以有效杀伤肿瘤干细胞，该疗法已在荷瘤小鼠体内显示出一定的抗肿瘤疗效[32]。动物实验显示，携带白细胞介素-12(IL-12)的溶瘤性单纯疱疹病毒(HSV)可使荷瘤小鼠脑肿瘤消退[33]。溶瘤病毒治疗胶质瘤进展较快，由于胶质瘤干细胞高度富集整合素如$\alpha_v\beta_3$或$\alpha_v\beta_5$，通过基因工程技术设计的溶瘤病毒可以通过这些整合素进入胶质瘤干细胞而发挥抗肿瘤作用，其中DNX-2401是一种具有肿瘤特异性和强感染能力的溶瘤病毒，已用于Ⅰ期临床试验且安全性良好、肿瘤体积明显缩小、患者生存期延长[34-35]。除直接的溶瘤作用外，趋化性增强的免疫细胞和细胞毒性T细胞也参与抗肿瘤过程，从而产生明显的临床疗效[35]。除脑胶质瘤外，溶瘤病毒对多种体部恶性肿瘤的肿瘤干细胞亦具有杀伤效应。在乳腺癌模型中，溶瘤病毒GLV-1h68可在肿瘤干细胞内选择性复制并杀伤高表达乙醛脱氢酶1(ALDH1)的肿瘤干细胞[36]；在卵巢癌模型中，拮抗趋化因子受体4(CXCR4)的溶瘤病毒对$CD44^+CD117^+$肿瘤干细胞具有明显杀伤作用[37]；在结肠癌模型中，靶向肿瘤干细胞标志物CD133的溶瘤腺病毒可以选择性感染$CD133^+$肿瘤干细胞[38]，溶瘤病毒与氟尿嘧啶(5-FU)联合应用对$CD133^+$和$CD44^+$肿瘤干细胞具有明显治疗效果[39]；在肝癌模型中，溶瘤性麻疹病毒可靶向并裂解$CD133^+$肿瘤干细胞[40]。此外，溶瘤病毒还具有调节荷瘤宿主机体免疫力的作用，使免疫系统可以更好地适应病毒抗肿瘤活性[41]。

3.靶向胶质瘤干细胞的嵌合抗原受体T细胞　过继性T细胞治疗(ACT)是一种个性化治疗，这种免疫细胞具有直接抗肿瘤活性。过继性T细胞治疗需首先从患者体内分离出浸润肿瘤的T细胞，在IL-2的刺激下，经体外培养使其具备特异性识别肿瘤的能力，然后再将其回输至患者体内[42]。与通过肿瘤相关抗原刺激固有免疫系统的主动免疫不同，过继转移的CAR-T细胞可以直接靶向肿瘤相关抗原而不依赖抗原提呈过程。嵌合抗原受体(CAR)可以靶向肿瘤表面抗原并激活T细胞，从而达到抗肿瘤作用[43]。相对于体内固有的数目少且功能低下的肿瘤特异性T细胞，CAR-T细胞可以在体外扩增至较高水平，从而诱导较强的细胞毒性免疫反应。

CAR-T细胞目前已成功用于血液系统恶性肿瘤的治疗，由于实体肿瘤表面缺乏特异性抗原，该疗法在实体肿瘤中的应用尚待深入探索[44]。晚近靶向肿瘤干细胞的CAR-T细胞疗法，已在各种类型肿瘤模型中进行观察研究，以评价其抗肿瘤活性：在前列腺癌模型中，针对EpCAM抗原的CAR-T细胞可以根除PC3M和PC3肿瘤模型中的肿瘤干细胞[45]；膜嵌合IL-15构建的CAR-T细胞在$CD19^+$白血病中可诱导生成靶向肿瘤干细胞的记忆性T细胞[46]；在结肠癌模型中，过继转移的$CD8^+$细胞毒性T细胞可特异性识别肿瘤干细胞抗原ASB4，进而选择性消灭肿瘤干细胞[47]。但是考虑到CAR-T细胞疗法对中枢神经系统的不良反应，如认知功能障碍、脑积水等，其治疗胶质瘤的报道尚不多见[48-49]。胶质母细胞瘤和胶质瘤干细胞中最常见的*EGFR*基因特异性突变——表皮生长因子受体变异体Ⅲ（EGFRvⅢ）目前已成为CAR-T细胞疗法的重要靶点。靶向EGFRvⅢ的CAR-T细胞疗法在荷瘤小鼠模型以及Ⅰ期临床试验（试验编号：NCT02209376）中可清除表达EGFRvⅢ的肿瘤细胞[50]，经逆转录载体转导，可使CAR-T细胞表达特异性IL-13Rα2或人表皮生长因子受体2（HER2），进而靶向杀伤胶质瘤干细胞；由于$CD133^+$胶质瘤干细胞高表达IL-13Rα2和HER2，故可被CAR-T细胞识别并杀伤[51-52]。上述研究表明，胶质瘤干细胞可能成为CAR-T细胞疗法的潜在靶点。

