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Review Article

A Review of Cyclooxygenase-2 Role in Fish

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Abstract

Cyclooxygenase (Cox) catalyses the first step in the synthesis of prostanoids, a large family of arachidonic acid (AA) and other polyunsaturated acids metabolites comprising prostaglandins, prostacyclin, and thromboxanes. Two isoforms of Cox are recognized: a constitutively isoform Cox-1 and an inducible isoform Cox-2. Cox-2 has been identified and characterized as an important moderator in a variety of physiologic and pathologic settings of fish, such as immunity, ovulation and adipogenesis. In spite of the great function of Cox-2 has been identified in fish, the evidence of regulation and molecular mechanism of Cox-2 remain unexplored. In this review, the roles and regulation of Cox-2 in fish physiologic and pathologic settings are summarized, and the molecular mechanisms underlying these effects are discussed.

Keywords: Cyclooxygenase-2; Immunity; Ovulation; Adipogenesis; Fish

Introduction

Oxygenated lipids are collectively called oxylipins, and many of them have biological activities. One of the most important groups of oxylipins in animals is the eicosanoids, which include prostanoids, lipoxins, leukotrienes, and hydroxyeicosatetraenoic acids, some of them are metabolites of Cox-2 [1]. Accumulated data of Cox-2 functions have been bright to light. In mammals, Cox-2 has been confirmed as an inducible enzyme in most tissues, and it can be rapidly induced by various extracellular and intracellular stimuli including growth factors, cytokines, mitogens and tumor promoters [2]. The induced Cox-2 plays important roles in physiologic and pathologic processes by regulating its signaling downstream [3,4]. Several critical reviews in relation to the role of Cox-2 on adipocytes biology, immunity and neurobiology have been published [5-8]. Nevertheless, these reviews were restricted to the regulatory effect of Cox-2 on mammalian cells or tissues. Compared with the mammals, there are fewer studies about the effect of Cox-2 in fish. Cox-2 has been identified in several fish species and characterized as a regulator of physiologic and pathologic processes [9-14]. However, the regulation and molecular mechanism of Cox-2 mostly remain unexplored in fish. Throughout this review, the regulation and the effects of Cox-2 on fish physiologic and pathologic processes metabolism are outlined and the underlying potential molecular mechanisms are discussed.

Characteristics of Cox-2 in fish

The mRNA of Cox-2 gene has been identified in many fish species. However, not all fish species possess the same forms of Cox-2. Both the rainbow trout (*Oncorhynchus mykiss*) and the zebrafish (*Danio rerio*) possess two Cox-2 forms, which named Cox-2a and -2b [15-18]. Whereas only one Cox-2 form has been found in the longhorn sculpin (*Myoxocephalus octodecemspinosus*) [17], pufferfish (*Takifugu rubripes*) [19], platyfish (*Xiphophorus maculatus*) [20], Nile tilapia (*Oreochromis niloticus*) [21], Japanese medaka (*Oryzias latipes*) [9], Mummichog (*Fundulus heteroclitus*) [22], rock bream (*Oplegnathus fasciatus*) [23], Atlantic salmon (*Salmo salar*) [24], gilthead sea bream (*Sparus aurata*) [25], Chinook salmon (*Oncorhynchus tshawytscha*) [26], European seabass (*Dicentrarchus labrax*) [21], Atlantic hagfish (*Myxine glutinosa*) [27] and large yellow croaker (*Larimichthys crocea*) [28]. In zebrafish and rainbow trout, both Cox-2a and Cox-2b possess AU-rich elements in their 3'-untranslated region implicating that both of them could be inducible. In zebrafish, two Cox-2 genes have different constitutive expression patterns which overlap in all sorts of organs [18]. In rainbow trout, both Cox-2a and Cox-2b mRNA are induced by 12-O-tetradecanoylphorbol-13-acetate (TPA), but only Cox-2a is induced by Lipopolysaccharides (LPS) [17]. All these results demonstrate that Cox-2a and Cox-2b gene could be regulated differentially, and their products may play potential pathophysiological roles which are different from each other.

