Prostaglandins & other Lipid Mediators 109–111 (2014) 14–22

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Review

Why do a wide variety of animals retain multiple isoforms of cyclooxygenase?

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ARTICLE INFO

Article history:
Received 30 October 2013
Received in revised form 10 March 2014
Accepted 26 March 2014
Available online 12 April 2014

Keywords:
Cyclooxygenase
Prostanoids
Animal kingdom
Genome duplication
Evolution

ABSTRACT

Cyclooxygenase (COX) has been cloned from the phyla Cnidaria, Mollusca, Arthropoda, and Chordata of the animal kingdom. Many organisms have multiple COX isoforms that have arisen from gene duplication. It is not well understood why there are multiple COX isoforms in the same organism, or when duplication of the *COX* gene occurred. Here, we summarize the current knowledge of the evolutionary history of COX in the animal kingdom and discuss the reasons why the multiple COX system has been retained so widely. The phylogenetic analysis suggests that all *COX* genes in animals may descend from a common ancestor and that the duplication of an ancestral *COX* gene might occur within each lineage after the divergence of the animal. In most instances, the expressions of multiple COX isoforms are separately regulated and these isoforms play different and important pathophysiological roles in each organism. This may be the reason why multiple COX isoforms are widely retained.

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http://dx.doi.org/10.1016/j.prostaglandins.2014.03.002
1098-8823/

1. Introduction

Oxygenated fatty acids are collectively named oxylipins. Many oxylipins have biological activities. One of the most pathophysiologically important groups of oxylipins in animals is the eicosanoids, which include prostanoids, leukotrienes, lipoxins, and hydroxyeicosatetraenoic acids [1]. Cyclooxygenase (COX), which is also known as prostaglandin (PG) H synthase or PG endoperoxide synthase (E.C. 1.14.99.1), catalyzes the initial step of prostanoid biosynthesis from polyunsaturated fatty acids. COX belongs to the heme-dependent myeloperoxidase superfamily and is a distant homolog of the pathogen-induced oxygenases and linoleate diol synthase of plants and fungi, respectively [2]. *COX* or *COX*-like genes have been found in animals, fungi, plants, unicellular organisms, and even in microbes [3,4].

All eutherians (also called placental mammals) that have been cloned so far have two isoforms of COX: COX-1 and -2. Moreover, multiple COX isoforms have been found in the many organisms, including invertebrates and vertebrates, which are known to express COX. It is not well understood when the evolutionary duplication of the *COX* gene occurred and why there are multiple isoforms of COX in a single organism. Here, we summarize the current knowledge of the evolutionary history of COX in the animal kingdom and discuss the reasons why the multiple COX system has been so widely retained (Table 1).

2. Characteristics of COX and its products

Prostanoids are produced when polyunsaturated fatty acids are released from the cellular membrane by phospholipase A_2 and then metabolized by COX and specific terminal prostanoid synthases. In mammals, arachidonic acid (5,8,11,14-eicosatetraenoic acid) is the major substrate for COX. This fatty acid is abundant in cell membranes, where it is esterified into glycerophospholipids. Upon stimulation of a target cell by relevant stimuli, phospholipase A_2 is activated and arachidonic acid is released from the phospholipids. COX has some unique characteristics. First, COX is a monotopic membrane-bound protein [5]; hence, it can only integrate into a single leaflet of the lipid bilayer. COX is largely located on the lumenal side of the endoplasmic reticulum membrane and the nuclear envelope [6]. After post-translational processing in the endoplasmic reticulum, the mature protein has an apparent molecular mass of 67–72 kDa and exists as a homodimer [7]. Additionally, COX is bifunctional: it catalyzes both a *bis*-oxygenase reaction (habitually referred to as the cyclooxygenase reaction), in which arachidonic acid is converted to PGG_2, and a peroxidase reaction, in which PGG_2 undergoes a 2-electron reduction to PGH_2 [8]. The *bis*-oxygenase and peroxidase sites are physically and functionally distinct within the COX protein [8]. Pharmacologists have long been interested in COX because it is the primary target of nonsteroidal anti-inflammatory drugs. These drugs, including aspirin and indomethacin, selectively inhibit the *bis*-oxygenase reaction. With the exception of aspirin, which covalently modifies the *bis*-oxygenase site by acetylating Ser-530 (in sheep COX-1) [9,10], these drugs compete directly with the substrate, arachidonic acid, for binding to the *bis*-oxygenase site and inhibit its activity, but they have little effect on peroxidase activity [11].

