Novel PIM Inhibitor PIM447 Produces Significant Anti-Tumor Effects in Human Hepatoblastoma Cells

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Hepatoblastoma is the most common liver tumor in children. Those with relapsed or metastatic disease continue to have a poor prognosis and require novel therapies to improve outcomes. PIM kinases have been identified to play a role in hepatoblastoma tumorigenesis. PIM447 has shown promise as a targeted PIM kinase inhibitor. I hypothesized that treatment of hepatoblastoma cells with PIM447 would result in decreased tumorigenesis in vitro. The human hepatoblastoma cell line HuH6 was examined in monolayer culture conditions. Cells were treated with PIM447 at increasing concentrations for 72 hours. Cell viability and proliferation were determined using alamarBlue/CellTiter96 assays. Migration and invasion were evaluated using 8um micropore transwell inserts coated with collagen and MatrigelTM, respectively. Migration was also assessed using a cell monolayer wounding (scratch) assay. WB was used to measure protein expression of PIM kinases and downstream targets, BAD and pBAD, as well as apoptotic markers cleaved PARP and cleaved caspase 3. Experiments were repeated in triplicate; statistical analysis was performed with Student's t-test. PIM447 treatment led to decreased cell viability and proliferation compared to untreated cells. Migration and invasion decreased after treatment. Scratch assay demonstrated a significant decrease in cell motility with treatment. Immunoblotting confirmed the presence and downregulation of downstream PIM targets BAD and pBAD and upregulation of apoptotic markers cleaved PARP and cleaved caspase 3 after treatment. PIM447 reduced viability, proliferation, and motility in HuH6 human hepatoblastoma cells and suppressed downstream targets of PIM, suggesting PIM447 should be further investigated as a novel therapeutic in hepatoblastoma.

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