Cox-2 is a membrane-associated protein and largely situated on the lumenal side of the nuclear envelope and the endoplasmic reticulum membrane [29]. Cox-2 can only integrate into a single leaflet of the lipid bilayer because of its monotypic membrane-bound characteristic [30]. After post-translational processing in the endoplasmic reticulum, the mature Cox-2 protein has an apparent molecular mass and binds to high-spin ferric heme to exist as homodimers [31]. In mammals, Cox-2 catalyze both a cyclooxygenase (also called bis-oxygenase) reaction, in which arachidonic acid (AA) is converted to Prostaglandin (PG) G2 by sequential oxygen additions at C-11 and C-15; and a peroxidase reaction, in which PGG2 undergoes a two-electron reduction to PGH2 followed by specific enzyme catalyzed reactions to yield PGD2, PGE2, PGF2α, PGI2 and TxA2 [31-35]. Prostaglandin receptors bind their specific PG to perform corresponding biology functions [3]. By using a combination of high performance liquid chromatography and mass spectrometry, conclusive evidences have been provided for the generation of Cox-2-derived products including PGD2/3, PGE2/3, PGF2/3α, PGI2 and low levels of TxA2 in fish [36]. However, the studies are just stuck on the surface of Cox-2, and the deep inner involvements of its molecular mechanism remain to be unearthed in fish.

The regulation and the effect of Cox-2 on immunity

The regulation and the effect of Cox-2 on immunity in response to pathogens: Cox-2 is an inflammatory related enzyme which is responsible for alteration of AA into PGs often associated with closely

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connected to the fish innate immune response [37-41]. Modulation of Cox-2 gene expression has been studied for parasite infections in many fish species. The Cox-2 mRNA expression was up-regulated in rainbow trout (*Oncorhynchus mykiss*) by *Myxobolus cerebralis*, *Tetracapsuloides bryosalmonae*, *Gyrodactylus derjavini* [42-44] and in sea bream (*Sparus aurata*) by *Photobacterium damselae* [45]. An increased induction of Cox-2 gene expression was detected in the LPS-stimulated kidney macrophage cell line from goldfish (*Carassius auratus*) [46] or Atlantic cod (*Gadus morhua*) [47], LPS-stimulated head kidney leukocytes from rainbow trout (*Oncorhynchus mykiss*) [48], and LPS-induced inflammatory responses in zebrafish (*Danio rerio*) [49-51]. The increased expression of Cox-2 may contribute to enhancing inflammation by converting AA into PGH2 to enhance inflammation during the initial phases of primary infections [46-50]. In contrast, the other substrate for Cox-2 is EPA, which is not only an inhibitor of AA metabolism, but also an alternative substrate for Cox-mediated synthesis of PGH3, an anti-inflammatory autacoid. Recent studies have reported that liver-specific expression of Fadsd6 or Elvol5a enhances the bio-synthesis of EPA and DHA in transgenic zebrafish, and this is sufficient to increase the survival rate in response to *Vibrio vulnificus* challenge by rapidly increasing the transcription of Cox-2 to convert EPA to PGH3 to diminish the inflammatory response [51]. Recent studies showed that the infections-induced over-expression of Cox-2 could be regulated by activator protein-1 (AP-1) and nuclear transcription factor kappa-B (NF-κB) pathways in zebrafish (*Danio rerio*) [49-50] and the *cis*-acting elements of NF-κB and AP-1 within Cox-2 promoter have been found in large yellow croaker (*Larmichthys crocea*) [52]. Therefore, pathogens induced Cox-2 gene expression could be increased via NF-κB and AP-1 to regulate inflammation.

The regulation and the effect of Cox-2 on immunity in response to fatty acids: As is known to all, fatty acids, which comprise the membrane phospholipids, contribute to the physical and functional properties of the plasma membrane. Free fatty acids exist at low levels in the cells, but the bulk of fatty acids is linked with other molecules to form complex lipids with different biology functions. As precursors of PGs and leukotrienes, fatty acids regulate gene expression by influencing transcription factor activation or intracellular signal transduction mechanisms [53-54].

