

Regulation of Aminoacylase Expression in Neuroblastoma

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Neuroblastoma, a cancer of the sympathetic nervous system, is the most common extracranial solid tumor in children. Neuroblastoma is remarkably heterogeneous, with some tumors undergoing spontaneous regression; unfortunately, most tumors are highly metastatic, unresponsive to treatment and usually fatal. NMYC amplification and increased BDNF/TrkB signaling are features of high-grade tumors, yet only ~25% of malignant tumors display these features. Thus, the identification of additional biomarkers and therapeutic targets is essential. Since aminoacylase 1 (ACY1), an amino acid deacetylase, serves as a tumor suppressor in renal cell carcinoma and small cell lung cancer, we investigated whether it or the other family members, aspartoacylase (ASPA, aminoacylase 2) or aminoacylase 3 (ACY3), could serve a similar function in neuroblastoma.

Aminoacylase expression was examined in TrkB-positive, NMYC amplified SMS-KCNR and TrkB-negative, non-NMYC amplified SK-N-AS and SK-N-SH neuroblastoma cell lines. In contrast to ACY1 and ACY3, whose expression was greater in the more aggressive SMS-KCNR and SK-N-AS lines, ASPA expression was greater in the least aggressive SK-N-SH line and significantly reduced in the most aggressive SMS-KCNR line. ACY1 and ACY3 expression was dramatically increased upon neuronal differentiation of SK-N-SH cells. Although not as robust, ASPA expression was specifically enriched in differentiated cells relative to arrested cells. Interestingly, ASPA has been previously shown to be a negative regulator of BDNF signaling in the CNS (Francis et al. [2006] J. Neurosci. Res. 84:151-69) and bioinformatics data mining of Kaplan-Meier survival data revealed that low ASPA expression is correlated with poor prognosis. Our findings suggest an involvement of ASPA in neuroblastoma with possible implications in BDNF/TrkB regulation.