Karolinska Institutet

**Institutionen för Kvinnors och Barns Hälsa**

# Eicosanoids in cancer: new therapeutic targets in neuroblastoma

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## ABSTRACT

Cancer is one of the most common causes of death for both children and adults in developed countries. Neuroblastoma is a cancer of the sympathetic nervous system that affects infants and young children. Neuroblastoma tumors are the most common solid extracranial tumors in children and are also the most deadly. About half of the patients diagnosed are classified as high-risk, and despite an intensive multimodal treatment, the survival rate for these patients is only 55%. The overall survival for all neuroblastoma patients is about 70%. A better biological understanding is required to develop novel targeted therapy that may improve the outcome for cancer patients. Therefore we need to search for additional targets for therapeutic interventions in neuroblastoma.

Inflammatory cells and mediators are important constituents of the local tumor environment that drives tumor progression. Treatment that inhibits inflammation can reduce tumor growth. Neuroblastoma cells are enriched in arachidonic acid, a pro-inflammatory omega-6 fatty acid, but deficient in anti-inflammatory omega-3 fatty acids. We have previously shown that neuroblastoma expresses high levels of cyclooxygenase-2 (COX-2), which converts arachidonic acid into prostaglandins and that treatment with COX inhibitors reduces neuroblastoma tumor growth. In this thesis, I have investigated the role of arachidonic acid-derived metabolites in cancer, with a special focus on neuroblastoma.

To understand the significance of a high COX-2 expression in neuroblastoma we investigated the role of prostaglandin $E_2$ ($PGE_2$), its pro-inflammatory metabolite. Neuroblastoma cells produce $PGE_2$ and express all four $PGE_2$ receptors. $PGE_2$ stimulates neuroblastoma cell growth, and inhibition of $PGE_2$ receptor signaling reduces cell survival. We also evaluated the potential of a more specific targeting of the COX-2 pathway to reduce $PGE_2$ production by inhibition of microsomal prostaglandin E synthase-1 (mPGES-1). Downregulation of mPGES-1 expression reduces the clonogenic capacity and the tumorigenic potential of prostate and lung cancer cells.

Another route for arachidonic acid metabolism is the 5-lipoxygenase (5-LO) pathway and the production of pro-inflammatory leukotrienes. We detected expression of all the enzymes that are required for leukotriene biosynthesis in neuroblastoma tumors and cell lines. Neuroblastoma cells produce leukotrienes that promote cell growth and survival. Treatment with 5-LO pathway inhibitors or leukotriene receptor antagonists induced apoptosis of neuroblastoma cells.

Very little is known about the role of inflammation in childhood cancers. We show here a progressive inflammatory tumor microenvironment that parallels neuroblastoma tumor growth in the transgenic TH-MYCN model of neuroblastoma. Treatment with a low dose of anti-inflammatory acetylsalicylic acid, aspirin, modulates inflammatory parameters and significantly reduces tumor growth.

In summary, this thesis shows that $PGE_2$ and the leukotrienes act as autocrine and/or paracrine growth and survival factors in neuroblastoma. This suggests that inhibition of $PGE_2$ and leukotriene signaling may represent novel targeted therapy for neuroblastoma.



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