Several monounsaturated or polyunsaturated fatty acids are involved in different immune functions, exerting their influence by generating lipid peroxides, synthesizing eicosanoid, changing membrane fluidity, regulating gene expression, modulating intestinal microbiota, or altering antigen presentation [55]. Compared to fish oil and linseed oil dietary, the soybean oil dietary could induce higher expression of Cox-2 in Senegalese sole (*Solea senegalensis*) [56]. The mRNA expression of Cox-2 is significantly decreased with the increasing level of dietary conjugated linoleic acid (CLA) and generally paralleled well with the expression of IL-1β, known as the immunological parameters in large yellow croaker (*Larmichthys crocea*) [57]. The reduction in dietary ARA/EPA results in a significant decrease of PGE2 concentration in kidney, brain and heart in turbot (*Scophthatmus maximus*) [58]. Besides, gilthead seabream (*Sparus aurata*) with higher levels of ARA in plasma neutral lipids shows the lower levels of PGE2 [59]. These results implicit that fatty acids influence the production of PGE2 involved in the regulation of Cox-2 transcription.

The regulation and the effect of Cox-2 on immunity in response to metals: The basic function of nutritionally vital metals is to provide some components of an essential enzymatic or biochemical reaction [60]. In higher vertebrates, metals have been studied in relation to their immunological roles, including iron (linked to hemoglobin), copper, zinc, and manganese (linked to antioxidant enzymes), calcium, phosphorus and magnesium (linked to hard tissue mineralization) and selenium (linked to glutathione peroxidase). However, high metals concentration also can be harmful for all living organisms because of their tendency to accumulate and toxicity persistence [61]. The levels of these metals exceeding permissible limits in different fish species has been demonstrated [61-65].

Mitogen-activated protein kinases (MAPKs) are a family of proline-directed Ser/Thr protein kinases, which play important roles in regulating cell physiology [66-67]. They include extracellular signal-regulated kinases 1&2 (ERK1/2) that is related to cell survival and proliferation [68], c-Jun N-terminal kinases (JNKs) and p38 MAPK cascades that contribute to the inflammation and programmed cell death [67-68]. The MAPKs pathways are well conserved across vertebrates and all members of the MAPK family have been identified in fish [70-71]. The expression of Cox-2 and the level of PGE2 show a significant increase after 24 h of exposure to copper in zebrafish (*Danio rerio*) larvae [72]. A recent study showed that the Cox-2 transcription could be up-regulated by the activity of MAPKs pathway in large yellow croaker [28]. In mammals, chronic lead-exposure increased the participation of Cox-2-derivated prostanoids induced by an early activation of ERK1/2 and a delayed activation of p38 MAPKs without effects on JNK [73]. Therefore, we could infer that the Cox-2 and its metabolite PGE2 are implicated in the resolution phase of inflammation induced by metals may through the MAPK pathway. However, the detailed mechanism need to be further researched.

The regulation and the effect of Cox-2 on ovulation

Cox-2 is also known as a key moderator for the reproductive function. Compared with the Cox-1, Cox-2 mRNA was expressed at rarely detectable levels in ovarian of adult female zebrafish (*Danio rerio*) [74-76] and brook trout (*Salvelinus fontinalis*) [77], while it is always expressed at a dominant level throughout the whole ovary in medaka fish (*Oryzias latipes*) [9]. Though the expression of Cox-2 is different among fish species, it is a crucial factor for ovulatory process. Some research on gene expression showed transcriptional changes of Cox-2 that support its role in ovulation and spawning. Research has shown that significant elevations in ovarian Cox-2 mRNA coincide with the approximate time of ovulation, while during the peri-spawning to post-spawning period Cox-2 level had returned to control levels in zebrafish (*Danio rerio*) [75-79]. When Cox-2 was inhibited by indomethacin (INDO), the process of ovulation was effectively obstructed [78-81]. This extremely transient change in mRNA Cox-2 expression suggests a tightly regulated system, which suggests that Cox-2 is involved in the development of follicle and helps to push the ovulatory process forward.

