**PROSTAGLANDINS AND ANGIOGENESIS IN EXPERIMENTAL CANCER**

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i lokal Kammaren, Blå Stråket 5, Sahlgrenska Universitetssjukhuset/Sahlgrenska, Göteborg, fredagen den 23 april 2010 kl. 9.00

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The thesis is based on the following papers:

I Hans Axelsson, Ulf Bagge, Kent Lundholm and Elisabeth Svanberg.
**A one-piece plexiglass access chamber for subcutaneous implantation in the dorsal skin fold of the mouse.**
*Int J Microcirc Clin Exp. 1997 Nov-Dec;17(6):328-9*

II Hans Axelsson, Christina Lönnroth, Wenhua Wang, Elisabeth Svanberg and Kent Lundholm
**Cyclooxygenase inhibition in early onset of tumor growth and related angiogenesis evaluated in EP1 and EP3 knockout tumor-bearing mice**
*Angiogenesis. 2005;8(4):339-48*

III Hans Axelsson, Christina Lönnroth, Marianne Andersson, Wenhua Wang and Kent Lundholm
**Global Tumor RNA Expression in Early Establishment of Experimental Tumor Growth and Related Angiogenesis following Cox-Inhibition Evaluated by Microarray Analysis.**
*Cancer Inform. 2007 May 1;3:125-39*

IV Hans Axelsson, Christina Lönnroth, Marianne Andersson and Kent Lundholm
**Mechanisms behind COX-1 and COX-2 inhibition of tumor growth in vivo**
*Manuscript*

Göteborg 2010

UNIVERSITY OF GOTHENBURG

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**Abstract:**

**Background and aim.** Genes, proteins and pathways have been identified and suggested as potential targets in tumor angiogenesis, but current anti-angiogenic therapies have provided only modest benefits in survival of cancer patients. Therefore, further understanding of underlying mechanisms of tumor induced angiogenesis is mandatory in order to develop effective anti-angiogenic treatments in cancer disease. We have therefore focused on the role prostanoids may have to support tumor vasculature in progressive tumor growth of tumors.

**Methods.** Two fundamentally different tumor models were used. MCG-101 tumors induced increased systemic levels of $PGE_2$ and showed high sensitivity to COX inhibition, while K1735-M2 tumors did not produce $PGE_2$ and were thus insensitive to COX inhibition regarding tumor growth in syngenic wild type mice. $EP_1$- and $EP_3$-receptor knockout tumor-bearing mice were also used. COX-inhibition was provided by indomethacin in the drinking water to block prostanoid synthesis in tumor and host tissues. Intravital microscopy was performed using a dorsal skin fold chamber technique for studies of early tumor growth and associated angiogenesis. Immunohistochemical and microarray analyses were applied.

**Results**. Indomethacin reduced tumor growth and tumor related vascular area in wild type mice bearing MCG-101 tumors, but did not affect these parameters in K1735-M2 tumors. There was an unchanged relationship between the load of malignant cells and supportive vascular area among different tumor growth conditions. Unselective COX inhibition reduced tumor growth in $EP_3$, but not in $EP_1$ knockouts without significant alteration in tumor vascular density in $EP_3$ knockouts. Indomethacin treatment influenced expression of a large number of genes (5% of >40 000 probes) responsible for important steps in carcinogenesis, inflammation, angiogenesis, apoptosis, cell cycle activity and proliferation, cell adhesion, carbohydrate & fatty acid metabolism and proteolysis in tumors on wild type mice. Affected genes were widely and uniformly distributed on chromosomes over the entire genome. Variation of COX-2 staining in MCG-101 tumors was significantly reduced following indomethacin treatment. Effects of altered prostanoid metabolism were significantly related to EGF-R expression in tumor tissue and transcripts of KRas, PI3K, JAK1, STAT3 and c-jun were down-regulated by indomethacin, while STAT1 and ELK1 did not show any such decline.

**Conclusion.** Indomethacin treatment reduced tumor cell proliferation and increased tumor cell apoptosis in MCG-101 tumors with associated adaptive alterations in tumor vasculature. These effects were best predicted by alterations in EGF-R expression in tumor tissue with main downstream effects through KRas signaling.

**Key words**: angiogenesis, dorsal skin fold chamber, prostanoids, $PGE_2$, indomethacin

**ISBN: 978-91-628-8079-8**