4.靶向胶质瘤干细胞的肿瘤疫苗　肿瘤疫苗可以激活宿主免疫系统，识别并杀伤肿瘤细胞，属主动免疫治疗。激活免疫系统的最佳途径是刺激多功能抗原呈递细胞（APC），如树突状细胞（DC）、巨噬细胞、B淋巴细胞（以下简称B细胞），其中以树突状细胞为最佳选择。树突状细胞自外周血单个核细胞（PBMC）中分离纯化，先由IL-4和粒细胞-巨噬细胞集落刺激因子（GM-CSF）刺激生成未成熟的树突状细胞，再以IL-1b、IL-6、前列腺素E2（PGE2）和肿瘤坏死因子-α（TNF-α）混合物成分刺激，获得成熟的树突状细胞[53]。树突状细胞疫苗治疗肿瘤的主要目的是产生特异性辅助性T细胞（Th），从而激活细胞毒性T细胞的抗肿瘤作用[54]。肿瘤细胞中可被树突状细胞识别的各种成分称为肿瘤相关抗原，激活的树突状细胞回输至患者体内后，通过向肿瘤特异性T细胞提呈肿瘤相关抗原以增强抗肿瘤免疫反应[55]。恶性实体肿瘤动物模型的观察结果业已显示，靶向肿瘤干细胞相关抗原的树突状细胞疫苗具有明确的疗效：在恶性黑色素瘤模型中，由肿瘤干细胞裂解物致敏的树突状细胞可使荷瘤小鼠分泌更多的INF-γ和IL-4，抑制肿瘤生长并延长小鼠存活期[56]；在卵巢癌模型中，包含NANOG肽的树突状细胞可以识别肿瘤干细胞并诱导高度特异性抗肿瘤T细胞免疫反应[57]；有研究显示，树突状细胞可通过共同提呈肿瘤特异性抗原和Toll样受体（TLR）激活宿主对黑色素瘤的免疫反应[58]，肿瘤细胞崩解后部分成分又可增强树突状细胞对主动免疫的刺激；临床研究显示，胶质瘤患者术后接受树突状细胞疫苗治疗安全、有效[59]。由此可见，肿瘤疫苗通过将肿瘤相关抗原更多地暴露给免疫细胞，激活免疫系统，产生抗肿瘤作用，因此，能否制备出有效识别肿瘤干细胞并激活免疫反应的树突状细胞疫苗是提高免疫治疗效果的关键。Jachetti等[60]的研究显示，与经分化肿瘤细胞致敏的树突状细胞相比，以耐受放射治疗的肿瘤干细胞致敏的树突状细胞可促使机体产生更强的T细胞毒性并分泌更多的IFN-γ。Dashti等[56]分别通过小鼠黑色素瘤细胞系B16F10和肿瘤干细胞裂解物致敏树突状细胞，发现经后者致敏的树突状细胞可明显延长荷瘤小鼠存活期。Ning等[61]发现，通过肿瘤干细胞裂解物致敏的树突状细胞可使接受免疫治疗的荷瘤小鼠产生较高水平的IgG，从而在补体存在的情况下增强其细胞毒性；此外，在黑色素瘤和鳞状细胞癌模型中，通过肿瘤干细胞致敏的树突状细胞可以使荷瘤小鼠体内产生更强的细胞毒性作用。胶质瘤干细胞具有相同的树突状细胞致敏能力，因此直接靶向这一肿瘤细胞亚群，进而建立针对胶质瘤的肿瘤疫苗有望成为有效的治疗方案[62]。临床试验显示，胶质母细胞瘤患者通过移植转染自体胶质瘤干细胞mRNA的树突状细胞，激发适应性免疫反应，使肿瘤消退，延长总生存期（OS）[63]。Finocchiaro和Pellegatta[62]经对一系列临床前研究结果的总结，得出以富含胶质瘤干细胞的细胞群致敏树突状细胞可以增强胶质瘤免疫治疗效果的结论，进而提出胶质瘤干细胞高表达的FABP7、GLAST、CD133、SOX2等是肿瘤疫苗免疫治疗的良好靶点，有利于提高胶质瘤患者整体生存率。制备胶质瘤干细胞肿瘤疫苗，需先将手术切除的肿瘤标本制备为单细胞悬液，然后在干细胞培养条件下分离单个胶质瘤干细胞并增殖为干细胞球，再提取胶质瘤干细胞mRNA

并转染至单个核细胞来源的树突状细胞。ICT-107疫苗是由6种合成多肽致敏自体外周血单个核细胞分化的树突状细胞，可靶向胶质瘤干细胞相关抗原，例如HER2、黑色素瘤缺乏因子2（AIM2）、gp100、IL-13Rα2、酪氨酸相关蛋白-2（TRP-2）、黑色素瘤抗原基因-1（MAGE1）等。Phuphanich等[64]在针对新发胶质母细胞瘤的标准治疗方案中增加了ICT-107疫苗治疗，结果显示，患者中位无进展生存期（PFS）为16.9个月、中位总生存期为38.4个月，部分患者接种该疫苗后经历再次手术切除，切除标本中胶质瘤干细胞数目明显减少，提示该疫苗可以诱导机体抗肿瘤免疫靶向杀伤胶质瘤干细胞。Wen等[65]的Ⅱ期临床试验是首个针对胶质瘤干细胞并获得阳性结果的免疫治疗的随机对照试验，观察新发胶质母细胞瘤患者手术和放化疗后加用树突状细胞疫苗对患者无进展生存期或总生存期的影响，其结果显示，ICT-107组患者中位无进展生存期延长2个月且差异具有统计学意义，总生存期也有所延长但未达到统计学意义。Vik-Mo等[63]研究发现，胶质瘤患者接受规范化综合治疗后于皮下注射胶质瘤干细胞疫苗，可成功诱导出增强的抗肿瘤免疫反应（7/10例）；接种疫苗的患者无进展生存期较对照者延长2.9倍且无严重不良反应。在生理状态下，中枢神经系统在主动免疫治疗过程中激活的树突状细胞较少，需补充造血干/祖细胞以提供树突状细胞并持续诱导有效的T细胞反应，造血干/祖细胞进入中枢神经系统后分化为$CD86^{+}CD11c^{+}MHC\,Ⅱ^{+}$细胞，呈现出活化树突状细胞表型和功能，从而激发细胞毒性免疫反应。造血干/祖细胞来源的细胞因高表达CD86等共刺激分子而表现出较强的抗肿瘤免疫作用[66]。近年来，SOX2作为一种维持胶质瘤干细胞的重要转录因子，被认为是主动免疫治疗的新靶点，SOX2肽疫苗可以显著增强全身和局部免疫反应，并在肿瘤模型中延长荷瘤动物存活期，无论是否联合化疗均可观察到确切的疗效[67]。因此，靶向SOX2等胶质瘤干细胞相关基因的疫苗可以为主动免疫治疗提供新的方案。

