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Review

# Regulation of intracellular cyclooxygenase levels by gene transcription and protein degradation

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**Abstract**

Cyclooxygenases-1 and -2 (COX-1 and -2) catalyze the committed step in prostaglandin formation. Each isozyme subserves different biological functions. This is, at least in part, a consequence of differences in patterns of COX-1 and COX-2 expression. COX-1 is induced during development, and COX-1 mRNA and COX-1 protein are very stable. These latter properties can explain why COX-1 protein levels usually remain constant in those cells that express this isozyme. COX-2 is usually expressed inducibly in association with cell replication or differentiation. Both COX-2 mRNA and COX-2 protein have short half-lives relative to those of COX-1. Therefore, COX-2 protein is typically present for only a few hours after its synthesis. Here we review and develop the concepts that (a) COX-2 gene transcription can involve at least six different *cis*-acting promoter elements interacting with *trans*-acting factors generated by multiple, different signaling pathways, (b) the relative contribution of each *cis*-acting COX-2 promoter element depends on the cell type, the stimulus and the time following the stimulus and (c) a unique 27 amino acid instability element located just upstream of the

*Abbreviations:* COX, cyclooxygenase; $PGH_2$, prostaglandin endoperoxide $H_2$; NSAIDs, nonsteroidal anti-inflammatory drugs; LPS, lipopolysaccharide; CRE, cAMP response element; SRE, sterol response element; NF-κB, nuclear factor-kappa B; AP-1, Activator Protein-1; IL-1, interleukin-1; TNF, tumor necrosis factor; PMA, phorbol myristate acetate; HUVEC, human umbilical vein endothelial cells; PPRE, peroxisome proliferator response element; TKR, Tyrosine Kinase receptor; CR, Cytokine Receptor; TLR4, Toll Like Receptor 4; IL-1R, Interleukin-1 Receptor; TNFR, Tumor Necrosis Factor Receptor; PKA, cAMP dependent Protein Kinase; CREB, cAMP Response Element Binding Protein; ATF, Activating Transcription Factor; PLC, Phospholipase C; PI3K, Phosphatidyl-inositol-3-kinase; PKC, Calcium dependent Protein Kinase; PAK, p21 Associated Kinase; ERK, Extracellular signal-Regulated Kinase; MKK, Mitogen Activated Protein Kinase Kinase, also called MEK; MKKK, Mitogen Activated Protein Kinase Kinase Kinase, also called MEKK; JNK, c-Jun N-term Kinase; C/EBP, CAAT Enhancer Binding Protein; AP-1, Activator Protein-1; NF-κB, Nuclear Factor-kappa B; USF, upstream signaling factors; CAK, Ceramide Activated Kinase; TAK-1, Transforming growth factor-beta Activated Kinase-1; MyD88, Myocyte Differentiation Factor; IRAK, Interleukin-1 Receptor Associated Kinase; TRAF, Tumor Necrosis Factor Receptor Associated Factor; ECSIT, Evolutionary Conserved Signaling Intermediate in Toll; TRADD, Tumor Necrosis Factor Receptor Associated Death Domain; RIP, TNF Receptor Interacting Protein; ASK1, Apoptosis Signal-regulating Kinase; NIK, Nuclear Factor-kappa B Inducing Kinase; IKK, Inhibitor of κB Kinase; IκB, Inhibitor of κB; TRIF, TIR (Toll/IL-1 Receptor) domain-containing adaptor-inducing IFN-β; TRAM, TRIF-related adaptor molecule; TBK1, TANK-Binding Kinase 1.

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C-terminus of COX-2 targets this isoform to the ER-associated degradation system and proteolysis by the cytosolic 26S proteasome.


*Keywords:* Prostaglandin endoperoxide H synthase; Aspirin; COX-2; Gene regulation; ER-associated protein degradation; Nonsteroidal anti-inflammatory drugs

**Contents**



## 1. Introduction

Cyclooxygenases-1 and -2 (COX-1 and -2)[1] convert arachidonic acid, hydrolyzed from cell membrane phospholipids by a phospholipase $A_2$, to prostaglandin endoperoxide $H_2$ ($PGH_2$), the precursor of the prostanoids–thromboxane $A_2$ and the prostaglandins ($PGD_2$, $PGE_2$, $PGF_{2\alpha}$ and $PGI_2$) [1–4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat inflammation, pain and fever, and these actions are generally attributed to inhibition of COX-2 [5–7]. Prostanoids are lipid mediators that normally act in a paracrine and autocrine manner to coordinate intercellular events stimulated by a circulating hormone [1]. Their over-production is associated with pathologies such as tumorigenesis and arthritis whereas atherogenesis is associated with decreased formation of certain prostanoids [8–12].

COX-1 and COX-2 are the products of different genes [1,13,14]. COX-1 is present in many but not all cell types [15] and when present is usually expressed constitutively. COX-1 gene expression is developmentally controlled and can be upregulated by tumor-promoting phorbol esters or growth factors as seen with primary megakaryocytes and megakaryoblast cell lines (Table 1) [16–20]. In contrast to COX-1, COX-2 expression is typically transient. Depending on the cell type COX-2 expression can be rapidly induced by bacterial endotoxin (LPS), cytokines such as IL-1, IL-2, and TNF-α, growth factors, and the tumor promoter phorbol myristate acetate (PMA) [1,13,14] (Table 2). It should be noted that some cells in lung [21], brain [22] and kidney [23], pancreatic β-cells [24], and gastrointestinal carcinomas [11,25,26] exhibit constitutive COX-2 expression.

[1] The generic name COX for the enzyme that is more accurately termed PGHS has been used in most of the manuscript. PGHS is a more accurate term because the enzyme has both a peroxidase (POX) and a COX activity.