The use of Cox-2 and PPARγ signaling in anti-cancer therapies (Review)

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Abstract. Increased production of the pro-inflammatory enzyme cyclooxygenase-2 (Cox-2) and altered expression and activity of peroxisome proliferator-activated receptor γ (PPARγ) have been observed in many malignancies. Both the PPARγ ligands and the Cox-2 inhibitors possess anti-inflammatory and anti-neoplastic effects *in vitro* and have been assessed for their therapeutic potential in several pre-clinical and clinical studies. Recently, multiple interactions between PPARγ and Cox-2 signaling pathways have been revealed. Understanding of the cross-talk between PPARγ and Cox-2 might provide important novel strategies for the effective treatment and/or prevention of cancer. This article summarizes recent achievements involving the functional interactions between the PPARγ and Cox-2 signaling pathways and discusses the implications of such interplay for clinical use.

Contents

1. Introduction

Despite extensive research during the last decade, the role of cyclooxygenase-2 (Cox-2) and peroxisome proliferator-activated receptor γ (PPARγ) in cancerogenesis remains controversial. Therefore, potential clinical outcomes of their respective inhibitors and activators are still elusive. Nevertheless, the effects of these agents are promising enough to prompt further research of the involved cell signaling pathways. Recently, this research has revealed multiple interactions between Cox-2 and PPARγ pathways that may be important for anti-cancer therapies.

Cyclooxygenase is the rate-limiting enzyme involved in the synthesis of prostaglandins (PGs). There are two isoforms of this enzyme, the constitutive Cox-1 and the inducible one, Cox-2. *cox-2* gene expression is induced by a wide variety of stimuli in cells of organisms fighting inflammatory disorders and cancer. Therefore, the level of the Cox-2 protein is elevated in various types of cancer cells in comparison with non-malignant tissues (1). A growing body of evidence suggests an association of Cox-2 with tumor development, aggressivity, resistance to standard therapy and unfavorable patient outcome. Cox-2 may participate in cancer development through multiple mechanisms, including stimulation of growth, migration, invasiveness, resistance to apoptosis and enhancement of angiogenesis (2).

In addition to a number of pre-clinical studies revealing the anti-proliferative and pro-apoptotic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and specific Cox-2 inhibitors, multiple population studies have documented that chronic intake of NSAIDs is associated with a decreased incidence of colorectal, prostate, bladder, breast and lung cancers (3-8). There is also clinical evidence demonstrating the reduction of colorectal polyps by the Cox-2 inhibitor celecoxib (9). Several pre-clinical and clinical studies have repeatedly demonstrated that specific Cox-2 inhibitors are promising enhancers of chemotherapy (10-13).

Nevertheless, the safety of Cox-2 inhibitors in anti-cancer therapies is still a matter of debate. Although the tumor-suppressive effects of NSAIDs were attributed to their ability to act as Cox-2 inhibitors, some effects of these agents cannot be explained by inhibition of Cox-2, as these drugs can also provoke responses in Cox-2-negative cells. This suggests that there are some Cox-2-independent pathways involved in the anti-cancer effects of these agents. Therefore, inhibition of Cox-2 activity and PG synthesis is not necessarily beneficial in general; moreover, it can induce even adverse effects (14,15). Considering both the benefits and risks of Cox-2 inhibition, there is still great concern regarding the potential use of Cox-2-specific inhibitors in combination with other anti-cancer therapeutics, including the PPAR ligands.