Ovulation is a release process of a mature fertilizable ovum from the ovarian follicle [82], which is analogous to pro-inflammatory responses [83-84]. The role of PGs during the ovulation has been

intensive investigation in a number of species, including goldfish (*Carassius auratus*), zebrafish (*Danio rerio*), Atlantic croaker (*Micropogonias undulatus*) and yellow perch (*Perca flavescens*) [85-88]. Many researchers have strongly suggested that PGs could promote the process of ovulation *in vivo* and *in vitro* under the modulation of Cox-2 in fish [88-92]. However, the nature of their role is somewhat contested, with the apparent position of PGs within the physiological cascade (upstream or downstream of ovulation) and the relevant isoform(s) varying from species to species [86,93-95]. More specifically, PGE2 interferes with the ovulation and is produced in the large preovulatory follicle under the regulation of Cox-2 [96-98]. The concentration of PGF2α in the ovarian was significantly increased at the time of spawning in zebrafish (*Danio rerio*) [75-76], and similarly, exogenous PGF2α significantly reduced the amount of oocytes remaining in the ovaries of Pacu (*Piaractus mesopotamicus*) [99]. Although these findings strongly imply that the generation of PGs is crucial for successful ovulation in fish, the specific function of PGs in ovulation and spawning remains poorly characterized in most species.

The regulation and the effect of Cox-2 on adipogenesis

In mammals, the functions of Cox-2 during adipogenesis are widely reported. In 3T3-L1 cells, the intracellular lipids accumulation is increased by the expression of Cox-2 [100], and repressed by a selective Cox-2 inhibitor pre-treating during the early phase of adipogenesis [101]. The explication of regulation mechanism and function of Cox-2 during adipogenesis also ascribe to the PG-mediated regulation of adipogenesis, which is complicated because of different functions of different PG [97]. PGD2 and its metabolite PGJ2 activate the progression of adipogenesis during the middle-late phase [96-98,102,103], while both PGE2 and PGF2α form a positive feedback loop that coordinately suppressed the early phase of adipogenesis through the increased Cox-2-mediated production of anti-adipogenic PGE2 and PGF2α themselves and his suppression is cleared by dysregulation of CREB-mediated Cox-2 expression [97-98]. In addition, PGI2 and PGJ2 (a metabolite product of PGD2) have been shown to bind PPARδ and PPARγ, respectively, to activate transcriptional targets directly [104].

In fish, Cox-2 also plays a role in lipometabolism. A high negative correlation is observed between plasma leptin and plasma PGE2 concentration in gilthead seabream (*Sparus aurata*), which is agree with the results found in mammals [105]. With the increase of dietary CLA level, an increasing lipid content of the whole body and muscle and a decreasing level of Cox-2 gene expression are observed, which may result from decreasing fatty acid oxidation reflecting by reduced transcription of PPARα in juvenile large yellow croaker *(Larmichthys crocea*) [57]. Due to the limited research about the function of Cox-2 in lipometabolism, it is hard to say how Cox-2 regulates adipogenesis. Deduced from studies in mammals, the regulation of Cox-2 in lipometabolism may through PPARs.

Concluding Remarks and Perspectives

In summary, Cox-2 is involved in immunoregulation, ovulatory and adipogenesis process and the function of Cox-2 mainly ascribe to diverse functions of diverse PGs. Though more and more researchers have been drawing attention by the various function of Cox-2, the study of Cox-2 in fish is still in the infant period compare to the mammals. Cox-2 has been identified in some fish species, but it is not clear why some of them loss one Cox-2 duplicate. The possibility that the vanished Cox-2 duplicate has not been identified cannot be ruled out. Modulation of Cox-2 gene expression is a complicated process that varies in responds to different stimulation and even in different cell types. These factors and conditions determine which transcription factors bind to the response elements of Cox-2 gene and the interplay among the diverse regulatory transcription factors also remains to be illuminated. In mammals, miR-143 and miR-137, involved in the MAPK and PI3K/AKT signaling pathway respectively, suppress translation or accelerate the degradation of the Cox-2 mRNA [106,107]. Up to now, no finding has been reported about the post-transcriptional modification of Cox-2 in fish. Thus, the detailed mechanisms about the transcription and translation of Cox-2 need to be elucidated. Cox-2 and its metabolic PGs play a conserved role in immunity, ovulation and adipogenesis in vertebrates, but there are still some differences between mammalian and non-mammalian species. The molecule mechanism of the mammalian does not wholly extend to non-mammalian vertebrate species. The detailed mechanism of Cox-2 and PGs signal to downstream effectors warrant further investigation in fish.

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