·脑胶质瘤免疫研究进展·

放射治疗对胶质母细胞瘤免疫状态的影响和意义

聂梦林 邱晓光

【摘要】 胶质母细胞瘤是成人最常见的脑部恶性肿瘤，预后不良。与其他实体肿瘤相比，胶质母细胞瘤有其特殊的肿瘤免疫学特性，因此靶向免疫检查点细胞程序性死亡蛋白1及其配体（PD1/PDL1）、细胞毒性T淋巴细胞相关抗原4（CTLA-4）在胶质母细胞瘤中的应用尚未明确。对于胶质母细胞瘤这样的免疫“冷肿瘤”而言，放射治疗可以提高其免疫原性，通过从放射治疗影响胶质母细胞瘤微环境、自然杀伤T细胞免疫状态、免疫细胞激活过程这三方面探寻放射治疗支持免疫治疗的证据，以及探讨如何调整放射治疗方案，以达到与免疫治疗配合的最优策略。

【关键词】 胶质母细胞瘤； 放射疗法； 免疫； 综述

The influence of radiotherapy on the immune status of glioblastoma

NIE Meng-lin, QIU Xiao-guang

Department of Radiotherapy, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China

Corresponding author: QIU Xiao-guang (Email: qiuxiaoguang@bjtth.org)

【Abstract】 Glioblastoma (GBM) is the most common adult primary brain tumor and carries a dismal prognosis. Surgery if possible following radiotherapy plus chemotherapy is still a standard first-line therapy due to checkpoint-blocking antibodies targeting programmed cell death protein 1 (PD1)/programmed cell death protein ligand 1 (PDL1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in GBM failed to show the same encouraging results for now. Radiotherapy may serve as a mechanism to improve tumor immunogenicity, especial for a immunologically "cold" tumor like GBM. In this review, we critically evaluate current evidence regarding radiation as an enhancer for immunotherapies through modulation of GBM microenvironment, natural killer T cell (NKT) status, immune processes and how these modulation could optimally argumentation immunotherapy. Insights from radiotherapy may unveil additional novel opportunities to help mobilize immunity against GBM.

【Key words】 Glioblastoma; Radiotherapy; Immunity; Review

Conflicts of interest: none declared

胶质母细胞瘤约占中枢神经系统恶性肿瘤的47.7%，目前的标准治疗方案是最大范围手术切除辅以放射治疗联合替莫唑胺（TMZ）化疗。由于其弥漫浸润性生长的生物学行为，手术难以完全切除，加之放射治疗对正常脑组织具有放射性损伤以及化疗耐药现象，肿瘤易复发，5年生存率仅5.6%[1]。因此，胶质母细胞瘤的临床治疗仍面临巨大挑战，亟待更为有效的治疗方法。免疫治疗是目前肿瘤治疗研究的焦点，尽管有些免疫治疗方法在其他肿瘤中显示出前所未有的疗效，但在胶质母细胞瘤患者中并未取得良好疗效，这与胶质母细胞瘤免疫治疗效果较差、肿瘤抗原负荷较低有关，因此胶质母细胞瘤亦被称为免疫“冷肿瘤”[2]，与丰富的肿瘤相关免疫抑制细胞浸润、免疫抑制因子分泌旺盛密切相关[3]。目前，研究者迫切希望能够通过某些方法改变胶质母细胞瘤免疫“冷肿瘤”状态，从而提高免疫治疗效果。目前的研究主要关注放射治疗如何改变胶质母细胞瘤的免疫状态，因此，全面了解放射治疗对免疫系统的影响及其在免疫治疗中的作用，可以为治疗策略带来新的思路。

中枢神经系统的生理结构具有独特性，与循环系统之间存在血-脑屏障，同时缺乏一般的淋巴引流，导致其在结构上形成隔离，物质交换相对闭塞。生理状态下，构成血-脑屏障的内皮细胞细胞间

doi：10.3969/j.issn.1672-6731.2020.02.009

作者单位：100070 首都医科大学附属北京天坛医院放疗科

通讯作者：邱晓光，Email：qiuxiaoguang@bjtth.org

黏附分子(ICAM)水平较低,外周免疫细胞仅能迁移到中枢神经系统血管周围间隙(PVS),无法进入脑实质[4],但中枢神经系统并非"免疫豁免区"[5],硬脑膜内存在丰富的淋巴网络,可将脑脊液吸收转运至颈深部淋巴结[6],称为脑淋巴系统。抗原呈递细胞(APC)通过脑淋巴系统将抗原提呈给颈部淋巴结内的T淋巴细胞(以下简称T细胞)[7]。在病理状态下,免疫细胞可以在干扰素-γ(IFN-γ)主导的化学趋化作用下被引导至脑实质[8],胶质母细胞瘤组织标本中可见肿瘤浸润淋巴细胞(TIL)即可证实这一观点[9]。此外,免疫球蛋白与新生儿Fc受体(FcRn)结合可在载体介导的转运作用下穿过血-脑屏障[10]。胶质母细胞瘤可以耐受中枢免疫系统,表现出与其他实体肿瘤相似的免疫逃逸特征,导致肿瘤恶性生长,此与胶质母细胞瘤的免疫抑制微环境、肿瘤杀伤免疫细胞的耗竭状态、肿瘤抗原致敏过程密不可分,本文拟从这三方面探讨放射治疗对肿瘤免疫状态的影响。

