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DRUG DELIVERY

Encapsulation improves therapeutic stem cell action

The recurrence and mortality rate of patients with glioblastoma multiforme (GBM) is close to 100%. At present, therapy consists of surgical debulking of the tumour followed by radiation therapy and chemotherapy. Preclinical studies have shown that therapeutically engineered stem cells may be well suited to treat GBM but these studies have highlighted the difficulty of delivering and retaining the cells in the target area. In a study published in *Nature Neuroscience*, Khalid Shah and colleagues describe a mouse resection model of GBM in which stem cells encapsulated in a biodegradable synthetic extracellular matrix (sECM) are able to home to the tumour, delay tumour regrowth and increase survival.

PHOTODISC

Most *in vivo* models of GBM focus on targeting the intact tumour, so to mimic the clinical scenario the authors first developed a mouse resection model using fluorescent human U87 GBM cells that can be visualized over time. They showed that resecting established tumours, which were generated by implanting low or high numbers of GBM cells, significantly prolonged survival.

Next, they assessed the survival of mouse neural stem cells (NSCs) in an sECM, as well as their ability to proliferate and secrete proteins, *in vitro* and *in vivo*. Interestingly, their viability in the fluorescent resection model was greater than non-encapsulated mouse NSCs, and over 4 days the cells were found to migrate out of the capsule and specifically home to the tumours. In this study, the cells were engineered to express and secrete TNF-related apoptosis-inducing ligand (TRAIL), a cytotoxic agent that induces apoptosis in approximately 50% of GBM cells. In culture, the encapsulated mouse NSC-TRAIL cells significantly reduced the viability of TRAIL-sensitive human GBM cells by activating caspase 3 and caspase 7 as well as caspase 8. Three days after implanting the cells in the resection cavity of the mouse model, an 80% decrease in residual tumour cells was observed, along with a marked increase in caspase 3 and caspase 7 activity. This suppression of tumour growth was maintained for over 40 days, and all of the treated mice were alive 42 days after resection. By contrast, the median survival of mice treated with encapsulated mouse NSCs that did not express TRAIL was 14.5 days following resection.

Finally, the authors carried out a similar assessment of the therapeutic potential of encapsulated TRAIL-expressing human bone marrow-derived mesenchymal stem cells (MSCs) on the TRAIL-sensitive primary human invasive glioma cell line GBM8. Similarly to the mouse NSCs, the human MSCs induced apoptosis of the malignant cells in a time- and caspase-dependent manner, and decreased tumour volume *in vivo*.

Together, these findings highlight the benefits of encapsulation for stem cell therapies. In the brain, transplanting sECM-encapsulated stem cells increased their retention time in the resection cavity, thus allowing them to exert their therapeutic action more effectively. Encapsulation of stem cells engineered with other antitumour agents or therapeutic proteins might be useful for the treatment of other pathologies besides GBM.

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ORIGINAL RESEARCH PAPER Kauer, T. M. *et al.* Encapsulated therapeutic stem cells implanted in the tumor resection cavity induce cell death in gliomas. *Nature Neurosci.* 25 Dec 2011 (doi:10.1038/nn.3019)