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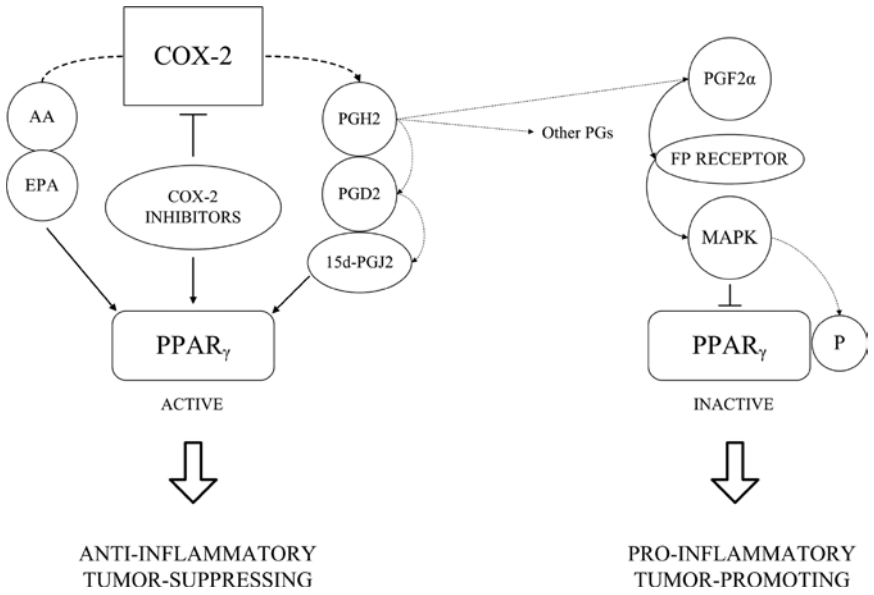

Figure 1. Cox-2 regulates the activity of PPARγ. Arachidonic acid (AA) and eicosapentaenoic acid (EPA) are substrates for Cox-2, and they undergo conversion to various prostaglandins (PGs). AA, EPA, Cox-2 inhibitors and certain prostaglandins (15d-PGJ2) bind and activate nuclear receptor PPARγ. Other prostaglandins (PGF2α) bind to the G-protein-coupled cell surface receptors (FP) and activate mitogen-activated protein kinases (MAPKs) that phosphorylate (P) PPARγ, thus inhibiting its activity.

PPARγ is a member of the nuclear hormone receptor superfamily functioning as a ligand-dependent transcription factor (16). PPAR affects gene expression either directly through binding to peroxisome proliferator response elements (PPREs) located upstream of controlled genes or indirectly by interfering with other pathways driven by transcription factors resulting in the silencing of gene transcription.

Natural ligands of PPARγ are mostly metabolites of arachidonic acid; they include polyunsaturated fatty acids, cyclopentenone prostaglandin 15-deoxy-D12,14 prostaglandin J2 (15d-PGJ2) and oxidized lipids (17,18). Synthetic ligands include the thiazolidinediones (such as troglitazone, pioglitazone and rosiglitazone) that have been clinically used in the treatment of type II diabetes (19-21).

Recently, the role of PPARγ in various human cancers has been intensively studied. PPARγ expression has been reported in a variety of tumors, including colon (22), breast (23), prostate (24-26), stomach (27), lung (28), pancreas (29), ovarian (30) and cervical tumors (31). Both natural and synthetic PPARγ ligands inhibit cancer cell growth *in vitro* and *in vivo* (32,33). These studies, coupled with clinical trials (34,35), suggest that PPARγ is a novel target for the development of novel and effective anti-cancer therapies.

However, there is considerable concern regarding the significance and safety of PPARγ ligands used as anti-cancer drugs (36). The mechanism of their action is still elusive, since both PPARγ-dependent and PPARγ-independent pathways mediate their anti-proliferative and pro-apoptotic effects. Furthermore, the biological significance of PPARγ is still a controversial issue. There are studies illustrating even tumor-promoting effects of PPARγ, in particular in colon and breast cancer models (37-39).

Therefore, both Cox-2 and PPARγ are considered as possible targets for anti-cancer therapy and prevention, but applications of Cox-2 inhibitors as well as PPARγ ligands in therapy remain controversial. Detailed understanding of the molecular mechanisms and signaling pathways may elucidate the pros and cons of their action and provide more effective therapeutical approaches. Recent findings involving the cross-talk between Cox-2 and PPAR signaling may have such therapeutically relevant implications. This review summarizes the current knowledge on the interplay between Cox-2 and PPARγ signaling pathways and focuses on the benefits and risks of the combined application of Cox-2 inhibitors and PPARγ ligands in anti-cancer therapy.