5.针对胶质瘤干细胞的自然杀伤细胞　以自然杀伤（NK）细胞为基础的过继免疫治疗无论对血液系统肿瘤还是实体肿瘤均是一种有前景的免疫治疗策略[68]。NK细胞抗肿瘤的基础依赖NK细胞及其活化性受体[如NK细胞活化性受体NKG2D、DNAX辅助分子1（DNAM-1）等]对肿瘤细胞表达的对应配体[如主要组织相容性复合物Ⅰ类链相关分子A和B（MICA和MICB）、人类巨细胞病毒糖蛋白UL-16结合蛋白（ULBP）、脊髓灰质炎病毒受体（PVR）、黏连蛋白2等]的识别，识别并激活后的NK细胞产生细胞毒性，进而杀伤肿瘤细胞。正常细胞可表达较高水平的被NK细胞抑制性受体识别的主要组织相容性复合物Ⅰ（MHCⅠ）类分子，从而免受NK细胞的攻击[69]。体外研究显示，胶质瘤干细胞可表达高水平的PVR和黏连蛋白2，NK细胞活化性受体DNAM-1可以特异性识别上述两种配体，进而杀伤胶质瘤干细胞[70]。大多数恶性肿瘤的肿瘤干细胞MHCⅠ类分子表达水平较低，刺激NK细胞抑制性受体的作用较弱，从另一方面活化NK细胞多条信号转导通路参与肿瘤干细胞中NK细胞配体的调节[71-72]，其中MICA、MICB和ULBP在肿瘤上皮间质转化（EMT）过程中上调，RAS/PI3K信号转导通路激活可促进NKG2D对应的配体在胶质瘤干细胞中的表达[73]。NK细胞可对病毒感染和肿瘤形成产生快速反应，在活化性受体阳性且抑制性受体阴性的情况下，NK细胞可直接裂解MHCⅠ缺失的肿瘤细胞或其他病原体[74]。有多项研究支持肿瘤干细胞是NK细胞免疫杀伤作用的易感靶点：Tseng等[75]的研究显示，与分化肿瘤细胞相比，NK细胞与口腔鳞癌干细胞、人胚胎干细胞、间充质干细胞、牙髓干细胞和人诱导型多能干细胞（iPSCs）进行共同孵育时，NK细胞毒性增强，IFN-γ分泌增加；Castriconi等[70]发现，源于胶质母细胞瘤的胶质瘤干细胞对经IL-2或IL-15激活的NK细胞介导的裂解物高度敏感；新鲜纯化的同种异体NK细胞可识别并杀伤结直肠癌来源的肿瘤干细胞，而分化的肿瘤细胞对NK细胞的敏感性较低，这种NK细胞对肿瘤干细胞和普通肿瘤细胞易感性的差异与肿瘤干细胞表面活化性受体对应配体的表达水平相关，肿瘤干细胞中特异性结合激活性受体NKp30和NKp44的配体表达水平明显高于非肿瘤干细胞[76]。上述研究表明，NK细胞过继免疫治疗有可能在根除残留肿瘤干细胞方面发挥积极作用，NK细胞除直接杀伤肿瘤干细胞外，还可诱导其分化。在肿瘤干细胞和IL-2同时存在的情况下，CD16可抑制NK细胞毒性并促进其细胞因子分泌，NK细胞这种状态称为“分裂无力”。NK细胞可分泌大量IFN-γ，诱导肿瘤干细胞中的MHCⅠ、分化受体和细胞程序性死亡蛋白配体1（PDL1）表达水平升高，并降低肿瘤干细胞标志物

CD44表达水平，这种诱导分化肿瘤干细胞的作用可使肿瘤细胞的生长和转移受到抑制[77]。由此可见，NK细胞通过两步机制抑制肿瘤进展，先杀伤一部分肿瘤干细胞，然后在NK细胞分裂停滞的状态下，诱导剩余肿瘤干细胞群体细胞分化[78]。

三、针对胶质瘤干细胞微环境免疫抑制的治疗策略

通过增强肿瘤特异性抗原表达促进抗肿瘤免疫反应以达到治疗效果的研究一直备受关注。晚近研究显示，肿瘤干细胞免疫微环境中存在一种抑制免疫反应的机制，干扰免疫系统的监视作用，免疫检查点在免疫抑制的肿瘤干细胞微环境中发挥关键作用，对这些免疫检查点进行干预已成为肿瘤免疫治疗的重要靶点[79-80]，其中细胞毒性T淋巴细胞相关抗原4（CTLA-4）和细胞程序性死亡蛋白1（PD1）是重要治疗靶点。CTLA-4亦称为CD152，是T细胞负性调节因子，与T细胞具有高度亲和性，从而导致其耗尽并抑制其活化[81-82]。PD1表达于各种免疫细胞中，如活化的T细胞、B细胞、NK细胞、树突状细胞[83]。多项研究显示，各种恶性肿瘤组织中均可检测到呈高表达的PD1及配体PDL1，与T细胞耗尽相关[84]，二者相互作用可明显抑制活化的T细胞分泌IFN-γ并使T细胞无功能化[85]。CTLA-4抑制抗肿瘤免疫反应的作用已被阐明，表明抗CTLA-4治疗可以解除T细胞的抑制作用，从而支持抗肿瘤免疫反应[86]。外周淋巴细胞CTLA-4表达水平下调可以改善胶质瘤患者预后[87]。胶质瘤进展期患者调节性T细胞（Treg）中的PD1表达上调，胶质瘤微环境中浸润的淋巴细胞中PD1表达亦上调[88]，PD1轴在肿瘤进展和免疫逃逸过程中发挥关键促进作用[89]。因此，在包括胶质瘤在内的恶性肿瘤中，阻断PD1信号转导通路可能是挽救免疫抑制并维持抗肿瘤免疫反应的有效方法。

针对胶质母细胞瘤微环境中免疫抑制的研究一直是神经肿瘤学的热点。胶质瘤中肿瘤相关巨噬细胞（TAMs）和小胶质细胞对肿瘤有明显促进作用[90]，这两种细胞功能严重依赖集落刺激因子1受体（CSF1R），阻断CSF1R，无论是在胶质瘤动物模型中还是胶质瘤患者中均显示出较好的疗效[91-92]。M2型TAMs在肿瘤微环境中可促进胶质瘤进展，当以CSF1R抑制剂为靶点时，TAMs可切换为抗肿瘤作用的M1型。PLX3397是一种可透过血-脑屏障的CSF1R抑制剂，可减少TAMs和小胶质细胞在肿瘤微环境中的募集[93]。另一种CSF1R抑制剂BLZ945，可显著抑制肿瘤进程并提高肿瘤模型中荷瘤动物的存活率，经BLZ945治疗后，M2型TAMs标志物表达水平减少，促肿瘤能力受到抑制[91]。虽然抑制CSF1R提供了一种具有前景的治疗策略，但有研究显示，PI3K、胰岛素样生长因子-1及其受体（IGF-1/IGF-1R）信号转导通路激活可能对GSF1R抑制剂耐药，因此，联合应用GSF1R抑制剂与PI3K、IGF1R抑制剂可延长胶质瘤患者总生存期[92]。

尽管在胶质瘤免疫治疗中各种免疫检查点的研究一直受到高度关注，但PD1和CTLA-4始终是最多被研究的分子，并经临床试验证实其对胶质瘤的作用切实有效[94]。目前业已取得临床进展的免疫治疗药物，以抗PD1抗体Nivolumab最受关注，但其在胶质瘤治疗中的疗效十分有限，联合应用免疫检查点抑制剂与标准治疗方案可以在一定程度上提高部分胶质瘤患者的生存期[95]，改善预后，减少药物不良反应[96]。此外，我们课题组的前期研究也显示，TAMs可被胶质瘤干细胞诱导并且发生恶性转化[97]，成为胶质瘤干细胞组织重构进程中的重要组成部分，此类恶性转化的免疫细胞亦构成胶质母细胞瘤高度异质性的细胞学基础[98]。

四、结论

胶质瘤干细胞和胶质瘤微环境决定了胶质瘤的发生进展。胶质瘤干细胞、各种免疫细胞与细胞因子之间的复杂多向相互作用，最终形成对肿瘤有支持作用的肿瘤免疫微环境，促进胶质瘤干细胞始动的肿瘤发生、增殖和侵袭。针对胶质瘤干细胞和胶质瘤微环境中免疫抑制机制的研究，有助于研发免疫治疗药物，从而针对潜在的胶质瘤治疗靶点更有效地杀伤肿瘤细胞。

利益冲突 无

参 考 文 献

[1] Paulino AC, Teh BS. Treatment of brain tumors[J]. N Engl J Med, 2005, 352:2350-2353.

