Neuroblastoma and the Warburg Effect: 

The Novel Glycolysis Inhibitor 3-BrOP Is Effective in Vitro and in Vivo

The Warburg effect is the dependence of cancer cells on glycolysis for ATP production despite aerobic conditions. A role for the Warburg effect in neuroblastoma has not been explored. The potent 3rd generation glycolysis inhibitor, 3-BrOP, makes the therapeutic inhibition of glycolysis feasible. We previously reported that 3-BrOP inhibits neuroblastoma and synergizes with the mTOR inhibitor, rapamycin. This led us to investigate the apoptotic mechanisms and therapeutic efficacy in a neuroblastoma xenograft model. All neuroblastoma cells, including the NB12 "stem cells", were sensitive to 3-BrOP, inducing substrate detachment within 6 hours, growth arrest, and subsequent death in 48 hours. IC50 values ranged from 6-12 micromolar, with >85% cell death observed by 72 hours. Surprisingly, ATP concentrations were below 10% of normal, implying an inability to compensate with ATP production via oxidative phosphorylation. Furthermore, a BAD-mediated intrinsic apoptotic mechanism was revealed, as caspase-9, 3 and PARP1 cleavage were detectable by 12, 24 and 48 hours respectively. Importantly, 3-BrOP dramatically inhibited SK-N-SH tumor growth by more than 75% and was associated with a 65% decrease in mean vessel density (p<0.001). 3-BrOP effectively inhibited tumor growth and decreased tumor angiogenesis. Based on these studies, neuroblastoma recapitulates the Warburg effect, providing a therapeutic opportunity for inhibition of glycolysis and a rational combination with mTOR inhibitors. The potential therapeutic role of 3-BrOP in neuroblastoma warrants further pre-clinical evaluation.

References
