TUMOUR IMMUNOLOGY

T cells home in on brain cancer

> the ALCAM homing system could potentially enhance anti-tumour T cell responses in the brain while maintaining a favourable safety profile

T cell-based immunotherapy is showing promise for the treatment of certain cancers, but the efficacy of this approach for brain cancers is limited by the poor ability of T cells to cross the blood–brain barrier (BBB). Reporting in *Nature*, Samaha et al. detail the development of a brain cancer-specific T cell homing system targeting activated leukocyte cell adhesion molecule (ALCAM).

T cell infiltration into the inflamed brain is driven by their interaction with ALCAM and other adhesion molecules (such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1)) that are expressed by activated brain endothelium. Indeed, antibodies targeting ALCAM and its T cell ligand CD6 are being clinically tested in multiple sclerosis and other inflammatory brain conditions. ALCAM is also expressed by cancer cells and can drive tumour invasion and metastasis, but its role on the tumour endothelium has not been established. In initial studies, the authors found that ALCAM is highly expressed by vascular cells in glioblastoma (GBM) and medulloblastoma, which are the most common brain cancers in adults and children, respectively. Furthermore, ALCAM was overexpressed on the surface of tumour-associated endothelial cells, but found mainly intracellularly in normal endothelial cells. GBM supernatant or transforming growth factor-β (TGFβ) promoted ALCAM expression on endothelial cells, indicating that ALCAM is upregulated by tumour factors.

Despite the high expression of ALCAM on tumour-associated endothelium, T cells were unable to transmigrate across the BBB in an in vitro model system comprising primary tumour endothelial cells (PTECs). By contrast, T cells readily migrated across a BBB comprising normal brain endothelial cells that had been activated with IL-6. This prompted the authors to examine the expression of other adhesion molecules on tumour-associated endothelium; in contrast to normal brain endothelial cells, they found that PTECs expressed lower levels of ICAM1 and no VCAM1. Therefore, the lack of ICAM1 and VCAM1 on brain tumour-associated endothelium seems to prevent T cells from accessing these tumours, despite the high levels of ALCAM.

The authors hypothesized that enhancing T cell anchorage to ALCAM could enable them to cross the cancer-associated BBB in the absence of other cellular adhesion molecules. In agreement with previous studies, they mapped the ALCAM-binding region of CD6 to its extracellular domain 3 (D3) and subsequently re-engineered CD6 'homing system' (HS) molecules comprising D3 monomers, trimers or pentamers and the intracellular signalling domain of CD6. In a microfluidics flow chamber model containing ALCAM$^+$ endothelium, HS T cells showed enhanced capture, slower rolling and faster arrest compared with control T cells. Moreover, engineered HS T cells were able to transmigrate across BBBs comprising PTECs in vitro.

Multimerization of the HS exodomain enhanced transmigration across BBBs, whereas removing the intracellular domain of CD6 from HS molecules diminished T cell transmigration. Therefore, ALCAM anchorage supports HS T cell transmigration across the BBB but other signalling events downstream of CD6 also contribute. Further analyses indicated that CD6 signalling in HS T cells promotes a conformational change in LFA1 that allows it to bind to ICAM1 with higher affinity. CD6 signalling in HS T cells also promoted cytoskeletal changes that supported T cell transmigration.

In a mouse model of GBM, intravenously transferred HS T cells showed enhanced homing to brain tumours compared with wild-type T cells, but did not infiltrate the spleen, lungs or kidneys. Finally, the authors compared the anti-tumour efficacy of wild-type and HS T cells engineered to express a chimeric antigen receptor (CAR) specific for a GBM-associated antigen. Only CAR HS T cells induced regression of established brain tumours. Moreover, mice with GBM treated with CAR T cells or wild-type T cells showed a median survival of 22 and 18 days, respectively, whereas animals treated with CAR HS T cells had a median survival of more than 60 days. Importantly, CAR HS T cells infiltrated brain tumours but did not enter other brain areas. This suggests that the ALCAM homing system could potentially enhance anti-tumour T cell responses in the brain while maintaining a favourable safety profile.

Yvonne Bordon

Credit: S. Bradbrook/Springer Nature Limited

ORIGINAL ARTICLE Samaha, H. et al. A homing system targets therapeutic T cells to brain cancer. *Nature* https://doi.org/10.1038/s41586-018-0499-y (2018)