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

av

Hans Axelsson
Leg. läkare

Fakultetsopponent:
Docent Henric Thorlacius
Enheten för kirurgi, Universitetssjukhuset MAS, Malmö

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.

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

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
PROSTAGLANDINS AND ANGIOGENESIS IN EXPERIMENTAL CANCER

Hans Axelsson
Department of Surgery, Institute of Clinical Sciences at Sahlgrenska Academy, University of Gothenburg, Sweden 2010

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 PGE2 and showed high sensitivity to COX inhibition, while K1735-M2 tumors did not produce PGE2 and were thus insensitive to COX inhibition regarding tumor growth in syngenic wild type mice. EP1- and EP3-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 EP3, but not in EP1 knockouts without significant alteration in tumor vascular density in EP3 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, PGE2, indomethacin

ISBN: 978-91-628-8079-8