一、放射治疗影响胶质母细胞瘤的免疫抑制微环境

胶质母细胞瘤微环境主要由肿瘤抗原暴露程度、细胞因子构成和肿瘤相关免疫细胞表型决定。(1)胶质母细胞瘤肿瘤抗原暴露程度低:抗原提呈过程需主要组织相容性复合物(MHC),而胶质母细胞瘤细胞MHC表达水平较低,导致免疫系统对肿瘤识别和抗原提呈过程受阻[11]。放射治疗后,MHCⅠ表达水平升高,使肿瘤相关抗原交叉提呈过程增强,进而提高$CD8^+$T细胞抗原识别能力[11];此外,放射治疗可使肿瘤细胞对免疫介导的细胞凋亡更加敏感[12]。(2)胶质母细胞瘤微环境改变:胶质母细胞瘤微环境包括转化生长因子-β(TGF-β)、前列腺素E2(PGE2)、白细胞介素-1(IL-1)、碱性纤维母细胞生长因子(bFGF)等多种免疫抑制因子[13-15]。其中,TGF-β可通过抑制T细胞激活和增殖,抑制IL-2生成,限制自然杀伤(NK)细胞活性和调节性T细胞(Treg)生成,进而导致免疫抑制[16]。与此同时,PGE2可与TGF-β协同作用,促使树突状细胞(DC)抑制T细胞增殖[17]。此外,TGF-β还可以通过维持胶质瘤干细胞(GSCs)功能而促进肿瘤血管生成,进而促进肿瘤生长和侵袭[18]。即使不发生肿瘤,放射治疗亦可使C57BL/6小鼠脑实质出现T细胞募集现象[19]。放射治疗后多种细胞因子和趋化因子表达改变,总体向促炎症反应方向倾斜,增强抗肿瘤免疫反应,干扰素水平显著升高。树突状细胞表面干扰素基因刺激蛋白(STING)可识别放射治疗后肿瘤细胞释放的DNA,从而刺激树突状细胞产生Ⅰ型干扰素。放射治疗效果与肿瘤免疫状态密切相关,依赖于有效的Ⅰ型干扰素和淋巴结引流[20-21]。IFN-γ是Ⅱ型干扰素,可上调MHCⅠ和NK细胞活化性受体NKG2D表达,增强肿瘤识别,抑制Treg细胞发育,增强$CD8^+$T细胞诱导作用[22],而由放射治疗介导的$CD8^+$T细胞产生的IFN-γ具有增强照射致炎症反应和抗肿瘤效果[23]。因此,干扰素和STING信号转导通路激活均为放射治疗诱导的适应性免疫反应的必须条件[24]。(3)胶质母细胞瘤中肿瘤相关巨噬细胞(TAMs)促进肿瘤浸润和生长:胶质母细胞瘤细胞中约半数为TAMs[25],其生物学状态在很大程度上可以影响肿瘤微环境和抗肿瘤效应。在生理状态下,微小胶质细胞是发挥抗原提呈作用的先天性免疫细胞[26],微小胶质细胞自卵黄囊迁移至原始大脑,随着神经系统的发育驻留在脑组织小胶质细胞中[27],成年后仍依靠自我更新维持功能[28]。唯有在病理状态下,绝大多数TAMs来源于骨髓,主要分布于血管旁区域,少数微小胶质细胞来源的TAMs分布于肿瘤旁区域[29]。造血干细胞(HSCs)起源的巨噬树突状前体细胞在骨髓中分化为单核细胞,随后进入血液循环[30],一旦抵达炎症组织即伴随单核细胞逐渐分化为巨噬细胞,发挥促血管生成和免疫抑制作用,因此亦称为骨髓来源抑制细胞(MDSC),进一步分为单核MDSC和颗粒MDSC[29]。单核MDSC通过上调精氨酸酶1(ARG1)、诱导T细胞凋亡、增强Treg细胞等方式发挥免疫抑制作用[31],为M2型MDSC;M1型则相反,表现为促炎症反应、高氧化代谢活性,有利于宿主免疫,但可能导致健康组织损伤。实际上,M1型和M2型细胞仅代表最极端的两种情况,体内二者并非严格两极分化[32]。TAMs中M1型和M2型亦混合存在,并且TAMs具有高度可塑性,可以根据环境因素进行M1型和M2型之间的相互转换[33]。尽管通过可溶性物质例如集落刺激因子1(CSF1)抑制剂BLZ945可将M2型成功转变为M1型,但是肿瘤细胞可重新将其逆转为M2型[34]。如何延长抗肿瘤M1型细胞的维持时间,尚待更深入的研究。放射治疗可激活先天性抗原呈递细胞微小胶质细胞,表达损伤相关分子模式(DAMP)分泌单核细胞趋化蛋白-1(MCP-1)等细胞因子[35];同时还可以引起一种后续作用持久的微小胶质细胞

偏向M1型的转化现象[36-37]。

胶质母细胞瘤微环境和外周循环中NK细胞数目相对较少[38]，经放射治疗和替莫唑胺化疗后，外周循环中T细胞和NK细胞数目进一步减少[39-40]，其表达的NKG2D水平亦相对较低[41]。此外，放射治疗还可使多种肿瘤细胞NKG2D配体表达水平升高，对NK细胞介导的细胞毒性作用更加敏感[42]。但是目前尚无胶质母细胞瘤微环境中浸润NK细胞对放射治疗反应的相关研究。

二、放射治疗影响耗竭的$CD8^+$T细胞

病毒可以引起慢性炎症反应，避免被免疫反应完全清除[43]。抗原持续暴露在$CD8^+$T细胞中，驱使其上调抑制性受体的表达，降低免疫杀伤强度[44]。这种免疫减弱、增殖减缓并伴随细胞因子分泌减少、代谢和转录改变等免疫细胞转变，称为免疫细胞“耗竭”。这种免疫耗竭机制为维持免疫稳态、防止免疫系统病态持续激活导致破坏性变态反应提供保护机制[45]，像病毒一样，肿瘤细胞所致免疫细胞耗竭正是利用了这一特点[46]。由于肿瘤具有异质性，故难以在肿瘤细胞中逆转T细胞的耗竭[47]。耗竭型T细胞通常伴随多种抑制性免疫检查点受体表达水平升高，如细胞程序性死亡蛋白1(PD1)[48]、细胞毒性T淋巴细胞相关抗原4(CTLA-4)、T细胞免疫球蛋白黏蛋白分子-3(TIM-3)[49]、淋巴细胞活化基因3(LAG-3)、具有免疫球蛋白和免疫受体酪氨酸抑制基序结构域的T细胞免疫受体(TIGIT)、T细胞活化的V域Ig抑制因子(VISTA)和CD39[50-52]，在胶质母细胞瘤$CD8^+$TIL细胞中呈高表达[53]；上述免疫检查点配体亦在胶质母细胞瘤进展的任意时期均呈高表达，完全限制了T细胞受体发挥作用[54]。众所周知，多种肿瘤可诱导T细胞耗竭以维持自身生长[55]，研究显示，胶质母细胞瘤亦存在严重的T细胞耗竭[53]。靶向免疫检查点分子以逆转T细胞耗竭的尝试已在多种肿瘤中初见成效。

1. PD1 慢性病毒感染时，效应性T细胞(Teff)高表达PD1，与基质细胞如抗原呈递细胞表达的细胞程序性死亡蛋白配体1(PDL1)相互作用后，产生衰减T细胞的作用，抑制T细胞增殖效果，这种效果可以通过中和抗PDL1抗体逆转。PD1信号转导通路调节免疫反应各个环节的作用复杂且不相同[56]，肿瘤细胞利用这一特点与肿瘤微环境进行双向选择，导致TAMs表达高水平的PDL1。有研究显示，胶质母细胞瘤中$PD1^+$TIL细胞数目和PDL1表达水平均显著升高，因此PD1/PDL1是潜在的胶质母细胞瘤治疗靶点[57-59]。