2. Cox-2 and regulation of PPARγ

Several components of the Cox-2 metabolic pathway were shown to activate PPARγ (Fig. 1). The molecules serving as substrates as well as products of Cox-2 enzymatic activity include the PPARγ ligands. Various polyunsaturated fatty acids (PUFAs), such as arachidonic (AA) and eicosapentaenoic acid (EPA), once released from the membrane phospholipids by phospholipase A2 (PLA2), can either be metabolized by Cox or enter the nucleus to activate PPARγ (40,41). The ability of PUFAs to activate PPARγ may depend on expression and activity of Cox-2. The effect of EPA on the transactivation function of PPARγ is weaker in pancreatic cancer cells expressing Cox-2 than in Cox-2-negative cells, presumably due to the rapid metabolization of EPA by Cox-2. Nevertheless, the EPA-induced growth inhibition of pancreatic (40) and colon cells (42) is mediated by the activation of PPARγ.

Various Cox-2 products can also bind and activate PPARγ. Cox-2 catalyzes formation of a chemically unstable prostaglandin H2 (PGH2) which can be further converted to various prostanoids (e.g., PGE2, PGD2 and PGF2α) by tissue-specific isomerases. Dehydration of these PGs leads to the formation of cyclopentenone prostaglandins PGA2, PGA1 and PGJ2 (43). 15d-PGJ2 is formed from PGJ2 by further nonenzymatic

rearrangements and dehydration. While prostaglandins PGE2, PGF2α and PGD2 transduce their signals through binding to the G-protein-coupled cell surface receptors (44), cyclopentenone prostaglandins (e.g., 15d-PGJ2) are known ligands of PPARγ.

While PGE2, which is considered to be the major Cox-2 product, possesses pro-inflammatory and tumor-promoting effects (45,46), accumulating data suggest that 15d-PGJ2 acts as an anti-inflammator (47). Therefore, both pro- and anti-inflammatory effects can be controlled by Cox-2. During the early phase of inflammation, Cox-2 expression and activity is induced and associated with increased synthesis of PGE2. During the later phase, Cox-2 may be involved in the resolution of acute inflammation by generating an alternate set of PGs, such as those of the cyclopentenone family (15). Anti-inflammatory effects of cyclopentanone PGs are mediated either by binding/activating PPARγ or by interaction with other target molecules, such as NF-κB or IκB kinase (43).

Although the anti-inflammatory effect of 15d-PGJ2 is well known and accepted, the results concerning the effects of cyclopentanone PGs on tumor growth are still conflicting. 15d-PGJ2 was found to possess anti-neoplastic properties; it inhibits cell growth, induces terminal differentiation and apoptotic cell death in a variety of tumor cells, thereby promoting phenotypic changes associated with a less malignant status (23,35,48). In contrast, there are reports demonstrating the tumor-promoting action of 15d-PGJ2 as well (49,50).

On the other hand, Cox-2 can produce metabolites inhibiting PPARγ. PGF2α, acting through its cell surface G-protein-coupled receptor, inhibits PPARγ through MAP kinase-dependent phosphorylation. The antagonistic effects of PGJ2 and PGF2α on the activity of PPARγ result in opposing effects of these compounds on adipocyte differentiation. PGJ2 stimulates, while PGF2α blocks, adipogenesis (51). Similarly, antagonistic effects of 15d-PGJ2 and PGF2α were observed in B lymphoma cells; 15d-PGJ2 induced apoptosis via PPARγ activation, while PGF2α pretreatment attenuated its cytotoxic effect (52).

