CHRD 2022: Abstract & Poster Submission Form

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Presenter Status

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○ Masters Student

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○ Non-Trainee

Research Category

◉ Basic Science

○ Clinical

○ Community Health / Policy

Role in the project

☐ Design

☑ Perform Experiments

☑ Analyze Data

☑ Write Abstract

☐

Title

Combined MEK and JAK/STAT3 pathway inhibition effectively decreases SHH medulloblastoma tumor progression

Background

Medulloblastoma (MB) is the most common primary malignant pediatric brain cancer and is divided into 4 molecularly distinct subgroups. SHH MB is characterized by activation of the SHH signalling pathway and is associated with an intermediate prognosis. However, these tumors exhibit extensive heterogeneity and include high-risk groups that account for most treatment failures. Furthermore, targeted therapies for SHH MB are lacking, as SHH pathway antagonists have limited clinical efficacy. We previously identified CD271 as a diagnostic and prognostic marker in SHH MB, with CD271+ cells exhibiting elevated levels of MAPK signaling. Targeting the MAPK pathway with the MEK inhibitor selumetinib attenuated SHH MB tumor progression; however animals eventually succumbed to disease progression.

Objective

We hypothesize that compensatory pathways play a role in SHH MB tumor progression and targeting these additional pathways will aid in enhancing survival.

Methods

RNA sequencing was performed to evaluate the molecular mechanisms underlying selumetinib resistance in SHH MB xenografts. Tumorsphere assays, collagen migration assays and in vivo orthotopic xenograft mouse models were utilized to evaluate the effects of combinatory drug treatments on SHH MB.

Results

RNA sequencing revealed an upregulation of the JAK/STAT3 pathway in selumetinib treated SHH MB xenografts. Thus, the effects of dual inhibition of MEK and JAK/STAT3 pathways on SHH MB cells were evaluated using both tumorsphere assays and 3D collagen migration assays. Inhibition with selumetinib and the JAK/STAT3 inhibitor pacritinib resulted in a significant decrease in tumorigenic properties such as tumorsphere growth, cell proliferation and migration in three different SHH MB cell models. In addition, combinatory MEK and JAK/STAT3 pathway inhibitors significantly reduced tumor growth and enhanced survival in two SHH MB xenograft models.

Conclusion

Our study revealed the JAK/STAT3 pathway as a compensatory pathway in response to selumetinib treatment and identified dual MEK and JAK/STAT3 inhibition as a potential combinatory therapeutic strategy for SHH MB.

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