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KEYWORDS – Brain tumor, tissue invasion, kinase signaling, protein-protein interaction

MAIN FIELDS OF RESEARCH; ABSTRACT

Medulloblastoma (MB) is an aggressively growing cerebellar tumor in children. The characteristic tendency of MB cells to locally infiltrate and to form leptomeningeal metastases distant from the primary tumor site, hampers the efficacy of current treatments. Hence, blocking tumor cell migration and local infiltration could prevent cerebellar metastases, restrict further leptomeningeal dissemination and reduce the evolution towards a more aggressive phenotype. Currently, we know little about the molecular determinants underlying MB cell dissemination, whereas a better mechanistic understanding of their regulation may provide clues for targeting cell infiltration and tumor dissemination. One important mediator of MB dissemination identified by our group is the serine/threonine protein kinase MAP4K4. It acts downstream of different growth factor (GF) receptors and modulates cortical F-actin cytoskeleton and membrane dynamics in invasive cell protrusions at the leading edge, thereby promoting MB cell motility and invasiveness. However, the mechanistic details of MAP4K4 function during tissue infiltration and cell dissemination and the molecules governing and mediating this process in MB have not been identified yet.
Our objective is to selectively target the molecular mechanisms that mediate the migratory behavior of MB tumor cells downstream of MAP4K4 function as a strategy to restrict tissue infiltration. Using a pull-down approach followed by functional screening for cell migration control in 3D, we would like to identify the relevant effectors of MAP4K4 and determine how signaling downstream of MAP4K4 is translated into a pro-migratory and –invasive cell phenotype in MB cells.

SPECIAL TECHNIQUES AND EQUIPMENT

Standard biochemical and molecular biology techniques, mass spectrometry, fluorescence microscopy, 2D and 3D in-vitro cell culture models, in vitro spheroid cell invasion assay.