INTEGRATED ANALYSIS IDENTIFIES DIFFERENT METABOLIC SIGNATURES WITHIN BOTH TUMOR-INITIATING CELLS AND STEM CELLS IN A MURINE GLIOBLASTOMA MODEL
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BACKGROUND: The metabolic preference of malignant gliomas for glycolysis as an energy source is a potential diagnostic and therapeutic target. As a result of the cellular heterogeneity of these tumors, however, the relation between glycolytic preference, tumor formation and tumor maintenance has remained unknown. To address this issue, we analyzed the metabolic profiles of isogenic glioma-initiating cells (GICs) and glioma stem cells (GSCs) in a syngeneic mouse model. METHODS: GICs were established by overexpression of H-RasV12-dsRed in Ink4a\(^{-}\)/Arf–null neural stem cells. Subpopulations of GICs were obtained by single-cell cloning, and clones differing in extracellular acidification potential were used for quantification of intracellular metabolites and related enzymes. Tumors formed after intracranial implantation of the GIC clones in mice were examined for pathological features of glioma and expression of glycolytic enzymes. GSCs were established by sphere culture of dsRed-positive cells from the primary tumors and assessed for metabolic characteristics. RESULTS: Malignant transformation of neural stem cells resulted in a distinct shift in metabolism, with a significant increase in lactic acid production as the most pronounced characteristic of all malignant cells. Interestingly however, both GICs and GSCs could adopt two different metabolic profiles. Some clones displayed high glucose consumption and lactate production, while others consumed more oxygen, produced more ATP and had a higher respiratory capacity. The glycolytic clones exhibited higher levels of key glycolytic enzymes such as hexokinase 2 and pyruvate kinase M2, and the clones relying on oxidative phosphorylation had lower levels of pyruvate dehydrogenase kinase 1. While all GICs had equal tumorigenic ability, the differential expression of the metabolic enzymes persisted in the tumors formed by these clones in vivo, as well as in the GSCs of the respective tumors. CONCLUSIONS: The metabolic characteristics of glioma cells appear early during malignant transformation and persist until the late stages of tumor formation. However, even isogenic clones may be heterogeneous in terms of metabolic features, with both GICs and GSCs being able to satisfy their bioenergetics needs not only through aerobic glycolysis, but also through oxidative phosphorylation. These results suggest that a more detailed understanding of the metabolic profile of glioma is imperative for effective diagnostic and therapeutic targeting. SECONDARY CATEGORY: n/a.