The product of the COX-catalyzed reaction, PGH_2, is the intermediate from which a variety of primary prostanoids, including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane (TX) A_2, are produced by terminal prostanoid synthases through reactions of isomerization, oxidation, or reduction. Terminal prostanoid synthases are a heterogeneous family of enzymes that are only expressed in specific cell types. In mammals, single types of PGI synthase [12] and TXA synthase [13], two types of PGD synthase [14],

Table 1
The protein IDs of COX isoforms mentioned in the text.[a]

Placental mammals
Human (*Homo sapiens*)
COX-1, NP_000953.2; COX-2, NP_000954.1
Sheep (*Ovis aries*)
COX-1, NP_001009476.1; COX-2, NP_001009432.1
Marsupials and egg-laying mammals
Tasmanian devil (*Sarcophilus harrisii*)
COX-1, ENSSHAP00000001746; COX-2, ENSSHAP00000019049
Tammar wallaby (*Macropus eugenii*)
COX-1, ENSMEUP00000006100; COX-2, ENSMEUP00000000284
The opossum (*Monodelphis domestica*)
COX-1a, XP_001370514.1; COX-1b1, XP_001370542.2; COX-1b2, XP_001370595.1;
COX-2-like, XP_001375945.1
Platypus (*Ornithorhynchus anatinus*)
COX-1-like, XP_001512281.2; COX-2-like, XP_001516281.2
Birds, reptiles, amphibians, and lobe-finned fishes
Turkey (*Meleagris gallopavo*)
COX-1-like, XP_003211401.1, COX-2-like, XP_003208549.1
Chicken or red jungle fowle (*Gallus gallus*)
COX-1, XP_425326.4; COX-2, NP_001161190.1
Zebra finch (*Taeniopygia guttata*)
COX-1, ENSTGUP00000007069; COX-2, ENSTGUP00000003584
Green Anole (*Anolis carolinensis*)
COX-1-like, XP_003230294.1; COX-2-like, XP_003223472.1
Chinese softshell turtle (*Pelodiscus sinensis*)
COX-1, ENSPSIP00000005203; COX-2, ENSPSIP00000011001
Western clawed frog (*Xenopus (Silurana) tropicalis*)
COX-1, NP_001258184.1; COX-2, NP_001025697.1
African clawed frog (*Xenopus laevis*)
COX-1, NP_001091389.1; COX-2, NP_001086946.1
Coelacanth (*Latimeria chalumnae*)
COX-1, ENSLACP00000001481; COX-2, ENSLACP00000021975
Ray-finned fishes
Platyfish (*Xiphophorus maculatus*)
COX-1-1, ENSXMAP00000003268; COX-1-2, ENSXMAP00000005187; COX-2b, ENSXMAP00000002436
Green spotted puffer (*Tetraodon nigroviridis*)
COX-1a, GSTENP00029010001; COX-1b, GSTENP00012293001; COX-2b, GSTENP00033631001
Pufferfish (*Takifugu rubripes*)
COX-1a, ENSTRUP00000042693; COX-1b, ENSTRUP00000046266; COX-2b, ENSTRUP00000010041
Atlantic croaker (*Micropogonias undulatus*)
COX-1, BAF52621.1; COX-2, BAF52620.1
Nile tilapia (*Oreochromis niloticus*)
COX-1-like, XP_003451513.1; COX-1-like, XP_003454212.1; COX-2-like, XP_003445100.2
Longhorn sculpin (*Myoxocephalus octodecemspinosus*)
COX-1a, ACO34913.1; COX-1b, ACH73272.1; COX-2b, ACH73267.1
Three-spined stickleback (*Gasterosteus aculeatus*)
COX-1a, ENSGACP00000018397; COX-1b, ENSGACP00000021267; COX-2b, ENSGACP00000009851
Japanese medaka (Oryzias latipes)
COX-1a, ENSORLP00000000625; COX-1b, ENSORLP00000006426; COX-2b, ENSORLP00000011863
Mummichog or Euryhaline Killifish (*Fundulus heteroclitus*)
COX-1a, ACH73266.1; COX-1b, ACH73265.1; COX-2, AAS21313.2
Atlantic cod (*Gadus morhua*)
COX-1, ENSGMOP00000015572; COX-2b, ENSGMOP00000011635
The brook trout (*Salvelinus fontinalis*)
COX-1, AAF14529.1; COX-2, AAD45896.1
Rainbow trout (*Oncorhynchus mykiss*)
COX-1b, NP_001117833.1; COX-2, NP_001117820.1; COX-2b, NP_001118139.1
Zebrafish (*Danio rerio*)
COX-1b, NP_705942.1; COX-2a, NP_705943.1; COX-2b, NP_001020675.1
Cartilaginous fishes and jawless vertebrates
Spiny dogfish shark (*Squalus acanthias*)
sCOX, AAL37727.1
Epaulette shark (*Hemiscyllium ocellatum*)
Partial COX-2, ADD59908.1
Sea lamprey (*Petromyzon marinus*)
lCOX, ACH73269.1; COX-1, ENSPMAP00000001004 (gene ID, ENSPMAG00000000916); COX-2a, ENSPMAP00000003793 (gene ID, ENSPMAG00000003485)
Atrantic hagfish (*Myxine glutinosa*)