

# PROSTANOIDS AND COLORECTAL CANCER

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs  
Universitet kommer att försvaras offentligt i hörsal Arvid Carlsson, Academicum,  
Medicinaregatan 3, Göteborg, fredagen den 12 november 2010, kl. 9.00

av

**Annika Gustafsson Astring**

Fakultetsopponent:

Professor Anita Sjölander

Institutionen för Laboratoriemedicin, Cellpatologi, Lunds Universitet, Skånes  
Universitetssjukhus, Malmö

Avhandlingen baseras på följande delarbeten:

- I **Gustafsson A**, Hansson E, Kressner U, Nordgren S, Andersson M, Wang W, Lönnroth C and Lundholm K. (2007) EP1-4 subtype, COX and PPARgamma receptor expression in colorectal cancer in prediction of disease-specific mortality. *International Journal of Cancer*. 121, 232-240
- II **Gustafsson A**, Hansson E, Kressner U, Nordgren S, Andersson M, Wang W, Lönnroth C and Lundholm K. (2007) Prostanoid receptor expression in colorectal cancer related to tumor stage, differentiation and progression. *Acta Oncologica*; 46: 1107-1112
- III **Gustafsson A**, Hansson E, Kressner U, Nordgren S, Andersson M, Lönnroth C, Lagerstedt KK and Lundholm K. (2010) Receptor and enzyme expression for prostanoid metabolism in colorectal cancer as related to tumor tissue PGE2. *International Journal of Oncology*; 36(2):469-78
- IV **Gustafsson Astring A**, Carén H, Andersson M, Lönnroth C, Lagerstedt KK and Lundholm K. COX-2 gene expression in colorectal cancer tissue related to regulating factors and promoter methylation status. *Submitted*



UNIVERSITY OF GOTHENBURG

# PROSTANOIDS AND COLORECTAL CANCER

**Annika Gustafsson Astring**

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

## ABSTRACT

Tumor disease is a main cause of death in Western countries and a most common malignancy is colorectal cancer (CRC). Growing tumors are dependent on interactions among several different cells as well as signaling pathways. Many tumors display increased expression of the enzyme cyclooxygenase-2 (COX-2) in conjunction with changes in tissue levels of prostanoids. However, COX-2 expression is usually unevenly distributed among cells in tumor tissue and several cell clones display little or no COX-2 expression. A frequent change of prostanoid metabolism in CRC is increased PGE<sub>2</sub> production, which appears to be involved in several different steps of tumor progression. Prostanoids bind to receptors on cell membranes with subsequent activation of different intracellular signaling pathways. Therefore, a general aim of this work was to evaluate changes in expression of prostanoid receptors and related factors involved in prostanoid metabolism in human CRC suggesting possible specific targets for interventions on prostanoid metabolism to attenuate progression. This aim was partly performed by analyses with realtime-PCR of tumor and normal colon tissue samples from human CRC obtained at surgery. Uneven distribution of COX-2 expression, as confirmed by IHC, could hypothetically be explained by gene silencing following DNA methylation. Therefore, methylation analysis of the COX-2 promoter was also performed. Furthermore, our patients received short-term pre-operative treatment with non-selective COX-inhibition (indomethacin) to evaluate changes in gene expression related to prostanoid levels determined by microarray.

Prostanoid receptor expression was decreased in tumor tissue and reduced concentration of prostanoids had no negative effect on tissue expression of most prostanoid receptors. By contrast, tumor tissue expression of the EP<sub>2</sub> subtype receptor showed negative prediction of patient survival. Methylation of COX-2 promoter sequences did not explain the lack of COX-2 expression in tumor tissue cells. Short-term pre-operative treatment with indomethacin was followed by pronounced alterations of gene expression in both tumor and normal colon tissue. Several differences in expression of genes known to regulate COX-2 expression, including transcriptional factors, occurred in relationship to COX-2 in tumor tissue. Our observations suggest that prostanoid metabolism is complex in CRC and involves several hundred genes in different cell types. Alterations in prostanoid metabolism was related to tumor stage progression and may offer therapeutical targets in addition to treatment with conventional COX inhibitors for chemoprevention of CRC, since such long-term treatment may be associated with considerable side effects in patients.

**Keywords:** Cyclooxygenase, PGE<sub>2</sub>, prostanoid receptors, colorectal cancer, transcription factors

**ISBN 978-91-628-8140-5**