Moreover, not only the Cox-2 substrates and products can be PPAR ligands, PPARγ activity can also be stimulated by Cox-2 inhibitors. Ibuprofen, indomethacin and some other NSAIDs can both inhibit Cox-1/Cox-2 and function as PPARγ ligands in various cell systems as well (53,54). Celecoxib, a selective Cox-2 inhibitor, binds and activates PPARγ in rat mesangial cells (55). NS-398, another selective inhibitor of Cox-2, has been found to increase expression of PPARγ, PPARα and PPARβ in human fibroblasts (56). PPARγ expression was up-regulated in lung tumors in mice treated with nimesulfide, another Cox-2-specific inhibitor, when compared to tumor tissue of untreated mice (57). Indomethacin and other NSAIDs as well as NS-398 induced growth suppression and apoptosis associated with activation of PPARγ in rheumatoid synovial cells. 15d-PGJ2 and troglitazone, other PPARγ ligands have a similar inhibitory effect on the growth of synovial cells (58). Mechanisms of celecoxib-induced inhibition of hepatocellular carcinoma cell growth involve up-regulation of PPARγ (59). Therefore, activation of PPARγ is considered as one of the Cox-2-independent mechanisms responsible for the anti-inflammatory and anti-neoplastic effects of NSAIDs. Induction of PPARγ can account for the puzzling fact that selective Cox-2 inhibitors display anti-proliferative properties in cells lacking Cox-2 expression. It has been demonstrated that JTE-522, a Cox-2-specific inhibitor, interferes with the growth of Cox-2-negative HCC cells. This growth arrest is, in part, mediated by up-regulation of PPARγ protein expression (60). We conclude that PPARγ activity can be induced by several Cox-2 inhibitors and possibly participates in mediating the effects that cannot be attributed to the Cox-2 inhibition itself.

3. PPARγ ligands as Cox-2 activators

There are numerous studies documenting PPARγ ligand-induced Cox-2 up-regulation. Endogenous PPARγ ligand 15d-PGJ2, as well as synthetic PPARγ agonists, stimulate *cox-2* expression and activity in several cell types (49,61-66). However, the mechanism of this up-regulation varies significantly in different cell types and according to the specificity of the activating stimulus. *cox-2* transcription can be directly activated by PPARγ itself, and the peroxisome proliferator responsive element (PPRE) was indentified in the *cox-2* promoter sequence (61). The artificial construct containing the *cox-2* promoter including PPRE was activated in cells cotransfected with vectors encoding PPARα, δ and γ. Similarly, PPRE in the *cox-2* promoter was required for the PPARγ ligand rosiglitazone-induced activation of the reporter (62,67). PPARγ-dependent activation of Cox-2 by rosiglitazone was observed in smooth muscle cells, and it was sensitive to the PPARγ antagonist (63).

Notably, several Cox-2 inhibitors (such as ibuprofen, sulindac sulfide, NS-398 and mefenamic acid) while inhibiting Cox-2 activity, also enhance its expression, possibly by binding and activating PPARγ (61). It was demonstrated that indomethacin and naproxen stimulate *cox-2* expression at concentrations that were shown to activate PPARγ (64). Detailed study of the mechanism of indomethacin-, flurbiprofen- and NS-398-induced Cox-2 expression was performed by Pang *et al* (68). They found that NSAIDs as well as 15d-PGJ2 induced the transcriptional activity of the Cox-2-reporter construct containing the PPRE, but had no effect on the Cox-2-reporter construct lacking the PPRE. These results revealed that stimulation of *cox-2* expression by NSAIDs involves PPARγ activation and provide the first direct evidence that the PPRE in the promoter is required for NSAID-induced Cox-2 expression.

On the other hand, there are multiple studies suggesting that Cox-2 activation induced by some PPARγ ligands is PPARγ-independent. In human synovial fibroblasts treated with both natural and synthetic PPAR ligands, Cox-2 mRNA and protein synthesis were up-regulated in a dose-dependent manner. It is interesting to note that synthetic ligands WY-14,643 and ciglitazone induce Cox-2 expression via PPAR/PPRE-dependent, promoter-based transcriptional activation, but 15d-PGJ2 probably does so by a PPAR-independent mechanism (64). Results obtained by Lee *et al* (65) in articular chondrocytes are in agreement with this observation; PPARγ antagonists do not block 15d-PGJ2-induced Cox-2 expression. However, not only 15d-PGJ2, but even synthetic PPARγ ligands perform PPAR-independent