2. CTLA-4 MHC的抗原呈递细胞在将抗原肽提呈至T细胞受体时T细胞即被激活，但T细胞的完全激活需抗原呈递细胞表达的CD80和CD86与T细胞受体CD28相结合产生的共刺激[60]。CTLA-4主要调节T细胞激活的早期阶段，起始于细胞内的一种蛋白质，伴随T细胞激活，易位至免疫突触，与CD28共定位[61-62]；CTLA-4与抗原呈递细胞表达的CD80、CD86的亲和力较CD28更高，降低CD28共刺激的强度，从而阻止T细胞的完全激活[63]；CTLA-4激活后可以限制T细胞与抗原呈递细胞之间的细胞间连接，限制T细胞增殖，减少细胞因子生成[64]；CTLA-4细胞内结构域可招募蛋白磷酸酶2A(PP2A)，降低参与T细胞受体信号级联的蛋白质磷酸化，产生调控性抑制作用[65]；CTLA-4还可通过增强免疫抑制性Treg细胞，进而阻碍$CD4^+$辅助性T细胞(Th)在维持免疫稳态中发挥关键作用[66-67]；抗CTLA-4抗体通过衰减CTLA-4免疫抑制作用，抑制Treg细胞活动，缓解T细胞衰竭。

3. TIM-3 TIM-3由分泌IFN-γ的Th1细胞、树突状细胞、单核细胞、$CD8^+$T细胞等表达[68-69]。对实体肿瘤和血液系统肿瘤临床前研究模型的观察显示，异常$CD8^+$T细胞高表达TIM-3[70-71]；黑色素瘤模型显示，TIM-3受体与肿瘤抗原特异性$CD8^+$T细胞衰竭有关，且可通过抗TIM-3抗体逆转[72]；实体肿瘤模型研究还显示，Treg细胞亦表达TIM-3[73]。临床前研究结果表明，联合应用抗PD1抗体与放射治疗后，胶质瘤模型小鼠存活时间延长近1倍[74]；抗CTLA-4和CD137激动剂抗体联合放射治疗胶质瘤模型小鼠100天存活率为50%，显著高于单纯药物治疗(20%)和单纯放射治疗(零)[75]；抗TIM-3和PD1抗体联合放射治疗，胶质瘤模型小鼠100天存活率可高达100%，显著高于单纯药物化疗或放射治疗(60%)[76]；抗GITR抗体联合放射治疗，胶质瘤模型小鼠100天存活率可自零增至24%[77]；抗CD13抗体联合放射治疗尚具有协同作用，所产生的抗肿瘤免疫反应更加持久[75]。上述临床前研究已有部分进入临床试验阶段[75-77]。胶质母细胞瘤免疫检查点临床研究显示，高级别胶质瘤微环境中PD1/PDL1的表达变化与患者预后相关[58,78]。在CheckMate-143试验中纳入首次复发的胶质母细胞瘤病例，无论单纯应用抗PD1抗体Nivolumab或Nivolumab与抗

CTLA-4抗体Ipilimumab联合应用，初期安全评价均未出现比单药治疗更多的不良反应，单药治疗毒性更低，患者9个月生存率为60%[79]，其Ⅲ期临床试验目前正在进行中。其他探讨抗PD1/PDL1抗体与抗血管生成药物、肿瘤疫苗、溶瘤病毒和其他免疫调节药物的联合应用效果的临床试验也在进行中（https://ClinicalTrials.gov）。探讨抗PD1/PDL1抗体与放射治疗联合应用的有效性和安全性的临床试验，迄今发现安全性尚可，毒性有限。但并非所有放射治疗导致的促炎症反应均可增强抗肿瘤免疫反应，放射治疗导致的IFN-γ分泌和低氧，均在肿瘤细胞和肿瘤相关免疫细胞中导致PDL1表达上调。

三、放射治疗影响肿瘤抗原对免疫细胞的激活

尽管单纯放射治疗无法治愈胶质瘤，但是确实可以杀灭部分胶质瘤细胞，特别是正在分裂的肿瘤细胞，亦可以诱导放射治疗无法杀灭的肿瘤细胞衰老[80]。肿瘤细胞死亡后释放的抗原对免疫反应至关重要，放射治疗导致的肿瘤细胞死亡可增强固有免疫系统和适应性免疫系统的抗肿瘤活性[81]，而且还可以促进免疫原性细胞死亡，主要通过DAMP之一的钙网蛋白转运、高迁移率族蛋白-1（HMGB1）和ATP胞外释放[82-85]、热休克蛋白（HSP）转位[81]、Fas死亡受体表达上调途径[12]。成熟的树突状细胞可以进入淋巴引流系统并回迁至区域淋巴结或脾，直接将抗原提呈给$CD4^+$Treg细胞或通过交叉提呈$CD8^+$T细胞，从而诱发抗原特异性免疫反应。上述途径均可直接或间接增强抗原呈递细胞对肿瘤抗原的交叉提呈，有助于$CD8^+$T细胞的早期激活。

放射治疗同样可以增强下游免疫反应和T细胞介导的细胞毒性作用，如调控肿瘤血管生成并促进T细胞外渗，从而增加TIL细胞数目。同时，放射治疗还可以诱导血-脑屏障通透性增加，影响细胞因子和趋化因子的表达，有利于外周T细胞浸润至胶质母细胞瘤微环境。放射治疗诱导的免疫反应不仅局限于照射野，而且还具有远隔效应，远隔效应系指单一肿瘤被照射后远隔部位肿瘤生长减缓[86]，此现象由免疫介导，且具有肿瘤类型特异性[87]。放射治疗与免疫检查点抑制剂结合可以增强这种远隔效应[88]。

鉴于放射治疗对免疫反应的多重作用，研究者致力于将放射治疗与免疫治疗相结合，以探索新的治疗模式。除免疫检查点抑制剂联合放射治疗外，还包括疫苗因子治疗、过继免疫治疗、Toll样受体（TLR）与放射治疗联合应用。临床前研究显示，肿瘤疫苗、IL-2、TLR、过继免疫治疗同样可使受试者从联合治疗中获益[89]。临床试验显示，ICT-107体外刺激自体树突状细胞，尽管耐受性良好，但仅1例人类白细胞抗原-A2（HLA-A2）阳性患者获益[90]；进一步针对HLA-A2阳性患者的试验由于资金不足而暂停。Rindopepimut是针对表皮生长因子受体变异体Ⅲ（EGFRvⅢ）的疫苗，Rindopepimut和替莫唑胺或贝伐单抗联合放射治疗的Ⅱ期临床试验结果令人鼓舞[91-92]，但Ⅲ期临床试验发现并无明显的生存获益，故被终止[93]。关于人表皮生长因子受体2（HER2）和巨细胞病毒（CMV）双特异性嵌合抗原受体T细胞（CAR-T）疗法安全性的Ⅰ期临床试验（试验编号：NCT01109095）显示，患者可以从该治疗方法中获益，耐受性良好，且无严重不良反应和细胞因子释放综合征[94]。

