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RESEARCH HIGHLIGHT

A Specific Peptide Vaccine Against IDH1(R132H) Glioma

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Malignant tumors of the central nervous system (CNS) have the poorest prognosis among the cancers. Gliomas are the most commonly occurring tumors of the CNS [1], accounting for almost 30% of all primary brain tumors and 80% of all malignant brain tumors [2]. In 2016, the World Health Organization (WHO) assigned gliomas into four grades (I–IV) based on molecular parameters and light microscopic features [3]; WHO grade I is the least malignant while grade IV is the worst. Glioma cells are believed to be derived from neuroglial stem or progenitor cells, and are characterized by active growth, strong invasion and rapid migration. Based on morphological similarities to the neuroglial cell types found in the normal brain, gliomas are histologically classified into astrocytomas, oligodendrogliomas, mixed oligoastrocytic gliomas, and ependymomas.

A set of molecular alterations have been discovered in grade II, III, and IV gliomas. The co-deletion of chromosome arms 1p and 19q, mutation in either IDH1 (isocitrate dehydrogenase 1) or IDH2, and mutation in the promoter of TERT (telomerase reverse transcriptase) are hallmark alterations that provide early evidence for glioma formation. These three alterations are essential for glioma, or are associated with overall survival [4]. IDH1 and IDH2 are isoforms isocitrate dehydrogenase, which decarboxylates isocitrate to α-ketoglutarate (α-KG) and reduces NADP to NADPH. Both are homodimeric enzymes, and have different subcellular locations: IDH1 resides in the cytoplasm and peroxisome, while IDH2 is located in the mitochondria. IDH-mutations cause the loss of native enzymatic activity, confer novel activity of reducing α-KG to 2-hydroxyglutarate and lead to histone and DNA hypermethylation. All of these finally cause genome-wide epigenetic changes and bias the cells to malignant transformation. Crucially, the most common mutation is the amino-acid substitution R132 of IDH1 and its analog [5]. IDH mutations are common in low grade gliomas (WHO grade II/III), and indicate a better prognosis, rather than in glioblastomas, and tend to manifest in younger patients. However, IDH mutations have a high incidence in recurrent glioblastomas, indicating that low-grade gliomas with IDH mutations usually relapse with malignant transformation to a higher grade [2]. Due to the universality and peculiarity of IDH mutations, they may become potential targets for the treatment of glioma.

For some patients with relatively benign tumors, the majority of neurosurgeons advocate a wait-and-scan strategy rather than neurosurgical procedures or histological verification of the diagnosis, and it is desirable to confirm the diagnosis by contrast-enhanced MRI after patients undergo resection. The conventional standard of care for WHO grade II/III includes maximum resection as feasible or biopsy accompanied by involved-field radiotherapy and adjuvant chemotherapy. For glioblastoma, the WHO grade IV glioma, the guiding principle for surgery is maximal safe resection, then 6 weeks of follow-up conventional radiotherapy in combination with temozolomide [6].