[2] Stupp R, Weber DC. The role of radio- and chemotherapy in glioblastoma[J]. Onkologie, 2005, 28:315-317.

[3] Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB. Identification of human brain tumour initiating cells[J]. Nature, 2004, 432:396-401.

[4] Yuan X, Curtin J, Xiong Y, Liu G, Waschsmann-Hogiu S, Farkas DL, Black KL, Yu JS. Isolation of cancer stem cells from adult glioblastoma multiforme[J]. Oncogene, 2004, 23:9392-9400.

[5] Duan J, Cui L, Zhao X, Bai H, Cai S, Wang G, Zhao Z, Zhao J,

Chen S, Song J, Qi C, Wang Q, Huang M, Zhang Y, Huang D, Bai Y, Sun F, Lee JJ, Wang Z, Wang J. Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: a systematic review and meta-analysis[J]. JAMA Oncol, 2019.[Epub ahead of print]

[6] Batlle E, Clevers H. Cancer stem cells revisited[J]. Nat Med, 2017, 23:1124-1134.

[7] Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, Fiocco R, Foroni C, Dimeco F, Vescovi A. Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma[J]. Cancer Res, 2004, 64:7011-7021.

[8] Folkins C, Man S, Xu P, Shaked Y, Hicklin DJ, Kerbel RS. Anticancer therapies combining antiangiogenic and tumor cell cytotoxic effects reduce the tumor stem-like cell fraction in glioma xenograft tumors[J]. Cancer Res, 2007, 67:3560-3564.

[9] Wicha MS. Cancer stem cell heterogeneity in hereditary breast cancer[J]. Breast Cancer Res, 2008, 10:105.

[10] Huang Z, Cheng L, Guryanova OA, Wu Q, Bao S. Cancer stem cells in glioblastoma-molecular signaling and therapeutic targeting[J]. Protein Cell, 2010, 1:638-655.

[11] Beier D, Hau P, Proescholdt M, Lohmeier A, Wischhusen J, Oefner PJ, Aigner L, Brawanski A, Bogdahn U, Beier CP. CD133(+) and CD133(−) glioblastoma-derived cancer stem cells show differential growth characteristics and molecular profiles [J]. Cancer Res, 2007, 67:4010-4015.

[12] Ogden AT, Waziri AE, Lochhead RA, Fusco D, Lopez K, Ellis JA, Kang J, Assanah M, Mc Khann GM, Sisti MB, Mc Cormick PC, Canoll P, Bruce JN. Identification of A2B5+CD133− tumor-initiating cells in adult human gliomas[J]. Neurosurgery, 2008, 62:505-514.

[13] Suvà ML, Rheinbay E, Gillespie SM, Patel AP, Wakimoto H, Rabkin SD, Riggi N, Chi AS, Cahill DP, Nahed BV, Curry WT, Martuza RL, Rivera MN, Rossetti N, Kasif S, Beik S, Kadri S, Tirosh I, Wortman I, Shalek AK, Rozenblatt-Rosen O, Regev A, Louis DN, Bernstein BE. Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells[J]. Cell, 2014, 157:580-594.

[14] Pallasch CP, Struss AK, Munnia A, König J, Steudel WI, Fischer U, Meese E. Autoantibodies against GLEA2 and PHF3 in glioblastoma: tumor-associated autoantibodies correlated with prolonged survival[J]. Int J Cancer, 2005, 117:456-459.

[15] Long W, Zhao W, Ning B, Huang J, Chu J, Li L, Ma Q, Xing C, Wang HY, Liu Q, Wang RF. PHF20 collaborates with PARP1 to promote stemness and aggressiveness of neuroblastoma cells through activation of SOX2 and OCT4[J]. J Mol Cell Biol, 2018, 10:147-160.

[16] Hägerstrand D, He X, Bradic Lindh M, Hoefs S, Hesselager G, Ostman A, Nistér M. Identification of a SOX2-dependent subset of tumor- and sphere-forming glioblastoma cells with a distinct tyrosine kinase inhibitor sensitivity profile[J]. Neuro Oncol, 2011, 13:1178-1191.

[17] Garros-Regulez L, Aldaz P, Arrizabalaga O, Moncho-Amor V, Carrasco-Garcia E, Manterola L, Moreno-Cugnon L, Barrena C, Villanua J, Ruiz I, Pollard S, Lovell-Badge R, Sampron N, Garcia I, Matheu A. mTOR inhibition decreases SOX2-SOX9 mediated glioma stem cell activity and temozolomide resistance [J]. Expert Opin Ther Targets, 2016, 20:393-405.

[18] Rani SB, Rathod SS, Karthik S, Kaur N, Muzumdar D, Shiras AS. MiR-145 functions as a tumor-suppressive RNA by targeting SOX9 and adducin 3 in human glioma cells[J]. Neuro Oncol, 2013, 15:1302-1316.

[19] Vanner RJ, Remke M, Gallo M, Selvadurai HJ, Coutinho F, Lee L, Kushida M, Head R, Morrissy S, Zhu X, Aviv T, Voisin V, Clarke ID, Li Y, Mungall AJ, Moore RA, Ma Y, Jones SJ, Marra MA, Malkin D, Northcott PA, Kool M, Pfister SM, Bader G, Hochedlinger K, Korshunov A, Taylor MD, Dirks PB. Quiescent SOX2(+) cells drive hierarchical growth and relapse in sonic hedgehog subgroup medulloblastoma[J]. Cancer Cell, 2014, 26:33-47.

[20] Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy[J]. Cancer Immun, 2012, 12:14.

