Identification of the Rho Guanine Nucleotide Exchange Factor, Trio as a Novel Therapeutic Target for Medulloblastoma Invasion

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Introduction

Medulloblastoma, accounting for 25% of pediatric brain tumors, is the most common solid primary childhood tumor. These tumors display cellular invasion into adjacent parenchyma, and subsequently CSF, causing metastasis and poor prognosis. We recently demonstrated that Rac1, a member of the Rho GTPase family, is essential for the invasive behavior medulloblastoma and that Rac1 is hyperactive in medulloblastoma tumors (Zavarella et al, J Neurosurg Pediatr. 2009 Aug;4(2):97-104). Here, we have identified Trio, a novel guanine nucleotide exchange factor (GEF), that mediates medulloblastoma invasion through the GTPases Rac1 and RhoG.

Methods

Specific depletions of Trio, Rac1, RhoG, and RhoA were achieved by small interfering RNA oligonucleotides (siRNA). Invasive behavior of medulloblastoma cells was studied by quantifying invasion through a novel 3-dimensional layer of reconstituted extracellular matrix (Matrigel). Rac1 activity was assessed by GLISA assay. Trio expression was evaluated through a medulloblastoma tissue microarray.

Results

Trio was identified based on increased expression in metastatic versus non-metastatic medulloblastoma tumors (Kool et al (2008), PLOS 3, e3088). siRNA-based depletion in 3-dimensional transwell assay revealed TRIO plays a critical role in Daoy and UW-228 medulloblastoma invasion. In addition to Rac1, Trio activates RhoG and RhoA. We examined the roles of these GTPases in medulloblastoma invasion, and found that siRNA-mediated depletion of RhoG and Rac1 inhibits invasion by 70%, whereas depletion of RhoA stimulates invasion. Notably, depletion of Trio has a relatively small effect on glioblastoma cell invasion, indicating its specificity for medulloblastoma. We found that Trio specifically activates Rac1 and that Trio is overexpressed in medulloblastoma tumor samples.

Conclusions

Our results indicate Trio is important for medulloblastoma invasion and metastasis. Moreover, the invasive role of Trio is likely mediated through Rac1 and/or RhoG. We propose that targeting Trio presents a novel therapeutic avenue for advanced medulloblastoma.

Learning Objectives

By the conclusion of this session, participants should be able to 1) Describe the importance of cell signaling pathways, specifically the Rho GTPase pathway, in medulloblastoma invasion, 2) Discuss in small groups better modalities for the administration of small-molecule inhibitors that target the Trio pathway, and 3) Understand the importance of control over medulloblastoma invasion

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