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Differentiation of neuroblastoma tumor cells with a neural growth factor

Neuroblastoma is the most common extra cranial solid cancer of childhood. Tumors arise from sympathoadrenal progenitors, and therefore, can form in any part of the sympathetic nervous system, or in the adrenal medulla. N-MYC is amplified in poor prognosis neuroblastoma. Mice with overexpression of N-MYC restricted to the neural crest lineage by the tyrosine hydroxylase promoter develop tumors similar to those found in humans, and thus are a mouse model of the human disease. It is likely that a loss of normal neuronal growth factor signaling, which plays a critical role in normal nervous system development, contributes to the disregulated development of neuroblastoma. In this study we have examined the effect of a number of growth factors that are found in the developing nervous system on cultured MYCN mouse tumor cells, including brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), nerve growth factor (NGF), and neurotrophin 3 (NT3). Significantly, 96 hour treatment with CNTF led to extensive process outgrowth as cells took on a mature neuronal phenotype. This effect was found to be concentration-dependent. 96 hour treatment with CNTF also led to a significant concentration-dependent decrease in ki67 staining, a marker of cellular proliferation. Furthermore, CNTF significantly increases survival after 72 hours of treatment. We have also found by flow cytometry that a significant percentage of the acutely isolated tumor cell population expresses the receptor for CNTF, ciliary neurotrophic factor receptor alpha (CNTFRa), and the proliferation marker ki67. Supporting a role for CNTF signaling in promoting a less aggressive tumor phenotype as we show here, microarray data from the Oncogenomics online database (http://home.ccr.cancer.gov/oncology/oncogenomics/) shows a correlation for increased survival in patients whose tumors express high levels of either CNTF, or CNTFRa. Taken together, these results suggest CNTF may have therapeutic potential in promoting differentiation of neuroblastoma tumor cells.

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