Cyclooxygenase-2 Polymorphism
Putting a Brake on the Inflammatory Response to Vascular Injury?
Francesco Cipollone, Carlo Patrono

Prostaglandin endoperoxide H synthase (PGHS) catalyzes the conversion of arachidonic acid to PGH₂, the first committed step in the biosynthesis of a range of lipid mediators, termed prostaglandins (PGs) and thromboxanes.1 PGHS has both cyclooxygenase (COX) and hydroperoxidase activities.2 Aspirin and a variety of nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the COX activity of PGHS3 (Figure 1).

Before 1991, only the isoform called PGHS-1, COX-1, or the constitutive enzyme had been described. At that time, Xie et al4 and Kujubu and Herschman5 discovered mRNAs whose expression was induced in chicken and mouse fibroblasts in response to src and tumor-promoting phorbol esters, respectively, and that encoded proteins having 60% amino acid sequence identity with COX-1. Subsequent work has shown that the new protein, called PGHS-2, COX-2, or the inducible isoform, is very similar to COX-1 in structure but differs substantially from COX-1 with respect to its pattern of expression and its biology.1 In particular, COX-2 can be upregulated by cytokines, growth factors, and tumor promoters,6,7 suggesting its relevance in inflammation and cancer.

Although initially characterized as an isozyme inducible in response to inflammatory or mitogenic stimuli, COX-2 is also expressed constitutively in many tissues (eg, brain and kidney).1 Moreover, the vast majority of human cell types in fact express both COX-isozymes under appropriate circumstances. Paradoxically, COX-2 induction has been described in association with physiological bone marrow stem cell differentiation8 as well as with neoplastic transformation of intestinal epithelial cells.7

The expression of both COX-1 and COX-2 is increased in the synovia of inflamed joints8 and in carotid atherosclerotic plaques.9 In addition, COX-2 is considered a critical gene in the inherited predisposition to colon cancer.10 Failure to characterize such an association may reflect the variable contribution of other functionally important events operating upstream or downstream of COX-2 expression and inhibition.18

The substantial degree of interindividual variability in the pharmacokinetic/pharmacodynamic relation in response to oral dosing with selective COX-2 inhibitors19 suggests that COX-2 polymorphism might contribute to the individual patient’s response to such treatment. However, no studies addressing this question have been reported yet.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Papafili and coworkers20 report the identification of a new variant in the COX-2 promoter, −765G>C, and show that this variant locates within a putative binding site for Sp1, and has significantly lower (−30%) promoter activity compared with the −765G allele. The 5’ flanking region of the human COX-2 gene, principally

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Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000035402.68085.A0

10.1161/01.ATV.0000035402.68085.A0

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involved in regulating gene transcription, contains canonical TATA box and several putative transcription-factor binding sites, including CRE, NF-κB, NF-IL-6, GRE, PEA-3, AP2, C/EBP, TGF-β, and multiple Sp1 response elements. In particular, Sp1 is considered a positive activator of COX-2 transcription and acts through G-rich elements. Interestingly, deletion and forced mutation experiments altering this sequence have identified critical regions involved in inducing COX-2 gene transcription.

Notably, in the present study, Papafili and coworkers report that, among patients undergoing elective coronary artery bypass graft (CABG) surgery, those carrying the −765C allele had significantly lower plasma levels of C-reactive protein (CRP) compared with patients homozygous for −765G. CRP, a sensitive marker of low-grade inflammation, has been shown to aid cardiovascular risk prediction in a variety of clinical settings, including patients undergoing CABG or percutaneous coronary intervention. Thus, patients with baseline CRP levels ≥3 mg/L had significantly increased risk of recurrent ischemia at 1 to 6 years after CABG surgery. In the study by Papafili et al, baseline CRP levels of patients carrying −765GC or −765CC were only marginally and not significantly lower as compared with carriers of −765GG (1.8±0.3 vs 2.1±0.2 mg/L). However, mean CRP values were significantly lower for carriers of −765GC or −765CC at all times after bypass surgery, with peak levels recorded on day 3 of 150±9 (GC+CC) and 174±6 mg/L (GG), respectively. Although the 14% difference in average peak levels of CRP was statistically significant (P<0.05), some caution is warranted in interpreting these results. Thus, first, carriage of the rare allele (GC+CC combined) did not prevent an 80-fold increase in post-surgery CRP levels versus baseline. Second, individual CRP levels of the three genotypes showed substantial overlap after CABG with no clear-cut separation of carriers of the rare allele (data not shown). As the authors rightly point out, it remains to be seen if this common promoter variant in COX-2 will have clinical relevance. In a variety of colon cancer cell lines, the presence of either G or C at −765 made no difference in the level of expression of COX-2, and a direct role of this prevalent polymorphism in colon carcinogenesis seems unlikely (SM Prescott, Huntsman Cancer Institute, University of Utah, written communication, 2002).

In the meantime, what sort of additional studies should be done to address the many open questions raised by this interesting study? First of all, we need to know whether a 30% lower COX-2 promoter activity is associated with lower prostanoid production in human cells expressing this isozyme in response to pathophysiologic stimuli. This could be accomplished by investigating COX-2 expression and PGE2 production in whole blood monocytes challenged with LPS in vitro. This whole blood assay can also allow assessing the individual susceptibility to COX-2 inhibition by traditional NSAIDs or coxibs, either in vitro or ex vivo, in patients carrying the −765C allele. This type of investigation should be complemented with the measurement of in vivo PGI2 production, a process largely dependent on COX-2 activity in humans.

Mechanistically, reduced COX-2 expression possibly associated with the −765C variant should not be equated with a cardioprotective phenotype given the multifaceted aspects of COX-2 in vascular and renal biology. Moreover, it should be considered that COX-2 is but one of at least 10 different proteins involved in the biosynthesis and cellular actions of a single lipid mediator such as PGE2 (Figure 1). Thus, multiple sites of regulation and potential polymorphisms should be evaluated in future studies.

Finally, we are beginning to understand that the functional read-outs of COX-2 expression (eg, regulation of matrix metalloproteinases in inflammatory cells) may be importantly
modulated by the variable expression of downstream PGH-isomerases (eg, PGD-synthase versus PGE-synthase) that may preferentially couple to COX-isozymes in different pathophysiologic settings relevant to dynamic plaque instability (Figure 2).9,29

Acknowledgments

Supported by a grant from the Italian Ministry of Research and Education to the Center of Excellence on Aging of the University of Chieti. The expert editorial assistance of Daniela Basilico is gratefully acknowledged.

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doi: 10.1161/01.ATV.0000035402.68085.A0
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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