四、优化放射治疗对免疫治疗的影响

有关如何选择放射治疗联合免疫治疗的最佳时机，目前尚无明确定论。一项有关非小细胞肺癌免疫治疗的最新临床研究表明，同步放化疗后行Durvalumab巩固治疗可以显著延长患者总生存期（OS）和无进展生存期（PFS），尤其是放射治疗结束后2周内即接受免疫治疗的患者比放射治疗后超过2周方行免疫治疗者生存获益更显著，因此同步放化疗与免疫治疗的间隔越短、患者获益越大[95]。已公布的或正在进行的大部分临床试验的研究对象主要为复发胶质母细胞瘤患者，均于标准治疗后再行免疫治疗，因此患者在接受免疫治疗的同时无法进行放射治疗。动物实验显示，相对于序贯治疗，免疫治疗同时联合放射治疗的预后更佳[75]，而且免疫治疗前即行替莫唑胺化疗可以减弱对免疫检查点抑制剂的免疫反应[96]。胶质母细胞瘤的标准治疗方案是最大程度手术切除并辅以药物化疗联合常规分割放射治疗。由于颅内水肿等原因，通常在治疗过程中应用皮质类固醇激素，其不良反应是诱发淋巴细胞减少症和免疫抑制[97-100]，即使是单纯施行分割放射治疗也仍可产生全身循环系统的淋巴细胞毒性作用[101]。立体定向放射治疗（SRT）的计划精度更高、单次照射剂量更大，对正常组织的损伤较小，相较于常规分割放射治疗，立体定向放射治疗更易造成肿瘤细胞死亡，增加DAMP释放，诱导免疫分子表达，增强免疫激活，从而引起更强效的抗肿瘤免疫反应，故立体定向放射治疗与免疫治疗

联合应用的模式可能更为有效。

随着基于免疫治疗策略的重要性和临床普及率的提高，当前研究热点主要集中于如何更好地利用放射线对免疫系统的激活作用。线性二次方程式可用于决定产生最佳生物学效应的分割放射治疗方案，不同照射体积、组织器官类型和剂量分割模式均对局部或全身免疫反应造成不同影响。立体定向放射治疗可以诱导免疫激活反应，产生远隔效应，当单次照射剂量过高时，可造成血管网受损，反而可能增加肿瘤乏氧状态，促进放射治疗抵抗效应。研究显示，较大剂量的单次分割照射可能抑制免疫激活机制：在OVA小鼠黑色素瘤模型中，分割照射剂量为7.5 Gy/次时，Treg细胞数目降至最低，获得的肿瘤免疫识别效应最佳；分割照射剂量＞12 Gy时，可激活DNA核酸外切酶Trex1，减少细胞质中DNA，从而降低免疫原性[102]。在既往一项转移性黑色素瘤局部放射治疗联合抗CTLA-4抗体的Ⅰ期临床试验中，对肺和骨转移灶予总剂量16～24 Gy/2～3次、肝和皮下转移灶予总剂量12～18 Gy/2～3次的照射，结果显示，未接受放射治疗的患者18%可达到部分缓解、18%达到稳定，其余病例均出现肿瘤进展[103]。近年来多项研究致力于优化分割模式，从而产生最佳放射治疗诱导的免疫激活反应[104]，从现有的研究可以看出，最佳治疗模式表现出明显的肿瘤依赖，但迄今针对胶质母细胞瘤的研究鲜有关注这一问题。一项照射剂量递增（25～40 Gy）的临床研究结果显示，分割照射剂量为5 Gy/次，肿瘤边缘外放5 mm，可耐受的最大总剂量为40 Gy，总生存期为15个月，与标准治疗方案获益相似（http://ClinicalTrials.gov，试验编号：NCT01120639）。因此，有关免疫治疗在传统放射治疗模式与新型联合治疗模式中的相对生物学效应，有待进一步研究。一项针对抗PD1-IgG4抗体REGN2810的Ⅰ期临床试验显示，REGN2810与单次剂量较大的分割照射模式联合应用，可以缩短肿瘤反应时间，并改善抗PD1/PDL1单克隆抗体耐药的肿瘤[105]。目前关于单次剂量较大的分割照射模式联合抗PD1/PDL1抗体阻断剂或吲哚胺-2，3-双加氧酶（IDO）抑制剂的临床试验正在进行中。

综上所述，放射治疗对中枢免疫系统的影响较为复杂，总体来说有助于发挥免疫治疗效果。探索放射治疗与免疫治疗联合应用的最佳方案，调整分割照射剂量和应用顺序，优化免疫治疗效果，是未来临床研究的方向。

利益冲突 无

参 考 文 献

[1] Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united states in 2011–2015[J]. Neuro Oncol, 2018, 20:iv1-86.

[2] Colli LM, Machiela MJ, Myers TA, Jessop L, Yu K, Chanock SJ. Burden of nonsynonymous mutations among TCGA cancers and candidate immune checkpoint inhibitor responses [J]. Cancer Res, 2016, 76:3767-3772.

[3] Tran TT, Uhl M, Ma JY, Janssen L, Sriram V, Aulwurm S, Kerr I, Lam A, Webb HK, Kapoun AM, Kizer DE, McEnroe G, Hart B, Axon J, Murphy A, Chakravarty S, Dugar S, Protter AA, Higgins LS, Wick W, Weller M, Wong DH. Inhibiting TGF-beta signaling restores immune surveillance in the SMA-560 glioma model[J]. Neuro Oncol, 2007, 9:259-270.

[4] Owens T, Bechmann I, Engelhardt B. Perivascular spaces and the two steps to neuroinflammation [J]. J Neuropathol Exp Neurol, 2008, 67:1113-1121.

[5] Perry VH. A revised view of the central nervous system microenvironment and major histocompatibility complex class Ⅱ antigen presentation [J]. J Neuroimmunol, 1998, 90:113-121.

[6] Louveau A, Harris TH, Kipnis J. Revisiting the mechanisms of CNS immune privilege[J]. Trends Immunol, 2015, 36:569-577.

[7] Mohammad MG, Tsai VW, Ruitenberg MJ, Hassanpour M, Li H, Hart PH, Breit SN, Sawchenko PE, Brown DA. Immune cell trafficking from the brain maintains CNS immune tolerance[J]. J Clin Invest, 2014, 124:1228-1241.

[8] Gorbachev AV, Kobayashi H, Kudo D, Tannenbaum CS, Finke JH, Shu S, Farber JM, Fairchild RL. CXC chemokine ligand 9/monokine induced by IFN-gamma production by tumor cells is critical for T cell-mediated suppression of cutaneous tumors [J]. J Immunol, 2007, 178:2278-2286.

