# Editorial

## COX-2 and Cancer

Prostaglandin endoperoxide H synthases 1 and 2, generically named COXs (cyclo-oxygenases) 1 and 2, are regulatory enzymes of the myeloperoxidase superfamily involved in the production of prostaglandins and other prostanoids. COX-1 is constitutively expressed in most tissues, whereas COX-2 expression is not significant under normal conditions. In humans, the COX-2 gene is located at the long arm of chromosome 1 (1q25.2-25.3), as a single copy gene with 8 kb.[1] Its expression is induced as a result of various stimuli, as pathogens, cytokines, nitric oxide, irradiation and growth factors, related to a variety of clinical situations, like inflammation, cancer, and labor. Under these stimuli COX-2 transcription is stimulated and this process is controlled at different levels by methylation or post-transcriptional mechanisms.[2]

Both COXs are largely located on the luminal side of the endoplasmic reticulum membrane and the nuclear envelope. In lesser amounts, they have been also found in lipid bodies, mitochondria, filamentous structures, vesicles and in the nucleus. These enzymes are bifunctional with a cyclo-oxygenase and a peroxidase activity. The primary products of COXs are the prostaglandins, short lived mediators which play a role in various physiological and pathophysiological processes, as fever, algesia, inflammation, thrombosis, parturition, mitogenesis, vasomotility, ovulation and renal function. COX-2 is non-selectively inhibited by non-steroid anti-inflammatory drugs (NSAID), as piroxicam, aspirin, indomethacin and diclofenac, and is selectively inhibited by other NSAID, as nimesulide, etodolac and meloxicam.

The oncogenic effects exerted by COX-2 seem to be related to stimulation of cell proliferation, angiogenesis and metastases, and to a decrease of apoptosis rate and immune surveillance to cancer. Effect on immune reaction to cancer cells seems to involve inhibition of blastogenesis of T-lymphoid cells and of cytotoxic activity of natural killer cells.[3]

COX-2 stand for a link between inflammation and cancer, together with other gene products that mediate suppression of apoptosis, increase of proliferation, angiogenesis and metastasis, like the tumor necrosis factor, interleukins and chemokines. The expression of these genes is regulated by the transcription factor NF-κB, which is active in the majority of the tumors. [4] Epidemiological data have demonstrated that chronic ingestion of NSAID is significantly associated with reduction of the incidence of cancer.[5] This finding has also been supported by experimental evidence in COX-2 knockout mice.[6] In addition to inhibition of COX-2 oncogenic effects, selective NSAID have been shown to act independently of COX-2 .[7]

COX-2 is also frequently overexpressed in many carcinomas, among which is breast cancer. Increased protein expression of this enzyme has been mostly associated with unfavorable outcome and/or with known markers of adverse prognosis, both in ductal carcinoma in situ and invasive.[8-13] On the other hand, this evidence has been contradicted by others.[14,15]

In this context, the article by MARTINS and coworkers in this issue represents a contribution for the debate of the clinical value of COX-2 immunoexpression in breast cancer. As discussed by these authors, the subject deserves further study to help answering some questions: A) Is there a place for the therapy with COX-2 inhibitors to prevent or to treat breast cancer in conjunction with established drugs? B) Does immunohistochemical expression of COX-2 represent a prognostic factor? C) Does this expression predict response to COX-2 inhibitors or help to select patients that would benefit from these drugs? Responding to these and other questions involve

the inherent difficulty of selecting single factors in such a complex mechanism as carcinogenesis. In every case, the understanding of molecular mechanisms related to COX-2 is emblematic of the current efforts assumed by oncologists in searching for target based therapies.

## References


1. Chandrasekharan NV, Simmons DL. The cyclooxygenases. Genome Biology 2004;5:241.
2. Harper KA, Tyson-Capper AJ. Complexity of COX-2 gene regulation. Biochem Soc Trans 2008;36:543-5.
3. Trifan OC, Hla T. Cyclooxygenase-2 modulates cellular growth and promotes tumorigenesis. J Cell Mol Med 2003;7:207-222.
4. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol 2006;72:1605-21.
5. Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer 2006;6:27.
6. Langenbach R, Loftin CD, Lee C, Tiano H. Cyclooxygenase-deficient mice. A summary of their characteristics and susceptibilities to inflammation and carcinogenesis. Ann N Y Acad Sci 1999;889:52-61.
7. Grösch S, Maier TJ, Schiffmann S, Geisslinger G. Cyclooxygenase-2 (COX-2)-independet anticarcinogenic effects of selective COX-2 inhibitors. J Natl Cancer Inst 2006;98:736-47.
8. Costa C, Soares R, Reis-Filho JS, Leitão D, Amendoeira I, Schmitt FC. Cyclo-oxygenase 2 expression is associated with angiogenesis and lymph node metastasis in human breast cancer. J Clin Pathol 2002;55:429-34.
9. Ristimäki A, Sivula A, Lundin J, Lundin M, Salminen T, Haglund C, et al. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Reseacry 2002;62:632-5.
10. Denkert C, Winzer KJ, Müller BM, Weichert W, Pest S, Köbel M, et al. Elevated expression of cyclooxygenase-2 is a negative prognostic factor for disease free survival and overall survival in patients with breast carcinoma. Cancer 2003;97:2978-87.
11. Perrone G, Santini D, Vincenzi B, Zagami M, La Cesa A, Bianchi A, et al. COX-2 expression in DCIS: correlation with VEGF, HER-2/neu, prognostic molecular markers and clinicopathological features. Histopathology 2005;46:561-8.
12. Cho MH, Yoon JH, Jaegal YJ, Choi YD, Lee JS, Lee JH, et al. Expression of cyclooxigenase-2 in breast carcinogenesis and its relation to HER-2/neu and p53 protein expression in invasive ductal carcinoma. The Breast 2006;15:390-8.
13. Nassar A, Radhakrishnan A, Cabrero IA, Cotsonis G, Cohen C. COX-2 expression in invasive breast cancer. Correlation with prognostic parameters and outcome. Appl Immunohistochem Mol Morphol 2007;15:255-9.
14. Kelly LM, Hill ADK, Kennedy S, Connolly EM, Ramanath R, Teh S, et al. Lack of prognostic effect of Cox-2 expression in primary breast cancer on short-term follow-up. EJSO 2003;29:707-10.
15. Ranger GS, Jewell A, Thomas V, Mokbel K. Elevated expression of cyclooxygenase-2 in breast cancer and ductal carcinoma in situ has no correlation with established prognostic markers. J Surg Oncol 2004;88:100-3



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