[21] Huang Q, Zhang QB, Dong J, Wu YY, Shen YT, Zhao YD, Zhu YD, Diao Y, Wang AD, Lan Q. Glioma stem cells are more aggressive in recurrent tumors with malignant progression than in the primary tumor, and both can be maintained long-term in vitro[J]. BMC Cancer, 2008, 8:304.

[22] Taylor TE, Furnari FB, Cavenee WK. Targeting EGFR for treatment of glioblastoma: molecular basis to overcome resistance[J]. Curr Cancer Drug Targets, 2012, 12:197-209.

[23] Peñuelas S, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma[J]. Cancer Cell, 2009, 15:315-327.

[24] Ikushima H, Todo T, Ino Y, Takahashi M, Miyazawa K, Miyazono K. Autocrine TGF-beta signaling maintains tumorigenicity of glioma-initiating cells through Sry-related HMG-box factors[J]. Cell Stem Cell, 2009, 5:504-514.

[25] Han J, Alvarez-Breckenridge CA, Wang QE, Yu J. TGF-β signaling and its targeting for glioma treatment[J]. Am J Cancer Res, 2015, 5:945-955.

[26] Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C, Hamner B, Oh EY, Gaber MW, Finklestein D, Allen M, Frank A, Bayazitov IT, Zakharenko SS, Gajjar A, Davidoff A, Gilbertson RJ. A perivascular niche for brain tumor stem cells [J]. Cancer Cell, 2007, 11:69-82.

[27] Esparza R, Azad TD, Feroze AH, Mitra SS, Cheshier SH. Glioblastoma stem cells and stem cell-targeting immunotherapies [J]. J Neurooncol, 2015, 123:449-457.

[28] Zhuang H, Yuan X, Zheng Y, Li X, Chang JY, Wang J, Wang X, Yuan Z, Wang P. A study on the evaluation method and recent clinical efficacy of bevacizumab on the treatment of radiation cerebral necrosis[J]. Sci Rep, 2016, 6:24364.

[29] Muik A, Stubbert LJ, Jahedi RZ, Geiβ Y, Kimpel J, Dold C, Tober R, Volk A, Klein S, Dietrich U, Yadollahi B, Falls T, Miletic H, Stojdl D, Bell JC, von Laer D. Re-engineering vesicular stomatitis virus to abrogate neurotoxicity, circumvent humoral immunity, and enhance oncolytic potency[J]. Cancer Res, 2014, 74:3567-3578.

[30] Pikor LA, Bell JC, Diallo JS. Oncolytic viruses: exploiting cancer's deal with the devil[J]. Trends Cancer, 2015, 1:266-277.

[31] Twumasi-Boateng K, Pettigrew JL, Kwok YY, Bell JC, Nelson BH. Publisher correction: oncolytic viruses as engineering platforms for combination immunotherapy[J]. Nat Rev Cancer, 2018, 18:526.

[32] Jiang H, Gomez-Manzano C, Lang FF, Alemany R, Fueyo J. Oncolytic adenovirus: preclinical and clinical studies in patients with human malignant gliomas[J]. Curr Gene Ther, 2009, 9:422-427.

[33] Cheema TA, Wakimoto H, Fecci PE, Ning J, Kuroda T, Jeyaretna DS, Martuza RL, Rabkin SD. Multifaceted oncolytic virus therapy for glioblastoma in an immunocompetent cancer stem cell model[J]. Proc Natl Acad Sci USA, 2013, 110:12006-12011.

[34] Jiang H, Gomez-Manzano C, Aoki H, Alonso MM, Kondo S, Mc

Cormick F, Xu J, Kondo Y, Bekele BN, Colman H, Lang FF, Fueyo J. Examination of the therapeutic potential of delta-24-RGD in brain tumor stem cells: role of autophagic cell death [J]. J Natl Cancer Inst, 2007, 99:1410-1414.

[35] Lang FF, Conrad C, Gomez-Manzano C, Yung WK, Sawaya R, Weinberg JS, Prabhu SS, Rao G, Fuller GN, Aldape KD, Gumin J, Vence LM, Wistuba I, Rodriguez-Canales J, Villalobos PA, Dirven CM, Tejada S, Valle RD, Alonso MM, Ewald B, Peterkin JJ, Tufaro F, Fueyo J. Phase Ⅰ study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma[J]. J Clin Oncol, 2018, 36:1419-1427.

[36] Wang H, Chen NG, Minev BR, Szalay AA. Oncolytic vaccinia virus GLV-1h68 strain shows enhanced replication in human breast cancer stem-like cells in comparison to breast cancer cells[J]. J Transl Med, 2012, 10:167.

[37] Gil M, Komorowski MP, Seshadri M, Rokita H, Mc Gray AJ, Opyrchal M, Odunsi KO, Kozbor D. CXCL12/CXCR4 blockade by oncolytic virotherapy inhibits ovarian cancer growth by decreasing immunosuppression and targeting cancer-initiating cells[J]. J Immunol, 2014, 193:5327-5337.

[38] Sato-Dahlman M, Miura Y, Huang JL, Hajeri P, Jacobsen K, Davydova J, Yamamoto M. CD133-targeted oncolytic adenovirus demonstrates anti-tumor effect in colorectal cancer [J]. Oncotarget, 2017, 8:76044-76056.

[39] Yoo SY, Bang SY, Jeong SN, Kang DH, Heo J. A cancer-favoring oncolytic vaccinia virus shows enhanced suppression of stem-cell like colon cancer[J]. Oncotarget, 2016, 7:16479-16489.

[40] Bach P, Abel T, Hoffmann C, Gal Z, Braun G, Voelker I, Ball CR, Johnston IC, Lauer UM, Herold-Mende C, Mühlebach MD, Glimm H, Buchholz CJ. Specific elimination of CD133+ tumor cells with targeted oncolytic measles virus [J]. Cancer Res, 2013, 73:865-874.

[41] Niemann J, Kühnel F. Oncolytic viruses: adenoviruses [J]. Virus Genes, 2017, 53:700-706.

[42] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer [J]. Science, 2015, 348:62-68.

[43] Kingwell K. CAR T therapies drive into new terrain[J]. Nat Rev Drug Discov, 2017, 16:301-304.

[44] Kosti P, Maher J, Arnold JN. Perspectives on chimeric antigen receptor T-cell immunotherapy for solid tumors [J]. Front Immunol, 2018, 9:1104.

[45] Deng Z, Wu Y, Ma W, Zhang S, Zhang YQ. Adoptive T-cell therapy of prostate cancer targeting the cancer stem cell antigen EpCAM[J]. BMC Immunol, 2015, 16:1.