[9] Chow BW, Gu C. The molecular constituents of the blood-brain barrier[J]. Trends Neurosci, 2015, 38:598-608.

[10] Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age[J]. Nat Rev Immunol, 2007, 7:715-725.

[11] Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, Schwendener R, Pruschy M, Knuth A, van den Broek M. Radiotherapy promotes tumor-specific effector $CD8^+$ T cells via dendritic cell activation[J]. J Immunol, 2012, 189:558-566.

[12] Garnett CT, Palena C, Chakraborty M, Tsang KY, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes[J]. Cancer Res, 2004, 64:7985-7994.

[13] Hao C, Parney IF, Roa WH, Turner J, Petruk KC, Ramsay DA. Cytokine and cytokine receptor mRNA expression in human glioblastomas: evidence of Th1, Th2 and Th3 cytokine dysregulation[J]. Acta Neuropathol, 2002, 103:171-178.

[14] Rodrigues JC, Gonzalez GC, Zhang L, Ibrahim G, Kelly JJ, Gustafson MP, Lin Y, Dietz AB, Forsyth PA, Yong VW, Parney IF. Normal human monocytes exposed to glioma cells acquire myeloid-derived suppressor cell-like properties [J]. Neuro Oncol, 2010, 12:351-365.

[15] Jackson C, Ruzevick J, Phallen J, Belcaid Z, Lim M. Challenges in immunotherapy presented by the glioblastoma multiforme microenvironment [J]. Clin Dev Immunol, 2011:ID732413.

[16] Fontana A, Bodmer S, Frei K, Malipiero U, Siepl C. Expression of TGF-beta 2 in human glioblastoma: a role in resistance to immune rejection[J]? Ciba Found Symp, 1991, 157:232-238.
[17] Su Y, Jackson EK, Gorelik E. Receptor desensitization and blockade of the suppressive effects of prostaglandin E(2) and adenosine on the cytotoxic activity of human melanoma-infiltrating T lymphocytes[J]. Cancer Immunol Immunother, 2011, 60:111-122.
[18] Tritschler I, Gramatzki D, Capper D, Mittelbronn M, Meyermann R, Saharinen J, Wick W, Keski-Oja J, Weller M. Modulation of TGF-beta activity by latent TGF-beta-binding protein 1 in human malignant glioma cells[J]. Int J Cancer, 2009, 125:530-540.
[19] Moravan MJ, Olschowka JA, Williams JP, O'Banion MK. Cranial irradiation leads to acute and persistent neuroinflammation with delayed increases in T-cell infiltration and CD11c expression in C57BL/6 mouse brain[J]. Radiat Res, 2011, 176:459-473.
[20] Takeshima T, Chamoto K, Wakita D, Ohkuri T, Togashi Y, Shirato H, Kitamura H, Nishimura T. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy[J]. Cancer Res, 2010, 70:2697-2706.
[21] Burnette BC, Liang H, Lee Y, Chlewicki L, Khodarev NN, Weichselbaum RR, Fu YX, Auh SL. The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity[J]. Cancer Res, 2011, 71:2488-2496.
[22] Dunn GP, Koebel CM, Schreiber RD. Interferons, immunity and cancer immunoediting[J]. Nat Rev Immunol, 2006, 6:836-848.
[23] Gerber SA, Sedlacek AL, Cron KR, Murphy SP, Frelinger JG, Lord EM. IFN-gamma mediates the antitumor effects of radiation therapy in a murine colon tumor[J]. Am J Pathol, 2013, 182:2345-2354.
[24] Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T, Huang X, Gajewski TF, Chen ZJ, Fu YX, Weichselbaum RR. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors[J]. Immunity, 2014, 41:843-852.
[25] Charles NA, Holland EC, Gilbertson R, Glass R, Kettenmann H. The brain tumor microenvironment[J]. Glia, 2012, 60:502-514.
[26] Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease[J]. Nat Rev Immunol, 2018, 18:225-242.
[27] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Merad M. Fate mapping analysis reveals that adult microglia derive from primitive macrophages[J]. Science, 2010, 330:841-845.
[28] Füger P, Hefendehl JK, Veeraraghavalu K, Wendeln AC, Schlosser C, Obermüller U, Wegenast-Braun BM, Neher JJ, Martus P, Kohsaka S, Thunemann M, Feil R, Sisodia SS, Skodras A, Jucker M. Microglia turnover with aging and in an Alzheimer's model via long-term in vivo single-cell imaging[J]. Nat Neurosci, 2017, 20:1371-1376.
[29] Chen Z, Feng X, Herting CJ, Garcia VA, Nie K, Pong WW, Rasmussen R, Dwivedi B, Seby S, Wolf SA, Gutmann DH, Hambardzumyan D. Cellular and molecular identity of tumor-associated macrophages in glioblastoma[J]. Cancer Res, 2017, 77:2266-2278.
[30] Shi C, Pamer EG. Monocyte recruitment during infection and inflammation[J]. Nat Rev Immunol, 2011, 11:762-774.
[31] Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours[J]. Nat Rev Immunol, 2012, 12:253-268.
[32] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation[J]. Nat Rev Immunol, 2008, 8:958-969.
[33] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm[J]. Nat Immunol, 2010, 11:889-896.
[34] Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage M1-M2 polarization balance[J]. Front Immunol, 2014, 5:614.
[35] Chen H, Chong ZZ, De Toledo SM, Azzam EI, Elkabes S, Souayah N. Delayed activation of human microglial cells by high dose ionizing radiation[J]. Brain Res, 2016, 1646:193-198.
[36] Monje ML, Vogel H, Masek M, Ligon KL, Fisher PG, Palmer TD. Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies[J]. Ann Neurol, 2007, 62:515-520.
[37] Li MD, Burns TC, Kumar S, Morgan AA, Sloan SA, Palmer TD. Aging-like changes in the transcriptome of irradiated microglia[J]. Glia, 2015, 63:754-767.
[38] Kmiecik J, Poli A, Brons NH, Waha A, Eide GE, Enger PØ, Zimmer J, Chekenya M. Elevated $CD3^+$ and $CD8^+$ tumor-infiltrating immune cells correlate with prolonged survival in glioblastoma patients despite integrated immunosuppressive mechanisms in the tumor microenvironment and at the systemic level[J]. J Neuroimmunol, 2013, 264:71-83.
[39] Fadul CE, Fisher JL, Gui J, Hampton TH, Côté AL, Ernstoff MS. Immune modulation effects of concomitant temozolomide and radiation therapy on peripheral blood mononuclear cells in patients with glioblastoma multiforme[J]. Neuro Oncol, 2011, 13:393-400.
[40] Chongsathidkiet P, Jackson C, Koyama S, Loebel F, Cui X, Farber SH, Woroniecka K, Elsamadicy AA, Dechant CA, Kemeny HR, Sanchez-Perez L, Cheema TA, Souders NC, Herndon JE, Coumans JV, Everitt JI, Nahed BV, Sampson JH, Gunn MD, Martuza RL, Dranoff G, Curry WT, Fecci PE. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors[J]. Nat Med, 2018, 24:1459-1468.
[41] Crane CA, Han SJ, Barry JJ, Ahn BJ, Lanier LL, Parsa AT. TGF-beta downregulates the activating receptor NKG2D on NK cells and $CD8^+$ T cells in glioma patients[J]. Neuro Oncol, 2010, 12:7-13.
[42] Kim JY, Son YO, Park SW, Bae JH, Chung JS, Kim HH, Chung BS, Kim SH, Kang CD. Increase of NKG2D ligands and sensitivity to NK cell-mediated cytotoxicity of tumor cells by heat shock and ionizing radiation[J]. Exp Mol Med, 2006, 38:474-484.
[43] Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection[J]. Cell, 2009, 138:30-50.
[44] Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion[J]. Nat Rev Immunol, 2015, 15:486-499.
[45] Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor[J]. Immunity, 1999, 11:141-151.
[46] Wherry EJ, Blattman JN, Murali-Krishna K, van der Most R, Ahmed R. Viral persistence alters CD8 T-cell

