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Basic Science

Abstract Title

Targeting Non-Genetic Kinase-Dependent Signaling Pathways to Prevent Group 3 Medulloblastoma Tumor Relapse

Authors

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Background

Brain tumors are the leading cause of cancer-related death in children, with medulloblastoma being the most common malignant type. Group 3 medulloblastoma (G3-MB) carries the worst prognosis, with a 5-year survival below 60%, driven by high recurrence rates following standard chemoradiotherapy (CRT). Since recurrent tumors retain their original molecular identity, non-genomic signaling adaptations likely drive resistance. We hypothesized that CRT induces aberrant kinase activation in G3-MB, promoting stemness and recurrence, and that targeting would improve outcomes.

Objective

We hypothesized that CRT induces aberrant kinase activation in G3-MB, promoting stemness and recurrence, and that targeting would improve survival outcomes.

Methods

Three patient-derived G3-MB cell lines were exposed to a clinically relevant CRT regimen to generate therapy-resistant (CRT-Res) cells, profiled using phospho-kinase arrays. Findings were validated in patient-derived orthotopic xenograft models, immunofluorescence and matched primary-relapse patient samples. SRC was inhibited via inducible CRISPR-Cas9 knockout and the blood-brain barrier-permeable inhibitor Saracatinib. In vivo efficacy was assessed in tumor-bearing mice treated with CRT with or without Saracatinib. Student's t-tests and one/two-way ANOVA were used for statistical analysis.

Results

Phospho-kinase profiling revealed selective upregulation of phosphorylated SRC (p-SRC) in CRT-Res G3-MB cells (>2-fold increase, $p < 0.05$), absent in SHH-MB cells, normal astrocytes, and neural stem cells. Elevated p-SRC was confirmed in recurrent xenograft tumors and matched relapse patient samples versus primary tumors. SRC knockout and Saracatinib treatment significantly reduced cell viability (~50% reduction, $p < 0.05$), tumorsphere formation, and stemness markers (SOX2, NOTCH1), while increasing differentiation marker TUBB3 and activating apoptotic and necroptotic cell death. In vivo, CRT combined with Saracatinib reduced tumor burden significantly and extended median survival by ~47% versus placebo ($p < 0.05$), with tissue profiling confirming target engagement and increased differentiation.

Conclusion

These findings support our hypothesis that SRC activation is a conserved, G3-MB-specific adaptation to CRT that sustains stemness and drives recurrence. Saracatinib selectively targets this vulnerability while sparing normal brain, representing a promising repurposing strategy for children with recurrent G3-MB.