Evaluation of vector mediated gene therapy of experimental gliomas using multi-modal imaging techniques.

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INTRODUCTION

Stem cells have the capacity to migrate towards sites of CNS injury like tumors [1]. These cells can integrate into the host cyto-architecture and can be engineered to disseminate bioactive molecules and viral vectors [2]. They are suitable cellular vehicles for vector-mediated gene therapy as they even track infiltrating tumors. The aim of this study was the image guided vector application and the assessment of the potency of stem cells in tumor therapy. Hereby, different non-invasive imaging modalities (MRI, PET, bioluminescence imaging/ BLI) were combined.

METHODS

Stem cells: Bone marrow-derived cells and luciferase expressing C17.2 stem cells were transducted with retroviral vectors expressing thymidine kinase (tk) of herpes simplex virus (HSV-tk). Tumors were induced by either 9LdsRed or Gli36dEGFR glioma cells.

Animal model: 10^5 to 10^6 glioma cells were implanted into the right striatum of the rats. After 7 to 10 days, stem cells expressing HSV-tk-GFP were injected in the periphery of the tumor. Animals in the therapeutic group received 30 mg kg^{-1} ganciclovir (i.p.). Animals were imaged 7 days after tumor implantation and 7-21 days thereafter.

MRI: MR images were acquired using a Bruker Biospin 4.7T and 7.0 T animal scanner. 3D gradient echo images with $T2^*$-weighting were acquired to evaluate the distribution of cells, pre-labeled with Endorem (Guerbet, France, TR/TE/pulse=150/20/30º, resolution 80 μm^3). Tumor assessment was performed after administration of T1-contrast agent using 3D FLASH, TR/TE/pulse=80/5/70º, resolution 150 μm^3. For rf irradiation (Helmholtz coil) and signal detection (surface coil), custom-built coils were used.

Multi-modal Imaging: MR images were co-registered and compared with BLI to visualize stem cell viability and migration as well as with PET-images to visualize tk expression by the implanted stem cells ([^{18}F]FHGB PET) and tumor growth ([^{11}C]MET PET).

RESULTS

Stem cells migrated into the tumor and initiated bystander-mediated therapeutic effects (killing of tumor cells due to ganciclovir phosphorylation by thymidine kinase). Multi-modal imaging provided information on the localization and growth of the tumors, enabled precise implantation of the stem cells, evaluated cell migration and distribution, assessed vector-mediated gene expression and provided information of the success of therapy (Figure 1). The successful treatment of glioma by stem cell mediated therapy was not only documented by the decrease of tumor cell viability using PET and BLI but also by the excellent correlation of tumor size determined by MRI with histology. High resolution of MRI provided information on the distribution of stem cells in the tumor tissue.

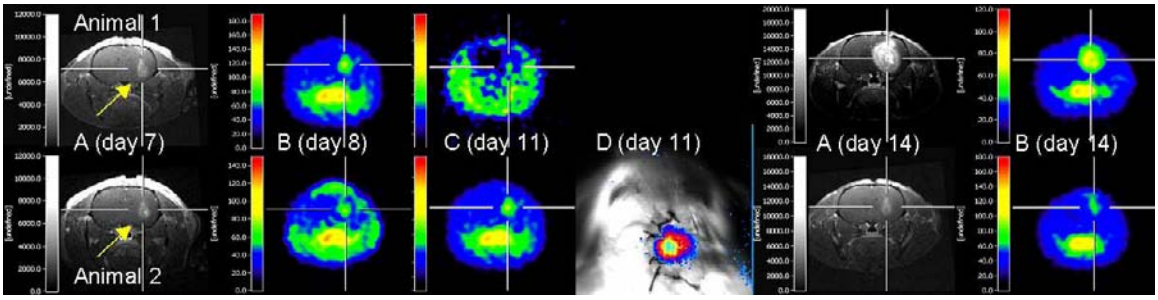

Fig.1: *In vivo* assessment of stem cell mediated tumor treatment. Repeated multi-modal *in vivo* imaging characterizes the dynamics of tumor growth (A = T1w MRI, B = [^{11}C] methionine PET), the tumor infiltration of HSV-tk stem cells (C = [^{18}F] FHGB PET) and the viability of luciferase positive tumor cells (D = BLI). Images were from a control animal (animal 1) and an animal treated with HSV tk stem cells (animal 2). Images at the first time points (7-8 days after tumor and 3 days after stem cell implantation) indicate viable tumor cells (A, B and D) and accumulation of stem cells (C). Images at the later time points show tumor growth for the untreated animal and shrinkage for treated animal.

CONCLUSION

Combination of different imaging techniques provides precise information on the success of cell-mediated therapies non-invasively, with high sensitivity. It was proven that stem cells are a successful vehicle to track tumors and deliver therapeutic agents.

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REFERENCES

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