Mesenchymal stem cell-mediated sodium iodide symporter (NIS) reporter gene delivery in an orthotopic glioblastoma mouse model

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The sodium iodide symporter (NIS) represents one of the most promising reporter genes for non-invasive radionuclide-based molecular imaging and therapy. We and others have investigated the capacity of NIS to induce radioiodine accumulation in non-thyroidal tumours using various gene delivery vehicles. Based on their excellent tumour-homing capacity, mesenchymal stem cells (MSCs) are promising tumour-selective gene delivery vehicles. In the current study, we applied MSCs for tumour-targeted NIS gene delivery to glioblastoma multiforme (GBM), as a clinically highly relevant tumour with urgent need for novel therapy approaches.

Brain tumours were established in C57BL/6 mice by orthotopic inoculation of the murine GBM cell line GL261. Immortalised bone marrow-derived syngeneic mouse MSCs were stably transfected with a NIS expressing plasmid driven by the constitutively active CMV-promoter (CMV-NIS-MSC) and functional NIS expression was demonstrated by 125I uptake. Four weeks after tumour implantation, CMV-NIS-MSCs were injected systemically via the tail vein and tumoural iodide uptake was monitored by 123I-scintigraphy. Injection of the NIS inhibitor perchlorate 30 min before radionuclide application served as control of NIS specificity. A strong tumoural 123I accumulation of 11.4 percent of the injected radiodiodide dose (% ID) was observed after CMV-NIS-MSC administration, while only 3.2 % ID were measured for the perchlorate control. Resected tumours were further analysed by ex vivo NIS immunofluorescence staining, revealing NIS-specific immunoreactivity primarily in perivascular regions.

Our promising preliminary experiments demonstrate strong recruitment of MSCs into GBM tumours in a syngeneic orthotopic mouse model and establish the use of NIS as a reporter gene to track MSC homing to GBM. The fact that attempts to target therapeutically active agents to the brain are faced with the serious challenge of the blood-brain-barrier further demonstrates the potential of our strategy. In future studies, we will address the efficacy of our approach to deliver therapeutically active radionuclides, e.g. 131I, to GBM using the dual function of NIS as reporter and therapy gene.

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