immunodominance and tissue distribution and results in distinct stages of functional impairment[J]. J Virol, 2003, 77: 4911-4927.

[47] Kala M, Chrobok J, Dvorák P. A surprising finding by a surgery for lumbar intervertebral disk herniation: Ewing's sarcoma[J]. Acta Univ Palacki Olomuc Fac Med, 1987, 117: 185-189.

[48] Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation[J]. J Exp Med, 2000, 192:1027-1034.

[49] Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, Zheng XX, Strom TB, Kuchroo VK. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity[J]. Nat Immunol, 2005, 6:1245-1252.

[50] Grosso JF, Kelleher CC, Harris TJ, Maris CH, Hipkiss EL, De Marzo A, Anders R, Netto G, Getnet D, Bruno TC, Goldberg MV, Pardoll DM, Drake CG. LAG-3 regulates $CD8^+$ T cell accumulation and effector function in murine self- and tumor-tolerance systems[J]. J Clin Invest, 2007, 117:3383-3392.

[51] Huang CT, Workman CJ, Flies D, Pan X, Marson AL, Zhou G, Hipkiss EL, Ravi S, Kowalski J, Levitsky HI, Powell JD, Pardoll DM, Drake CG, Vignali DA. Role of LAG-3 in regulatory T cells[J]. Immunity, 2004, 21:503-513.

[52] Wherry EJ. T cell exhaustion[J]. Nat Immunol, 2011, 12:492-499.

[53] Woroniecka K, Chongsathidkiet P, Rhodin K, Kemeny H, Dechant C, Farber SH, Elsamadicy AA, Cui X, Koyama S, Jackson C, Hansen LJ, Johanns TM, Sanchez-Perez L, Chandramohan V, Yu YA, Bigner DD, Giles A, Healy P, Dranoff G, Weinhold KJ, Dunn GP, Fecci PE. T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma[J]. Clin Cancer Res, 2018, 24:4175-4186.

[54] Mohme M, Schliffke S, Maire CL, Runger A, Glau L, Mende KC, Matschke J, Gehbauer C, Akyuz N, Zapf S, Holz M, Schaper M, Martens T, Schmidt NO, Peine S, Westphal M, Binder M, Tolosa E, Lamszus K. Immunophenotyping of newly diagnosed and recurrent glioblastoma defines distinct immune exhaustion profiles in peripheral and tumor-infiltrating lymphocytes[J]. Clin Cancer Res, 2018, 24:4187-4200.

[55] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy[J]. Nat Rev Cancer, 2012, 12:252-264.

[56] Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway[J]. Nat Rev Immunol, 2018, 18:153-167.

[57] Garber ST, Hashimoto Y, Weathers SP, Xiu J, Gatalica Z, Verhaak RG, Zhou S, Fuller GN, Khasraw M, de Groot J, Reddy SK, Spetzler D, Heimberger AB. Immune checkpoint blockade as a potential therapeutic target: surveying CNS malignancies[J]. Neuro Oncol, 2016, 18:1357-1366.

[58] Berghoff AS, Kiesel B, Widhalm G, Rajky O, Ricken G, Wohrer A, Dieckmann K, Filipits M, Brandstetter A, Weller M, Kurscheid S, Hegi ME, Zielinski CC, Marosi C, Hainfellner JA, Preusser M, Wick W. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma[J]. Neuro Oncol, 2015, 17:1064-1075.

[59] 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.

[60] Collins AV, Brodie DW, Gilbert RJ, Iaboni A, Manso-Sancho R, Walse B, Stuart DI, van der Merwe PA, Davis SJ. The interaction properties of costimulatory molecules revisited[J]. Immunity, 2002, 17:201-210.

[61] Egen JG, Allison JP. Cytotoxic T lymphocyte antigen-4 accumulation in the immunological synapse is regulated by TCR signal strength[J]. Immunity, 2002, 16:23-35.

[62] Linsley PS, Bradshaw J, Greene J, Peach R, Bennett KL, ittler RS. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement[J]. Immunity, 1996, 4:535-543.

[63] Linsley PS, Greene JL, Brady W, Bajorath J, Ledbetter JA, Peach R. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors[J]. Immunity, 1994, 1:793-801.

[64] Riley JL, Mao M, Kobayashi S, Biery M, Burchard J, Cavet G, Gregson BP, June CH, Linsley PS. Modulation of TCR-induced transcriptional profiles by ligation of CD28, ICOS, and CTLA-4 receptors[J]. Proc Natl Acad Sci USA, 2002, 99:11790-11795.

[65] Lee KM, Chuang E, Griffin M, Khattri R, Hong DK, Zhang W, Straus D, Samelson LE, Thompson CB, Bluestone JA. Molecular basis of T cell inactivation by CTLA-4[J]. Science, 1998, 282:2263-2266.

[66] Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S. Immunologic self-tolerance maintained by CD25(+) CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4[J]. J Exp Med, 2000, 192:303-310.

[67] Peggs KS, Quezada SA, Chambers CA, Korman AJ, Allison JP. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies[J]. J Exp Med, 2009, 206:1717-1725.

[68] Monney L, Sabatos CA, Gaglia JL, Ryu A, Waldner H, Chernova T, Manning S, Greenfield EA, Coyle AJ, Sobel RA, Freeman GJ, Kuchroo VK. Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease[J]. Nature, 2002, 415:536-541.