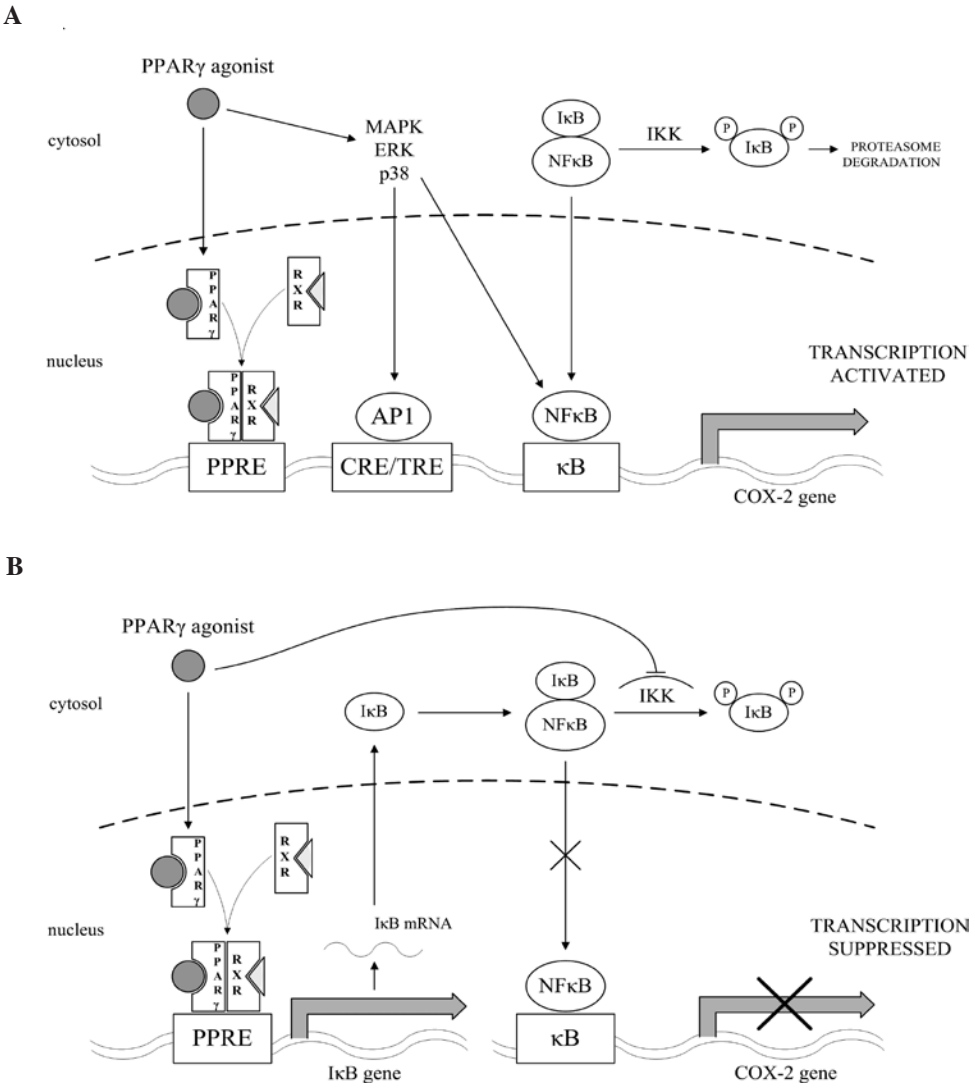

Figure 2. PPARγ ligands can induce (A) or suppress (B) expression of *cox-2*. (A) The PPARγ agonists can induce expression of *cox-2* in either a PPARγ-dependent or -independent manner. PPARγ-dependent activation is initiated by interaction of the PPARγ-specific ligand with nuclear receptor that forms a heterodimer with ligand-activated retinoic X receptor (RXR). The PPARγ/RXR heterodimer then binds the peroxisome proliferator responsive element (PPRE) in the promoter region of the *cox-2* gene and activates its transcription. PPARγ-independent activation can be also induced by PPARγ agonists by stimulation of the MAPK pathway that results in activation of NF-κB and AP-1. These transcription factors also regulate transcription of *cox-2*. (B) PPARγ agonists can also suppress cytokine-induced expression of *cox-2* by both a PPARγ-dependent and -independent manner. The PPARγ/RXR heterodimer up-regulates transcription of IκB that prevents NF-κB from activating transcription of *cox-2*. PPARγ agonists can also inhibit the IκB kinase (IKK), thus preventing IκB phosphorylation (P), translocation of NF-κB to the nucleus and transcription of its target genes.

