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Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection

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Immunotherapies have revolutionized intervention strategies for many primary cancers, but have not improved the outcomes of glioblastoma multiforme (GBM), which remains one of the most lethal malignant cerebral tumours. Here we present an injectable hydrogel system that stimulates tumoricidal immunity after GBM surgical resection, which mitigates its relapse. The hydrogel comprises a tumour-homing immune nanoregulator, which induces immunogenic cell death and suppression of indoleamine 2,3-dioxygenase-1, and chemotactic CXC chemokine ligand 10, for a sustained T-cell infiltration. When delivered in the resected tumour cavity, the hydrogel system mimics a 'hot' tumour-immunity niche for attacking residual tumour cells and significantly suppresses postoperative GBM recurrence. Our work provides an alternative strategy for conferring effective tumoricidal immunity in GBM patients, which may have a broad impact in the immunotherapy of 'cold' tumours after surgical intervention.

Glioblastoma multiforme (GBM) represents a formidable challenge in the clinic with a dismal prognosis and a high recurrence rate[1–3]. The development of immunotherapies has changed the treatment landscape of various malignancies[4,5] and has garnered US Food and Drug Administration approval for use in treating an increasing number of malignancies[6]; however, treatment options for GBM remain conspicuously absent from the list of approved treatments[7]. GBM treatment still largely depends on surgical resection, radiotherapy and/or chemotherapy, which fail to address its highly infiltrative nature, and often leave behind microscopic tumour satellites and inevitably result in relapse[8,9]. The lack of progress in immunotherapies for brain tumours can be attributed to the so-called 'cold' brain tumour immune milieu[10], which is characterized by the enrichment of immune suppressors[7] together with a paucity of cytotoxic T-lymphocyte infiltration[11–13].

The presence of the blood–brain barrier and the absence of lymphatic drainage are believed to restrict the entry of blood-borne immune and inflammatory cells into the central nervous system (CNS), which leads to the exclusion of systemic immune surveillance from the brain[14,15]. However, recent immunological insight from preclinical and clinical studies in neuro-oncology has refuted this classic dogma that the CNS is immune privileged[16]. The recruitment of activated blood-borne T cells can provide unprecedented opportunities for the development of immunotherapies against GBM[17]. Activated T cells that express CXC chemokine receptor 3 (CXCR3) are potentially recruited via the CNS expression of CXC chemokine ligand 10 (CXCL10)[18]. A bioinformatics analysis based on the database of The Cancer Genome Atlas (TCGA) (Fig. 1a) together with protein analysis by immunohistochemical staining (Supplementary Fig. 1a) and western blotting (Supplementary Fig. 1b,c) of the GBM patients showed that isocitrate dehydrogenase 1 (IDH1) was upregulated, which had a negative correlation with the survival of the patients (Fig. 1b). According to the latest World Health Organization classification, glioblastomas are divided into IDH-wildtype GBM, IDH-mutant GBM and not-otherwise-specified glioblastoma[19]. Approximately 90% of IDH mutations occur with IDH1. The overexpressed IDH1 mutant causes downregulation of leukocyte chemotaxis by reducing the secretion of interferon-γ (IFN-γ)-inducible chemokines, which include CXCL10[20]. As a consequence, IDH1-mutated tumours suppress the infiltration and accumulation of T cells at tumour sites. Replenishing the negative regulation of IDH1 via the local delivery of CXCL10 may be conducive to traffic activated blood-borne immune T cells into the CNS and attack the tumour cells.

Indoleamine 2,3-dioxygenase-1 (IDO1), an endogenous immunosuppressive mediator, stimulates the accumulation of regulatory T cells (Tregs) and suppresses T-cell activity by depleting tryptophan (Trp) from the microenvironment[21,22]. Bioinformatics analyses revealed that IDO1 was highly expressed in brain tissues from GBM patients (163 cases) compared with that from normal brain tissues (207 cases) (Fig. 1c). More importantly, stratification of patients by IDO1 expression revealed an overall survival advantage for GBM patients with a lower IDO1 expression (Fig. 1d). Consistent with the bioinformatic results, IDO1 protein levels in tumour tissues were also obviously elevated compared with those in adjacent normal brain tissues in GBM patients (Supplementary Fig. 1). Additionally, evidence indicated that certain chemotherapeutics, such as mitoxantrone (MIT) trigger immunogenic cell death (ICD) of tumour cells and induce dendritic cell (DC) maturation and subsequent T-cell activation[23,24]. Small interfering RNA that target IDO1 (siIDO1) co-delivered with MIT may both relieve the immune brakes related to Tregs and increase the tumour-associated antigens, and thereby

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