[46] Hurton LV, Singh H, Najjar AM, Switzer KC, Mi T, Maiti S, Olivares S, Rabinovich B, Huls H, Forget MA, Datar V, Kebriaei P, Lee DA, Champlin RE, Cooper LJ. Tethered IL-15 augments antitumor activity and promotes a stem-cell memory subset in tumor-specific T cells[J]. Proc Natl Acad Sci USA, 2016, 113:E7788-7797.

[47] Miyamoto S, Kochin V, Kanaseki T, Hongo A, Tokita S, Kikuchi Y, Takaya A, Hirohashi Y, Tsukahara T, Terui T, Ishitani K, Hata F, Takemasa I, Miyazaki A, Hiratsuka H, Sato N, Torigoe T. The antigen ASB4 on cancer stem cells serves as a target for ctl immunotherapy of colorectal cancer[J]. Cancer Immunol Res, 2018, 6:358-369.

[48] Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, Yeung C, Liles WC, Wurfel M, Lopez JA, Chen J, Chung D, Harju-Baker S, Özpolat T, Fink KR, Riddell SR, Maloney DG, Turtle CJ. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells[J]. Cancer Discov, 2017, 7:1404-1419.

[49] Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, Halton E, Wang X, Senechal B, Purdon T, Cross JR, Liu H, Vachha B, Chen X, DeAngelis LM, Li D, Bernal Y, Gonen M, Wendel HG, Sadelain M, Brentjens RJ. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia [J]. Cancer Discov, 2018, 8:958-971.

[50] Choi BD, O'Rourke DM, Maus MV. Engineering chimeric antigen receptor T cells to treat glioblastoma[J]. J Target Ther Cancer, 2017, 6:22-25.

[51] Ahmed N, Salsman VS, Kew Y, Shaffer D, Powell S, Zhang YJ, Grossman RG, Heslop HE, Gottschalk S. HER2-specific T cells target primary glioblastoma stem cells and induce regression of autologous experimental tumors[J]. Clin Cancer Res, 2010, 16:474-485.

[52] Brown CE, Starr R, Aguilar B, Shami AF, Martinez C, D'Apuzzo M, Barish ME, Forman SJ, Jensen MC. Stem-like tumor-initiating cells isolated from IL13Rα2 expressing gliomas are targeted and killed by IL13-zetakine-redirected T cells[J]. Clin Cancer Res, 2012, 18:2199-2209.

[53] Datta J, Terhune JH, Lowenfeld L, Cintolo JA, Xu S, Roses RE, Czerniecki BJ. Optimizing dendritic cell-based approaches for cancer immunotherapy[J]. Yale J Biol Med, 2014, 87:491-518.

[54] Cho DY, Lin SZ, Yang WK, Hsu DM, Lee HC, Lee WY, Liu SP. Recent advances of dendritic cells (DCs)-based immunotherapy for malignant gliomas [J]. Cell Transplant, 2009, 18:977-983.

[55] Sheng KC, Pietersz GA, Wright MD, Apostolopoulos V. Dendritic cells: activation and maturation: applications for cancer immunotherapy [J]. Curr Med Chem, 2005, 12:1783-1800.

[56] Dashti A, Ebrahimi M, Hadjati J, Memarnejadian A, Moazzeni SM. Dendritic cell based immunotherapy using tumor stem cells mediates potent antitumor immune responses[J]. Cancer Lett, 2016, 374:175-185.

[57] Wefers C, Schreibelt G, Massuger LF, de Vries IJ, Torensma R. Immune curbing of cancer stem cells by CTLs directed to NANOG[J]. Front Immunol, 2018, 9:1412.

[58] Zhu M, Ding X, Zhao R, Liu X, Shen H, Cai C, Ferrari M, Wang HY, Wang RF. Co-delivery of tumor antigen and dual toll-like receptor ligands into dendritic cell by silicon microparticle enables efficient immunotherapy against melanoma [J]. J Control Release, 2018, 272:72-82.

[59] Inogés S, Tejada S, de Cerio AL, Gállego Pérez-Larraya J, Espinós J, Idoate MA, Dominguez PD, de Eulate RG, Aristu J, Bendandi M, Pastor F, Alonso M, Andreu E, Cardoso FP, Valle RD. A phase Ⅱ trial of autologous dendritic cell vaccination and radiochemotherapy following fluorescence-guided surgery in newly diagnosed glioblastoma patients[J]. J Transl Med, 2017, 15:104.

[60] Jachetti E, Mazzoleni S, Grioni M, Ricupito A, Brambillasca C, Generoso L, Calcinotto A, Freschi M, Mondino A, Galli R, Bellone M. Prostate cancer stem cells are targets of both innate and adaptive immunity and elicit tumor-specific immune responses[J]. Oncoimmunology, 2013, 2:E24520.

[61] Ning N, Pan Q, Zheng F, Teitz-Tennenbaum S, Egenti M, Yet J, Li M, Ginestier C, Wicha MS, Moyer JS, Prince ME, Xu Y, Zhang XL, Huang S, Chang AE, Li Q. Cancer stem cell vaccination confers significant antitumor immunity [J]. Cancer Res, 2012, 72:1853-1864.

[62] Finocchiaro G, Pellegatta S. Immunotherapy with dendritic cells loaded with glioblastoma stem cells: from preclinical to clinical