cox-2 induction. Troglitazone-induced Cox-2 expression in human lung epithelial A549 cells was not mediated via PPARγ but via activation of the ERK and PI3K pathways instead (66). Another signaling transducer involved in *cox-2* up-regulation by PPARγ ligands is MAPK p38. Both 15d-PGJ2 and synthetic PPARγ ligand GW7845 induced Cox-2 synthesis in the MC615 cartilage cell line. Pretreatment of the cells with the p38-specific inhibitor repressed expression of Cox-2 induced by both 15d-PGJ2 and GW7845 (69). In neuronal cells, p38 was also involved in Cox-2 induction by 15d-PGJ2, and again an involvement of PPARγ was excluded (70). These findings correspond with the fact, that p38 is an activator of NF-κB during inflammation and *cox-2* belongs among theNF-κB-regulated genes (71,72). This suggests a possible signaling pathway leading to Cox-2 up-regulation by 15d-PGJ2 without PPARγ participation.

In conclusion, both natural and synthetic PPARγ ligands are able to activate *cox-2* expression either by PPARγ-dependent or -independent mechanisms, and the latter might be mediated via activation of the MAPK pathway (Fig. 2A).

4. PPARγ ligands as Cox-2 suppressors

There are also studies reporting that PPARγ ligands have two opposing effects on *cox-2* expression. Although NSAIDs can increase the basal Cox-2 level, they inhibit cytokine-induced *cox-2* expression. For example, flufenamic acid inhibits lipopolysaccharide (LPS)- and tumor necrosis factor α (TNFα)-induced *cox-2* expression in RAW 264.7 and HT-29 cells, whereas it induces *cox-2* expression in the absence of LPS or TNFα. However, the inhibitory effect of NSAIDs on cytokine-induced *cox-2* expression is mediated rather via

NF-κB inhibition than PPARγ activation, while NSAID-induced *cox-2* expression is mediated through signaling pathways that do not require the activation of MAPKs and NF-κB, but might involve activation of PPARγ (73). Not only NSAIDs but also endogenous PPARγ ligand 15d-PGJ2 inhibits IL-β-induced Cox-2 up-regulation. Also in this case, Cox-2 down-regulation is mediated by NF-κB inhibiton but not by PPARγ activation (74).

However, in cells with overexpressed and constitutively active Cox-2, some PPARγ activators can inhibit *cox-2* expression as well (75,76). It is notable that some studies proved PPARγ involvement in Cox-2 down-regulation (77), while others described Cox-2 down-regulation as a PPARγ-independent phenomenon (76). Hazra and Dubinett (76) used dominant negative PPARγ to show that ciglitazone decreases *cox-2* promoter activity in a PPARγ-independent manner. On the other hand, Bren-Mattison *et al* (77) showed that PPARγ overexpression suppresses *cox-2* transcription. This discrepancy is explained by the fact that Cox-2 is not down-regulated due to PPARγ trans-repressing effect but due to the inhibition of some other transcription factors such as NF-κB or C/EBP. The *cox-2* gene is under the control of NF-κB and is negatively regulated by various PPARγ ligands via either PPARγ-dependent or -independent repression of NF-κB (17). PPARγ can inhibit NF-κB by stimulation of IκB transcription (78). PPARγ-induced IκB synthesis accounts for at least some of the anti-inflammatory effects of PPARγ ligands (79-81). 15d-PGJ2 can inhibit NF-κB independently of PPARγ as well, either by inhibiting the IκB kinase, therefore preventing IκB phosphorylation and degradation (82,83), or directly by interacting with NF-κB (84).

In conclusion, 15d-PGJ and some synthetic PPARγ ligands can down-regulate the cytokine-stimulated and in some cases unstimulated *cox-2* expression through inhibition of NF-κB or other transcription factors which can occur either via PPARγ-dependent or PPARγ-indepedent mechanisms (Fig. 2B).