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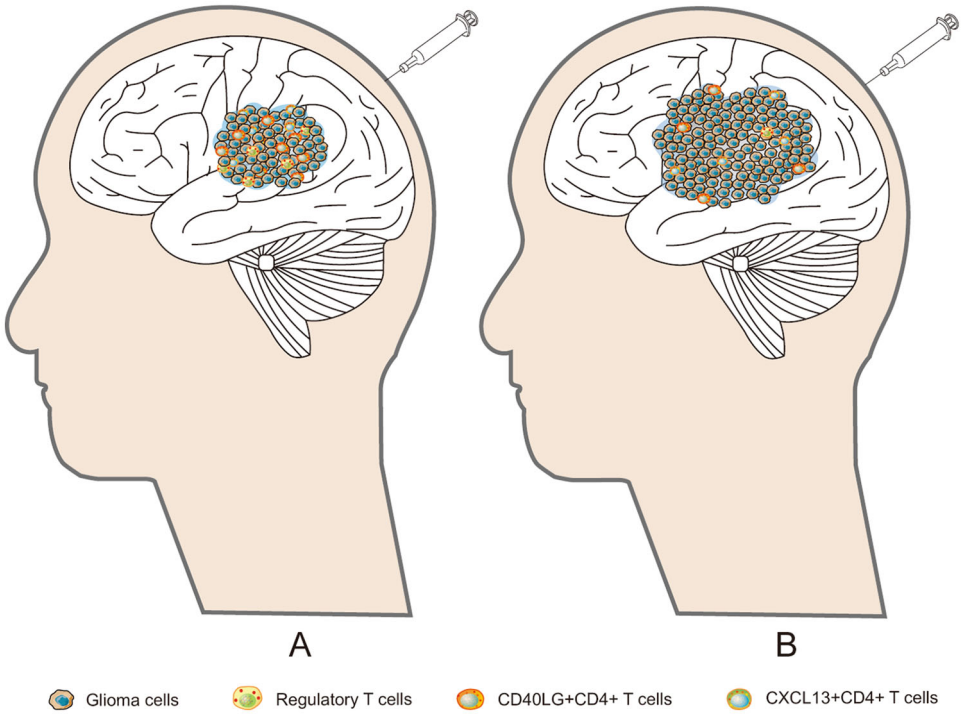

Fig. 1 IDH1 vaccine (IDH-vac) effectively induces an IDH1-specific immune response. Pseudoprogression (PsPD) is associated with the onset of peripheral IDH1-vac-induced immune responses and indicates a better prognosis. There are three clusters of $CD4^+$ T cells within the PsPD lesion of patients: regulatory T cells, activated $CD40LG^+CD4^+$ T cells, and $CXCL13^+CD4^+$ T cells, which play important roles in the induction of immune responses. Patients expressing these three clusters had a longer survival (**A**) while a poor survival was found in the two immune response-free glioma patients (**B**).

With the advances in immunology, cell biology, and molecular biology, tumor immunotherapy has created a new era in the treatment of cancers. Enormous efforts have made to investigate immunotherapy against glioma. The CNS is structurally and functionally unique, with a complex immune system [7]. At present, immunotherapy research in glioma can be broadly categorized into vaccine therapies, immune checkpoint blockade, and chimeric antigen receptor T-cell therapies. Numerous groups have reported clinical trial failure of attempts capitalize on immune checkpoint blockade to treat glioblastomas. The obstacles to using immune checkpoint blockade to treat glioblastoma include a low tumor mutation burden and extensive intratumoral heterogeneity. Although it is feasible, safe, and potentially efficacious to use CAR T cells for brain tumor treatment, it also faces challenges. For instance, the heterogeneous expression of target antigens in tumor cells are the key to successful CAR T cell therapy, and this requires either targeting multiple antigens or the development of CAR T cell designs that induce significant epitope spreading. Vaccines use the adaptive immune system and target glioma antigens including EGFRvIII, IDH R132H, Wilms tumor 1. Dendritic cell (DC) vaccines for brain tumors have been developed, and DCVax-L, an autologous tumor lysate-pulsed DC vaccine, has advanced to a phase III trial and may improve the overall survival of glioblastoma patients [8].

