MB-23. CO-INHIBITION OF THE SONIC HEDGEHOG AND CXCR4 PATHWAYS UNIQUELY BLOCKS TUMOR INITIATING CELL FUNCTION IN MEDULLOBLASTOMA
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Medulloblastoma is the most common malignant brain tumor of childhood. Even with current intensive treatments there is significant morbidity and mortality associated with this diagnosis. Recent hope for improved outcome derives from the stratification of medulloblastoma into four molecular subtypes and the promise that subtype-specific targeted therapy will be more efficacious and less toxic. However, even within specific subtypes there can be variable outcomes, suggesting that further subclassification will be required. We previously showed that CXCR4, a G-protein coupled receptor, is differentially expressed in the Sonic hedgehog (Shh) subtype of medulloblastoma and its activation is required for maximal medulloblastoma growth in vitro and in vivo. We investigated the utility of combining inhibition of both the Shh and CXCR4 pathways in a preclinical model of Shh-medulloblastoma. We measured anti-tumor activity and effects on tumor subtransplantation efficiency of single agents and combined treatment with the Shh antagonist GDC-0449 (vismodegib) and the CXCR4 antagonist AMD3100. We found that combined therapy had the greatest anti-tumor effect and that only inhibition of both pathways abrogated tumorigenicity upon subtransplantation. These results indicated that dual-inhibition was affecting the tumor initiating cell (TIC) population. We used flow cytometry to further investigate this possibility and found that dual inhibition resulted in the loss of a subpopulation of cells with high CXCR4 and CD15 surface expression. Concordant with this diminution in the putative TIC population we found decreased expression of the stem cell markers Sox2, Nanog and Oct4 in doubly treated tumors. Decreased expression of these stem cell markers was associated with increased presence of the repressive histone mark H3K27me3 at their promoters. Together these data indicate that the Shh and CXCR4 signaling pathways in medulloblastoma converge in the subpopulation of TICs to regulate stem cell activity. Dual inhibition may therefore represent a powerful new approach to medulloblastoma cure.