Influence of the BMP pathway on cell cycle regulation and its differentiation inducing potential on brain tumor initiating cells

P-010

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Introduction: Glioblastoma multiforme is the most common type of brain tumor, and several alterations of the cell cycle and DNA repair mechanisms have led to increasing resistance against chemotherapy. Latest findings suggest that a subset of tumor cells, the brain tumor initiating cells (BTIC) with stem cell like properties, are responsible for initiation and maintenance of the disease. Approximately 1-1000 out of 1.000.000 cells within a glioma is a BTIC. These cells are thought to bring about relapse and metastasis through their tumorigenic potential and chemotherapeutic resistance1,2. Design of a specific therapeutic strategy against BTICs may improve overall survival and quality of life for patients with gliomas. The aim is to examine a novel, experimental therapy against malignant gliomas by differentiating their BTIC population. Building on our previous work3, where we demonstrated that BMP-7 treatment decreases the proliferation of Gli36ΔEGFR-LITG glioma cells up to 50% via a cell cycle arrest in G1 phase, we will further characterize and compare the effect of the BMP-pathway on cell cycle regulation of different glioma cell lines and "glioma stem cells".

Methods: We want to determine (i) whether BMP treatment, alone or in combination with state-of-the-art chemotherapeutic agents, could be applied in a disease-tailored therapy against gliomas by depleting their BTIC pool and (ii) whether our reporter construct (LITG) can quantify the responses to such a treatment in culture and in vivo. Glioma cell lines, primary glioma cell cultures and BTICs with different genetic profiles are being utilized to analyze the influence of BMP-7 and BMP pathway inhibitors on cell cycle regulating protein expression, cell viability and caspase activation as well as its differentiation-induction potential in culture. BTIC will be transduced with lentiviral reporter vectors to image changes in cell cycle regulation, differentiation status and BMP pathway activity non-invasively in vivo upon treatment.

Results: Western blot data indicates that BMP-7 treatment causes an arrest in cell cycle progression in the established glioma cell line A172 by influencing the expression of the key cell cycle regulators (p53 , p21 E2F-1). Furthermore we have shown the differentiation-induction potential of BMP-7 on BTICs in culture optically and on the protein level. Upon BMP-7 treatment and respective growth-factor withdrawal the expression of the neural stem cell marker Mshi1 is clearly downregulated. Currently we focus on the design of a lentiviral reporter vector for imaging the observed BMP-Pathway reponses.

Conclusions: Antagonizing the proliferative potential of BTICs by targeting the BMP pathway, thereby triggering cellular differentiation of malignant stem cells, could provide a promising means of improving the prognosis for patients with gliomas.

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