5. Cox-2 inhibitors and PPARγ ligands can act synergistically to suppress Cox-2 and activate PPARγ

Despite the facts disclosed in the previous sections documenting the complex and somewhat ambivalent interplay between Cox-2 and PPARγ pathways, several studies indicate a possible coordinated effects of Cox-2 inhibitors and PPARγ activators and suggest the combined treatment as a promising therapeutic strategy.

Simultaneous targeting of Cox-2 and PPARγ was found to result in the synergistic inhibition of mammary cancer development (85). Treatment of MDA-MB-231 breast cancer cells with NS-398 (a Cox-2 inhibitor) or ciglitazone (a PPARγ ligand) inhibited cell proliferation and markedly increased rates of apoptosis. Compared to using both agents separately, combined treatment resulted in the synergistic inhibition of cell proliferation and induction of apoptosis. Thus, the combinatorial targeting of Cox-2 and PPARγ possesses a stronger anti-neoplastic effect *in vitro* than targeting each molecule separately (86). This result was confirmed with a different combination of the Cox-2 inhibitor (celecoxib) and PPARγ agonist (F-L-Leu) in animal breast cancer models (87,88). Celecoxib and F-L-Leu cooperated in the growth inhibition of a mouse mammary adenocarcinoma cell (MMAC-1) line *in vitro*. In mice the combined diet of celecoxib and F-L-Leu delayed the median age of death due to mammary tumors more effectively than celecoxib alone (88).

Breast cancer is not the only possible candidate for combinatorial therapy with Cox-2 inhibitors and PPARγ ligands, as the combination of NS-398 and rosiglitazone exerted synergistic effects in the inhibition of proliferation and induction of apoptosis of human pancreatic carcinoma cells as well (89). Narayanan *et al* (90) showed that low doses of celecoxib in combination with DHA which functions as a PPAR ligand in prostate cancer cells could be a highly promising strategy for prostate cancer chemoprevention while minimizing undesired side effects. Combined treatment with DHA and celecoxib increased PPARγ expression and activity, decreased the Cox-2 level, inhibited cell growth and induced apoptosis more efficiently than each agent alone.

Badawi *et al* (87) examined the effect of a combination of celecoxib and F-L-Leu on the development of methylnitrosourea (MNU)-induced rat mammary gland carcinogenesis. They found that celecoxib and F-L-Leu significantly reduced tumor incidence and multiplicity in a synergistic manner. The molecular mechanism underlying the anti-cancer effect of these agents is partially based on Cox-2 down- and PPARγ up-regulation. Both celecoxib and F-L-Leu separately inhibit the production of Cox-2 and PGE2 and up-regulate expression of PPARγ. Combined treatment further potentiates these effects.

6. Conclusion

There is cross-talk between the Cox-2- and PPARγ-driven pathways. An inverse correlation between Cox-2 and PPARγ expression/activity was demostrated to occur in various types of human cancers, and it significantly affects carcinogenesis (22,23,91,92); the weaker the expression of PPARγ, the higher the level of Cox-2/PGE2 and the more tumor development progresses (23,93). Inhibition of Cox-2 and activation of PPARγ prevent cancer growth *in vitro* and *in vivo*. There is now strong evidence documenting that both Cox-2 inhibitors and PPARγ agonists exert their anti-tumor effects not only via their respective targets, Cox-2 and PPARγ. Various Cox-2-independent anti-inflammatory and anti-neoplastic effects of NSAIDs can be mediated via PPARγ activation (60), and Cox-2 suppression might be responsible for the anti-cancer effects of PPARγ ligands (77). Combined treatment with both classes of agents can exert an additive, if not synergistic, inhibition in human cancer (87). However, the interplay between these systems is very complex. Several components of the Cox-2 metabolic pathway regulate PPARγ activity, and PPARγ ligands modulate *cox-2* expression, both positively and negatively, both in PPARγ-dependent and PPARγ-independent manners. Although several studies have demonstrated the synergistic anti-cancer effects of PPARγ ligands in combination with Cox-2 inhibitors, particularly in breast cancer models, further pre-clinical and clinical trials are required to clarify the role that simultaneous Cox-2 inhibition and PPARγ activation may play in the treatment of human cancer.

Acknowledgements

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