Apparently, vaccination against brain tumors could be a promising therapeutic approach. After treatment with $IDH1(R132H)^+$-specific peptide vaccine (IDH1-vac), it has been reported that $IDH1(R132H)^+$ tumors in syngeneic MHC-humanized mice induce specific therapeutic T helper cell responses [9]. IDH1 mutations in tumor cells can change the amino-acid sequences of proteins, which called tumor neoantigens; the vaccines exposed to MHC II molecules are non-autoantigens, which subsequently induce an immune response [10]. However, whether IDH1-vac works in clinical trials is still unclear. Recently, Dr. Michael Platten's research group at the German Cancer Research Center conducted a multicenter, single-arm, open-label, first-in-humans phase I trial in 33 patients with newly-diagnosed WHO grade III and IV $IDH1(R132H)^+$ astrocytomas [11]. They screened these 33 patients and collected information on tumor location, gender, age, WHO classification, methylation class, therapy, and resection. Then sterile, endotoxin-free vaccine containing 300 ± 30 μg peptide was administered to the patients. The results showed that IDH-vac is safe and tolerable, and in terms of curative effect, IDH -vac significantly prolongs the pseudoprogression (PsPD) and survival time of patients. The new antigen IDH1 (R132H) is immunogenic across multiple HLA alleles and effectively induced an IDH1-specific immune response and the two-year progression-free rate of patients with immune responses to IDH-vac was 0.82 (95% CI 0.623–0.921), however, two patients who did not mount an IDH1-vac-induced immune response showed progression within two years. Compared to a molecularly-matched control cohort, the patients given

IDH-vac had a higher incidence rate of PsPD. Specifically, PsPD was associated with the onset of peripheral IDH1-vac-induced immune responses and indicated a better prognosis. However, there was no relationship between PsPD and the assessed tumor-intrinsic molecular markers. Meanwhile, the authors established an exploratory mutation-specificity score (MSS) to incorporate the duration and level of IDH1-vac-induced T cell immune responses specifically to IDH1(R132H)' Patients who stayed below the median MSS had a 2-year progression-free rate of 0.4% (95% CI 0.052–0.753) while the rate was 0.8% in patients above the median MSS.

In addition to central imaging review, molecular pathology, and immune monitoring, the authors used deep T cell receptor (TCR) sequencing from the patient samples. The results suggested that there were three clusters of $CD4^+$ T cells within the PsPD lesion: regulatory T cells, activated $CD40LG^+CD4^+$ T cells, and $CXCL13^+CD4^+$ T cells, and the latter were significant for antitumor immunity (Fig. 1). Single-cell RNA-seq and TCR sequencing confirmed that the $CD40LG^+CD4^+$ and $CXCL13^+CD4^+$ T cell clusters were dominated by TCR 14. After IDH1-vac administration, TCR14 was enriched 50.6-fold in the PsPD lesions compared with the peripheral blood of the patients. This indicated the IDH1-vac-induced clonal expansion of IDH1(R132H)-specific TH cells that infiltrated into the resected lesion. Single-cell sequencing of T cells from peripheral blood and tissue samples provided significant insights into the systemic and local immune responses induced by vaccines and the biological mechanism of vaccine-induced PsPD. In addition, they verified that TCR14 reacts to IDH1(R132H) after it is co-cultured with autologous antigen-presenting cells.

The treatment process of vaccination is more convenient than radiotherapy, chemotherapy, and surgery. However, there are still several flaws: first, the authors did not set up a control group in the experiment; controls according to the variables would have made the experimental results more convincing. Second, IDH mutations have also been identified in acute myeloid leukemia and myelodysplastic syndromes as well as glioma, so the question arises whether IDH1-vac is also a feasible approach to treating other IDH-mutant diseases [12]. Finally, the authors only used IDH as a single target of the vaccine, which increases the possibility of immune escape and means that the vaccine is ineffective for non IDH-mutated patients, resulting in a limited scope of application. If the vaccine can target multiple glioma mutations, it may be able to expand the scope of application and benefit more glioma patients.

In general, this is the first comprehensive report on the results of a multicenter, single arm, open label, phase I clinical trial in glioma patients, and indicates that therapeutic vaccination for glioma maybe a hopeful and feasible therapeutic modality. Based on the convincing preclinical data, the authors provided an exploit potential positive interactions between standard of care and vaccination, also the IDH-vac targeted a shared clonal driver mutation, which may provide a basis for future trials that target MHCII-restricted clonal shared and personalized neoepitopes in cancer immunotherapy. Although gliomas remain universally lethal, with the ongoing advances in precision medicine, investigators can choose appropriate combinations of immunotherapy for each particular cancer to facilitate personalized therapeutic selection for each patient.

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