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Dynamic insights into the cellular heterogeneity of malignant gliomas

Fach/Einrichtung: Neurologie
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Background Gliomas especially GBM are the most frequent primary malignant brain tumor characterized by poor survival due to its extreme resistance to available treatments. The genetic and phenotypic diversities of glioma cells are greatly promoted by each other as well as the microenvironment, leading to dynamic intratumoral heterogeneity at both clonal and cellular level, which could explain the failure of targeted therapies dependent on individual markers. As a recently described phenotype of astrocytoma, TMs conduct a continuous long-distance interaction between cells and are heterogeneously distributed in tumor with high relevance to malignance and therapy response.

Objectives This study aimed to add to our current knowledge about tumor cell heterogeneity in gliomas, providing a proof-of-principle that in vivo MPLSM over many days and weeks can be combined with different in vivo marker systems for tumor cell heterogeneity to shed light on the dynamics of cellular heterogeneity in gliomas.

Methods SR101 was injected into mouse model carrying cranial window to distinguish TM+ and TM- cells in vivo and ex vivo. Immunostaining with tumor sections from patients and xenograft was performed to identify the stem cell markers correlated with TMs. In vivo reporter systems based on GFP expression driven by nestin/NFκB responsive promoter elements were established to dynamically monitor TMs and molecular changes in response to irradiation and laser ablation using MPLSM. The images were quantified to analyze the correlation between TMs and molecular level. FACS was utilized to measure the molecular changes upon treatment and to sort ex vivo cells according to GFP intensity.

Results TM interconnectivity of glioma cells strongly correlated with SR101 uptake

from astrocytic networks. Nestin was preferentially expressed by the TM+ glioma cell subpopulation and significantly increased in surviving cells after irradiation. Similarly, a gradual enrichment of NFκB expression especially in TM+ cells was observed after radiation treatment. Additionally, laser ablation mimicking surgical lesion induced a significant migration of NFκB+ cells towards the damaged center. Ex vivo experiment also revealed that NFκB+ population displayed much higher spheres formation ability than NFκB- cells.

Conclusions The TM-phenotype of GBM cells is highly correlated with both nestin and NFκB activation, which can dynamically change after trauma and radiation, supporting an active glioma response to irradiation and surgical treatments.