SOX2 IDENTIFIES THE TREATMENT-REFRACTORY STEM CELL POPULATION IN GROUP 2 MEDULLOBLASTOMA
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BACKGROUND: Brain tumors represent the leading cause of childhood cancer mortality, of which medulloblastoma (MB) is the most frequent malignant pediatric brain tumor. Recent studies have demonstrated the presence of several MB molecular subgroups, each distinct in terms of prognosis and predicted therapeutic response. Although, group 2 MBs characterized by activation of the sonic hedgehog (Shh) signaling pathway have been of particular therapeutic interest, treatment-resistance has posed a significant challenge. Given the identification of brain tumor-initiating cells (BTICs), which have the ability to initiate and maintain tumor growth while promoting resistance to radio- and chemotherapy, we investigated the mechanistic profile of treatment-resistant Shh-dependent MB BTICs. METHODS: Through investigating a differential stem cell gene expression profile of 325 primary human MBs, followed by a subsequent series of step-wise knockdown, overexpression, chromatin immunoprecipitation (ChIP), and in vitro self-renewal analyses we assessed the mechanistic role of Sox2 as a novel downstream target of Shh effector proteins, Gli1 and Gli2. We further determined the clinical utility of this mechanism by treating our MB BTICs with conventional radio- and chemotherapy per the Children’s Oncology Group (COG) protocol for MB patients in order to assess the validity of Sox2 as a marker of Shh-dependent treatment-refractory MB BTICs. RESULTS: Activation and inhibition of the Shh pathway and Sox2 expression using small molecule Shh agonists and antagonists, respectively, were observed only in distinct subsets of tumor cells (CD15+B TICs). ChIP experiments further demonstrated the presence of a differential Shh signaling mechanism within distinct cell populations of the bulk tumor mass as Gli proteins showed Sox2 promoter binding only in CD15+B TICs. The functional relevance of this cell-specific signaling mechanism was assessed through an in vitro and in vivo increase in treatment-resistant Sox2+ MB BTICs following conventional and combinational radio- and chemotherapy with Shh pathway inhibitors. CONCLUSIONS: Our work demonstrates for the first time that Sox2 expression in MB is regulated by the Shh signaling pathway and Sox2+ MB BTICs represent the treatment-resistant clone in Group 2 MBs, suggesting a need for combinational therapy as tumors evolve over the course of treatment. Aside from implicating developmental genes and pathways in oncogenesis, we have also demonstrated the importance of studying cancer at a cellular level, as distinct differences in rare subsets of tumor cells may not otherwise be appreciated with genomic profiling of the bulk tumor mass. SECONDARY CATEGORY: Neuropathology & Tumor Biomarkers.