studies[J]. Cancer Immunol Immunother, 2016, 65:101-109.
[63] Vik-Mo EO, Nyakas M, Mikkelsen BV, Moe MC, Due-Tonnesen P, Suso EM, Sæbøe-Larssen S, Sandberg C, Brinchmann JE, Helseth E, Rasmussen AM, Lote K, Aamdal S, Gaudernack G, Kvalheim G, Langmoen IA. Therapeutic vaccination against autologous cancer stem cells with mRNA-transfected dendritic cells in patients with glioblastoma [J]. Cancer Immunol Immunother, 2013, 62:1499-1509.
[64] Phuphanich S, Wheeler CJ, Rudnick JD, Mazer M, Wang H, Nuño MA, Richardson JE, Fan X, Ji J, Chu RM, Bender JG, Hawkins ES, Patil CG, Black KL, Yu JS. Phase Ⅰ trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma[J]. Cancer Immunol Immunother, 2013, 62:125-135.
[65] Wen PY, Reardon DA, Armstrong TS, Phuphanich S, Aiken RD, Landolfi JC, Curry WT, Zhu JJ, Glantz M, Peereboom DM, Markert JM, LaRocca R, O'Rourke DM, Fink K, Kim L, Gruber M, Lesser GJ, Pan E, Kesari S, Muzikansky A, Pinilla C, Santos RG, Yu JS. A randomized double-blind placebo-controlled phase Ⅱ trial of dendritic cell vaccine ICT-107 in newly diagnosed patients with glioblastoma [J]. Clin Cancer Res, 2019, 25:5799-5807.
[66] Wildes TJ, Grippin A, Dyson KA, Wummer BM, Damiani DJ, Abraham RS, Flores CT, Mitchell DA. Cross-talk between T cells and hematopoietic stem cells during adoptive cellular therapy for malignant glioma[J]. Clin Cancer Res, 2018, 24:3955-3966.
[67] Favaro R, Appolloni I, Pellegatta S, Sanga AB, Pagella P, Gambini E, Pisati F, Ottolenghi S, Foti M, Finocchiaro G, Malatesta P, Nicolis SK. SOX2 is required to maintain cancer stem cells in a mouse model of high-grade oligodendroglioma [J]. Cancer Res, 2014, 74:1833-1844.
[68] Ljunggren HG, Malmberg KJ. Prospects for the use of NK cells in immunotherapy of human cancer [J]. Nat Rev Immunol, 2007, 7:329-339.
[69] Tallerico R, Garofalo C, Carbone E. A new biological feature of natural killer cells: the recognition of solid tumor-derived cancer stem cells[J]. Front Immunol, 2016, 7:179.
[70] Castriconi R, Daga A, Dondero A, Zona G, Poliani PL, Melotti A, Griffero F, Marubbi D, Spaziante R, Bellora F, Moretta L, Moretta A, Corte G, Bottino C. NK cells recognize and kill human glioblastoma cells with stem cell-like properties[J]. J Immunol, 2009, 182:3530-3539.
[71] Tallerico R, Conti L, Lanzardo S, Sottile R, Garofalo C, Wagner AK, Johansson MH, Cristiani CM, Kärre K, Carbone E, Cavallo F. NK cells control breast cancer and related cancer stem cell hematological spread[J]. Oncoimmunology, 2017, 6:E1284718.
[72] Voutsadakis IA. Expression and function of immune ligand-receptor pairs in NK cells and cancer stem cells: therapeutic implications[J]. Cell Oncol (Dordr), 2018, 41:107-121.
[73] López-Soto A, Huergo-Zapico L, Galván JA, Rodrigo L, de Herreros AG, Astudillo A, Gonzalez S. Epithelial-mesenchymal transition induces an antitumor immune response mediated by NKG2D receptor[J]. J Immunol, 2013, 190:4408-4419.
[74] Lanier LL. Natural killer cell receptor signaling[J]. Curr Opin Immunol, 2003, 15:308-314.
[75] Tseng HC, Arasteh A, Paranjpe A, Teruel A, Yang W, Behel A, AlvaJ A, Walter G, Head C, Ishikawa TO, Herschman HR, Cacalano N, Pyle AD, Park NH, Jewett A. Increased lysis of stem cells but not their differentiated cells by natural killer cells; de-differentiation or reprogramming activates NK cells[J]. PLoS One, 2010, 5:E11590.
[76] Tallerico R, Todaro M, Di Franco S, Maccalli C, Garofalo C, Sottile R, Palmieri C, Tirinato L, Pangigadde PN, La Rocca R, Mandelboim O, Stassi G, Di Fabrizio E, Parmiani G, Moretta A, Dieli F, Kärre K, Carbone E. Human NK cells selective targeting of colon cancer-initiating cells: a role for natural cytotoxicity receptors and MHC class Ⅰ molecules [J]. J Immunol, 2013, 190:2381-2390.
[77] Jewett A, Tseng HC. Tumor induced inactivation of natural killer cell cytotoxic function; implication in growth, expansion and differentiation of cancer stem cells[J]. J Cancer, 2011, 2:443-457.
[78] Kaur K, Nanut MP, Ko MW, Safaie T, Kos J, Jewett A. Natural killer cells target and differentiate cancer stem-like cells/undifferentiated tumors: strategies to optimize their growth and expansion for effective cancer immunotherapy [J]. Curr Opin Immunol, 2018, 51:170-180.
[79] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy[J]. Nat Rev Cancer, 2012, 12:252-264.
[80] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy [J]. Cancer Cell, 2015, 27:450-461.
[81] Du Four S, Maenhout SK, Niclou SP, Thielemans K, Neyns B, Aerts JL. Combined VEGFR and CTLA-4 blockade increases the antigen-presenting function of intratumoral DCs and reduces the suppressive capacity of intratumoral MDSCs [J]. Am J Cancer Res, 2016, 6:2514-2531.
[82] Chikuma S. CTLA-4, an essential immune-checkpoint for T-cell activation[J]. Curr Top Microbiol Immunol, 2017, 410:99-126.
[83] Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, Iyer AK. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome[J]. Front Pharmacol, 2017, 8:561.
[84] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, ZangX. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway[J]. Trends Mol Med, 2015, 21:24-33.
[85] Que Y, Xiao W, Guan YX, Liang Y, Yan SM, Chen HY, Li QQ, Xu BS, Zhou ZW, Zhang X. PD-L1 expression is associated with foxp3+ regulatory t-cell infiltration of soft tissue sarcoma and poor patient prognosis[J]. J Cancer, 2017, 8:2018-2025.
[86] Fecci PE, Heimberger AB, Sampson JH. Immunotherapy for primary brain tumors: no longer a matter of privilege[J]. Clin Cancer Res, 2014, 20:5620-5629.
[87] Fong B, Jin R, Wang X, Safaee M, Lisiero DN, Yang I, Li G, Liau LM, Prins RM. Monitoring of regulatory T cell frequencies and expression of CTLA-4 on T cells, before and after DC vaccination, can predict survival in GBM patients [J]. PLoS One, 2012, 7:E32614.
[88] Dejaegher J, Verschuere T, Vercalsteren E, Boon L, Cremer J, Sciot R, Van Gool SW, De Vleeschouwer S. Characterization of PD-1 upregulation on tumor-infiltrating lymphocytes in human and murine gliomas and preclinical therapeutic blockade [J]. Int J Cancer, 2017, 141:1891-1900.
[89] Liu Z, Ravindranathan R, Kalinski P, Guo ZS, Bartlett DL. Rational combination of oncolytic vaccinia virus and PD-L1 blockade works synergistically to enhance therapeutic efficacy [J]. Nat Commun, 2017, 8:14754.
[90] Poon CC, Sarkar S, Yong VW, Kelly JJ. Glioblastoma-associated microglia and macrophages: targets for therapies to improve prognosis[J]. Brain, 2017, 140:1548-1560.
[91] Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, Olson OC, Quick ML, Huse JT, Teijeiro V, Setty M, Leslie CS, Oei Y, Pedraza A, Zhang J, Brennan CW, Sutton JC, Holland EC, Daniel D, Joyce JA. CSF-1R