[69] Anderson AC, Anderson DE, Bregoli L, Hastings WD, Kassam N, Lei C, Chandwaskar R, Karman J, Su EW, Hirashima M, Bruce JN, Kane LP, Kuchroo VK, Hafler DA. Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells[J]. Science, 2007, 318:1141-1143.

[70] Zhou Q, Munger ME, Veenstra RG, Weigel BJ, Hirashima M, Munn DH, Murphy WJ, Azuma M, Anderson AC, Kuchroo VK, Blazar BR. Coexpression of Tim-3 and PD-1 identifies a $CD8^+$ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia[J]. Blood, 2011, 117:4501-4510.

[71] Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK, Anderson AC. Targeting TIM-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity[J]. J Exp Med, 2010, 207:2187-2194.

[72] Loke P, Allison JP. PD-L1 and PD-L2 are differentially regulated by Th1 and Th2 cells[J]. Proc Natl Acad Sci USA, 2003, 100:5336-5341.

[73] Yan J, Zhang Y, Zhang JP, Liang J, Li L, Zheng L. TIM-3 expression defines regulatory T cells in human tumors[J]. PLoS One, 2013, 8:E58006.

[74] Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, Durham N, Meyer C, Harris TJ, Albesiano E, Pradilla G, Ford E, Wong J, Hammers HJ, Mathios D, Tyler B, Brem H, Tran PT, Pardoll D, Drake CG, Lim M. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas[J]. Int J Radiat Oncol Biol Phys, 2013, 86:343-349.

[75] Belcaid Z, Phallen JA, Zeng J, See AP, Mathios D, Gottschalk

C, Nicholas S, Kellett M, Ruzevick J, Jackson C, Albesiano E, Durham NM, Ye X, Tran PT, Tyler B, Wong JW, Brem H, Pardoll DM, Drake CG, Lim M. Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model[J]. PLoS One, 2014, 9: E101764.

[76] 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.

[77] Patel MA, Kim JE, Theodros D, Tam A, Velarde E, Kochel CM, Francica B, Nirschl TR, Ghasemzadeh A, Mathios D, Harris-Bookman S, Jackson CC, Jackson C, Ye X, Tran PT, Tyler B, Coric V, Selby M, Brem H, Drake CG, Pardoll DM, Lim M. Agonist anti-GITR monoclonal antibody and stereotactic radiation induce immune-mediated survival advantage in murine intracranial glioma[J]. J Immunother Cancer, 2016, 4:28.

[78] Nduom EK, Wei J, Yaghi NK, Huang N, Kong LY, Gabrusiewicz K, Ling X, Zhou S, Ivan C, Chen JQ, Burks JK, Fuller GN, Calin GA, Conrad CA, Creasy C, Ritthipichai K, Radvanyi L, Heimberger AB. PD-L1 expression and prognostic impact in glioblastoma[J]. Neuro Oncol, 2016, 18:195-205.

[79] Omuro A, Vlahovic G, Lim M, Sahebjam S, Baehring J, Cloughesy T, Voloschin A, Ramkissoon SH, Ligon KL, Latek R, Zwirtes R, Strauss L, Paliwal P, Harbison CT, Reardon DA, Sampson JH. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase Ⅰ cohorts of CheckMate 143[J]. Neuro Oncol, 2018, 20:674-686.

[80] Zhang L, Cheng F, Wei Y, Zhang L, Guo D, Wang B, Li W. Inhibition of TAZ contributes radiation-induced senescence and growth arrest in glioma cells[J]. Oncogene, 2019, 38:2788-2799.

[81] Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy[J]. Annu Rev Immunol, 2013, 31:51-72.

[82] Medzhitov R. Toll-like receptors and innate immunity[J]. Nat Rev Immunol, 2001, 1:135-145.

[83] Facci L, Barbierato M, Marinelli C, Argentini C, Skaper SD, Giusti P. Toll-like receptors 2, -3 and -4 prime microglia but not astrocytes across central nervous system regions for ATP-dependent interleukin-1β release[J]. Sci Rep, 2014, 4:6824.

[84] Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P, Yang H, Amigorena S, Ryffel B, Barrat FJ, Saftig P, Levi F, Lidereau R, Nogues C, Mira JP, Chompret A, Joulin V, Clavel-Chapelon F, Bourhis J, Andre F, Delaloge S, Tursz T, Kroemer G, Zitvogel L. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy[J]. Nat Med, 2007, 13:1050-1059.

[85] Ohshima Y, Tsukimoto M, Takenouchi T, Harada H, Suzuki A, Sato M, Kitani H, Kojima S. Gamma-irradiation induces P2X(7) receptor-dependent ATP release from B16 melanoma cells[J]. Biochim Biophys Acta, 2010, 1800:40-46.

[86] Ehlers G, Fridman M. Abscopal effect of radiation in papillary adenocarcinoma[J]. Br J Radiol, 1973, 46:220-222.

[87] Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, Formenti SC. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated[J]. Int J Radiat Oncol Biol Phys, 2004, 58:862-870.

[88] Bramhall RJ, Mahady K, Peach AH. Spontaneous regression of metastatic melanoma-clinical evidence of the abscopal effect[J]. Eur J Surg Oncol, 2014, 40:34-41.

[89] Nelson MH, Bowers JS, Bailey SR, Diven MA, Fugle CW, Kaiser AD, Wrzesinski C, Liu B, Restifo NP, Paulos CM. Toll-like receptor agonist therapy can profoundly augment the antitumor activity of adoptively transferred CD8(+) T cells without host preconditioning[J]. J Immunother Cancer, 2016, 4: 6.

[90] Wen P, Reardon D, Phuphanich S, Aiken R, Landolfi J, Curry W, Zhu JJ, Glantz M, Peereboom D, Markert J, Larocca R, O'Rourke D, Fink K, Kim L, Gruber M, Lesser G, Pan E, Santos R, Pinilla C, Yu J. IMCT-20 association of survival and progression-free survival with immune response in Hla-A2+ newly-diagnosed Gbm patients in randomized double-blind placebo-controlled phase 2 trial of dendritic cell (DC) immunotherapy with ICT-107[J]. Neuro-Oncology, 2015, 17: V111-112.

[91] Zussman BM, Engh JA. Outcomes of the ACT Ⅲ study: rindopepimut (CDX-110) therapy for glioblastoma[J]. Neurosurgery, 2015, 76:N17.

[92] Schuster J, Lai RK, Recht LD, Reardon DA, Paleologos NA, Groves MD, Mrugala MM, Jensen R, Baehring JM, Sloan A, Archer GE, Bigner DD, Cruickshank S, Green JA, Keler T, Davis TA, Heimberger AB, Sampson JH. A phase Ⅱ, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT Ⅲ study[J]. Neuro Oncol, 2015, 17:854-861.

[93] Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, Ashby L, Mechtler L, Goldlust SA, Iwamoto F, Drappatz J, O'Rourke DM, Wong M, Hamilton MG, Finocchiaro G, Perry J, Wick W, Green J, He Y, Turner CD, Yellin MJ, Keler T, Davis TA, Stupp R, Sampson JH; ACT Ⅳ trial investigators. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRv Ⅲ-expressing glioblastoma (ACT Ⅳ): a randomised, double-blind, international phase 3 trial[J]. Lancet Oncol, 2017, 18:1373-1385.

[94] Ahmed N, Brawley V, Hegde M, Bielamowicz K, Wakefield A, Ghazi A, Ashoori A, Diouf O, Gerken C, Landi D, Kalra M, Yi Z, Rooney C, Dotti G, Gee A, Heslop H, Gottschalk S, Powell S, Grossman R, Wels W, Kew Y, Baskin D, Zhang J, New P, Hicks J. Autologous HER2 CMV bispecific CAR T cells are safe and demonstrate clinical benefit for glioblastoma in a Phase Ⅰ trial[J]. J ImmunoTher Canc, 2015, 3(Suppl 2):11.

[95] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroglu M; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage Ⅲ non-small-cell lung cancer[J]. N Engl J Med, 2017, 377:1919-1929.

[96] Mathios D, Kim JE, Mangraviti A, Phallen J, Park CK, Jackson CM, Garzon-Muvdi T, Kim E, Theodros D, Polanczyk M, Martin AM, Suk I, Ye X, Tyler B, Bettegowda C, Brem H, Pardoll DM, Lim M. Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM[J]. Sci Transl Med, 2016, 8:370RA180.

[97] Rosen EM, Fan S, Rockwell S, Goldberg ID. The molecular and cellular basis of radiosensitivity: implications for

understanding how normal tissues and tumors respond to therapeutic radiation[J]. Cancer Invest, 1999, 17:56-72.
[98] Grossman SA, Ye X, Lesser G, Sloan A, Carraway H, Desideri S, Piantadosi S; NABTT CNS Consortium. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide[J]. Clin Cancer Res, 2011, 17:5473-5480.
[99] Campian JL, Piotrowski AF, Ye X, Hakim FT, Rose J, Yan XY, Lu Y, Gress R, Grossman SA. Serial changes in lymphocyte subsets in patients with newly diagnosed high grade astrocytomas treated with standard radiation and temozolomide[J]. J Neurooncol, 2017, 135:343-351.
[100] Yovino S, Grossman SA. Severity, etiology and possible consequences of treatment-related lymphopenia in patients with newly diagnosed high-grade gliomas[J]. CNS Oncol, 2012, 1:149-154.
[101] Yovino S, Kleinberg L, Grossman SA, Narayanan M, Ford E. The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells[J]. Cancer Invest, 2013, 31:140-144.
[102] Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation[J]. Int J Radiat Oncol Biol Phys, 2012, 83:1306-1310.
[103] Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH, Minn AJ. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer[J]. Nature, 2015, 520:373-377.
[104] Ko EC, Benjamin KT, Formenti SC. Generating antitumor immunity by targeted radiation therapy: role of dose and fractionation[J]. Adv Radiat Oncol, 2018, 3:486-493.
[105] Papadopoulos KP, Crittenden MR, Johnson ML, Lockhart AC, Moore KN, Falchook GS, Formenti S, Carvajal RD, Leidner RS, Naing A, Rosen LS, Weiss GJ, Iii WC, Gao B, Paccaly A, Stankevich E, Trail P, Fury MG, Lowy I. A first-in-human study of REGN2810, a monoclonal, fully human antibody to programmed death-1 (PD-1), in combination with immunomodulators including hypofractionated radiotherapy (hfRT)[J]. J Clinic Oncol, 2016, 34:3024.

（收稿日期：2020-01-18）

·小词典·

中英文对照名词词汇（四）

T细胞免疫球蛋白黏蛋白分子
T cell immunoglobulin and mucin-containing protein（TIM）

T细胞免疫球蛋白黏蛋白分子-3
T cell immunoglobulin and mucin-containing protein-3（TIM-3）

T细胞受体 T cell receptor（TCR）

细胞外基质 extracellular matrix（ECM）

效应性T细胞 effector T cell（Teff）

新城疫病毒 newcastle disease virus（NDV）

信号传导与转录激活因子3
signal transducer and activator of transcription 3（STAT3）

Ⅰ型单纯疱疹病毒 herpes simplex virus-1（HSV-1）

1型神经纤维瘤病 neurofibroma 1（NF1）

血管内皮生长因子
vascular endothelial growth factor（VEGF）

血管周围间隙 perivascular spaces（PVS）［Virchow-Robin间隙 Virchow-Robin spaces（VRS）］

烟雾病 moyamoya disease（MMD）

烟雾综合征 moyamoya syndrome（MMS）

Toll样受体 Toll-like receptor（TLR）

一氧化氮合酶 nitric oxide synthase（NOS）

胰岛素样生长因子-1 insulin-like growth factor-1（IGF-1）

乙醛脱氢酶1 aldehyde dehydrogenase 1（ALDH1）

吲哚胺-2，3-双加氧酶 indoleamine-2, 3-dioxygenase（IDO）

诱导型多能干细胞 induced pluripotent stem cells（iPSCs）

原发性中枢神经系统淋巴瘤
primary central nervous system lymphoma（PCNSL）

造血干细胞 hematopoietic stem cells（HSCs）

真核翻译起始因子2α
eukaryotic translation initiation factor 2α（eIF2α）

肿瘤干细胞 tumor stem cells（TSCs）

肿瘤坏死因子-α tumor necrosis factor-α（TNF-α）

肿瘤浸润淋巴细胞 tumor infiltrating lymphocyte（TIL）

肿瘤微环境 tumor microenvironment（TME）

肿瘤相关巨噬细胞 tumour-associated macrophages（TAMs）

肿瘤相关抗原 tumor-associated antigen（TAA）

肿瘤治疗电场 tumor-treating fields（TTF）

主要组织相容性复合物
major histocompatibility complex（MHC）

主要组织相容性复合物Ⅱ
major histocompatibility complexⅡ（MHCⅡ）

转化生长因子-β transforming growth factor-β（TGF-β）

自然杀伤T细胞 natural killer T lymphocyte（NKT）

自身免疫性垂体炎 autoimmune hypophysitis（AH）

Wiskott-Aldrich综合征 Wiskott-Aldrich syndrome（WAS）

总生存期 overall survival（OS）