inhibition alters macrophage polarization and blocks glioma progression[J]. Nat Med, 2013, 19:1264-1272.
[92] Quail DF, Bowman RL, Akkari L, Quick ML, Schuhmacher AJ, Huse JT, Holland EC, Sutton JC, Joyce JA. The tumor microenvironment underlies acquired resistance to CSF - 1R inhibition in gliomas[J]. Science, 2016, 352:AAD3018.
[93] Coniglio SJ, Eugenin E, Dobrenis K, Stanley ER, West BL, Symons MH, Segall JE. Microglial stimulation of glioblastoma invasion involves epidermal growth factor receptor (EGFR) and colony stimulating factor 1 receptor (CSF-1R) signaling[J]. Mol Med, 2012, 18:519-527.
[94] Preusser M, Lim M, Hafler DA, Reardon DA, Sampson JH. Prospects of immune checkpoint modulators in the treatment of glioblastoma[J]. Nat Rev Neurol, 2015, 11:504-514.
[95] Chandran M, Candolfi M, Shah D, Mineharu Y, Yadav VN, Koschmann C, Asad AS, Lowenstein PR, Castro MG. Single vs. combination immunotherapeutic strategies for glioma[J]. Expert Opin Biol Ther, 2017, 17:543-554.
[96] Kim JE, Patel MA, Mangraviti A, Kim ES, Theodros D, Velarde E, Liu A, Sankey EW, Tam A, Xu H, Mathios D, Jackson CM, Harris-Bookman S, Garzon-Muvdi T, Sheu M, Martin AM, Tyler BM, Tran PT, Ye X, Olivi A, Taube JM, Burger PC, Drake CG, Brem H, Pardoll DM, Lim M. Combination therapy with anti-PD-1, anti - TIM - 3, and focal radiation results in regression of murine gliomas[J]. Clin Cancer Res, 2017, 23:124-136.
[97] Hong L, Ma J, Zhu H, Cai H, Dong J, Li M, Huang Q, Wang A. STAT3 signaling pathway regulates glioma stem cells induced host macrophage malignance[J]. Translat Canc Res, 2016, 5: 805-816.
[98] Ji XY, Shi J, Dai XX, Sheng YJ, Xue YP, Liu JC, Cai HH, Dai XL, Chen YM, Zhang YS, Huang Q, Dong J. Relevant molecular characteristics analysis on malignant transformation of interstitial cells induced by tumor stem cells in glioma microenvironment[J]. Zhonghua Yi Xue Za Zhi, 2018, 98:3339-3344.[季晓燕, 施佳, 戴晓晓, 盛余敬, 薛彦平, 刘加驰, 蔡洪华, 代兴亮, 陈延明, 张永胜, 黄强, 董军. 胶质瘤干细胞微环境间质细胞恶性转化及相关分子特征分析[J]. 中华医学杂志, 2018, 98:3339-3344.]

（收稿日期:2020-01-18）

·小词典·

中英文对照名词词汇(二)

集落刺激因子1受体
colony stimulating factor 1 receptor(CSF1R)
脊髓灰质炎病毒 poliovirus(PV)
O^6-甲基鸟嘌呤-DNA甲基转移酶
O^6-methylguanine-DNA methyltransferase(MGMT)
碱性纤维母细胞生长因子
basic fibroblast growth factor(bFGF)
胶质瘤干细胞 glioma stem cells(GSCs)
胶质母细胞瘤 glioblastoma(GBM)
ATP结合盒转运子G2
ATP-binding cassette transporter G2(ABCG2)
进行性多灶性白质脑病
progressive multifocal leukoencephalopathy(PML)
精氨酸酶1 arginase 1(Arg1)
颈内动脉 internal carotid artery(ICA)
巨细胞病毒 cytomegalovirus (CMV)
抗原呈递细胞 antigen-presenting cell(APC)
立体定向放射外科 stereotactic radiosurgery(SRS)
粒细胞-巨噬细胞集落刺激因子
granulocyte-macrophage colony-stimulating factor(GM-CSF)
淋巴细胞活化基因 lymphocyte-activation gene(LAG)
淋巴细胞活化基因3 lymphocyte-activation gene 3(LAG-3)
淋巴细胞性垂体炎 lymphocytic hypophysitis(LYH)
1-磷酸鞘氨醇 sphingosine-1-phosphate(S1P)
磷脂酰肌醇3-激酶 phosphatidylinositol 3-kinase(PI3K)
磷脂酰丝氨酸 phosphatidylserine(PS)
慢性淋巴细胞白血病 chronic lymphocytic leukemia(CLL)
美国国立癌症研究所 National Cancer Institute(NCI)
美国食品与药品管理局
Food and Drug Administration(FDA)
免疫相关反应标准 Immune-related Response Criteria(irRC)
鸟氨酸氨基甲酰转移酶4
ornithine carbamyl transferase 4(OCT4)
前列腺素E2 prostaglandin E2(PGE2)
嵌合抗原受体 chimeric antigen receptor(CAR)
嵌合抗原受体T细胞
chimeric antigen receptor T cell(CAR-T)
3-羟基-3-甲基戊二酰辅酶A
3-hydroxy-3-methylglutaryl coenzyme A(HMG-CoA)
CC趋化因子配体9 chemokine (C-C motif) ligand 9(CCL9)
全脑放射治疗 whole brain radiation therapy(WBRT)
缺氧诱导因子 hypoxia inducible factor(HIF)
热休克蛋白 heat shock protein(HSP)
人表皮生长因子受体
human epidermal growth factor receptor(HER)
人类白细胞抗原A1 human leukocyte antigen-A1(HLA-A1)
人类免疫缺陷病毒 human immunodeficiency virus(HIV)
溶瘤病毒 oncolytic viruses(OVs)
溶血磷脂酰胆碱 lysophosphatidylcholine(LPC)
肉毒碱棕榈酰基转移酶 carnitine palmitoyltransferase(CPT)
色氨酸-2,3-双加氧酶 tryptophan-2, 3-dioxygenase(TDO)
上皮间质转化 epithelial mesenchymal transition(EMT)
神经干细胞 neural stem cells(NSCs)
神经肌肉接头 neuromuscular junction(NMJ)
神经系统副肿瘤综合征
paraneoplastic neurological syndrome(PNS)