


Overview on the Discovery and Development of Anti-Inflammatory Drugs: Should the Focus Be on Synthesis or Degradation of PGE₂?

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Abstract: Inflammation is a protective response that develops against tissue injury and infection. Chronic inflammation, on the other hand, is the key player in the pathogenesis of many inflammatory disorders including cancer. The cytokine storm, an inflammatory response flaring out of control, is mostly responsible for the mortality in COVID-19 patients. Anti-inflammatory drugs inhibit cyclooxygenases (COX), which are involved in the biosynthesis of prostaglandins that promote inflammation. The conventional non-steroidal anti-inflammatory drugs (NSAIDs) are associated with gastric and renal side-effects, as they inhibit both the constitutive COX-1 and the inducible COX-2. The majority of selective COX-2 inhibitors (COXIBs) are without gastric side-effects but are associated with cardiac side-effects on long-term use. The search for anti-inflammatory drugs without side-effects, therefore, has become a dream and ongoing effort of the Pharma companies. As PGE₂ is the key mediator of inflammatory disorders, coming up with a strategy to reduce the levels of PGE₂ alone without affecting other metabolites may form a better choice for the development of next generation anti-inflammatory drugs. In this direction the options being explored are on synthesis of PGE₂-mPGES-1; PGE₂ degradation through a specific PG dehydrogenase, 15-PGDH, and by blocking its activity mediated through a specific PGE receptor, EP4. As leukotrienes formed via the 5-lipoxygenase (5-LOX) pathway also play an important role in the mediation of inflammation, efforts are also being made to target both COX and LOX pathways. This review focuses on addressing the following three points: 1) How NSAIDs and COXIBs are associated with gastric, renal and cardiac side-effects; 2) Should the focus be on the targets upstream or downstream of PGE₂; and 3) the status of alternative targets being explored for the discovery and development of anti-inflammatory drugs without side-effects.

Keywords: inflammation, cyclooxygenase, COX, NSAIDs, COXIBs, microsomal PGE synthase-1, mPGES-1, 15-hydroxy prostaglandin dehydrogenase, 15-PGDH, 5-lipoxygenase, 5-LOX

Introduction

Inflammation is the body's general response to protect itself against injury or infection. An acute inflammation process is a short-term reaction, which occurs in response to injury or infection. During this phase the immune system releases an army of white blood cells to surround and defend the area, leading to a visible redness and swelling. In view of this, inflammation is crucial; without it, simple infections could be dangerous. A prolonged or chronic inflammation, on the other hand, is the root cause of many inflammatory disorders, including cancer.

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The prostaglandin (PG) biosynthesis or cyclooxygenase (COX) pathway is an essential component of inflammatory responses, generating a class of physiologically active lipid mediators called prostanoids. The COX pathway is activated by lipopolysaccharides (LPS),¹ cytokines,² xenobiotics, including metal compounds^{3,4} and fluoride.^{5,6} Membrane bound unsaturated 20-carbon containing fatty acid, arachidonic acid (AA), is the most predominant precursor for PG biosynthesis. A variety of stimuli, both physiological as well as pathological, lead to the release of AA by the action of various phospholipases, gets oxygenated via COX, lipoxygenase (LOX), and cytochrome P450 dependent monooxygenase (MOX) enzymes⁷ to generate prostaglandins (PGs), leukotrienes (LTs) and epoxy eicosatrienoic acids (EETs), collectively termed as eicosanoids. In the case of PGs formed via the COX pathway, AA is initially converted to an unstable prostaglandin G₂ (PGG₂), which is further reduced by the peroxidase activity of the same enzyme to a stable prostaglandin H₂ (PGH₂). PGH₂ is further converted to biologically active PGs such as prostaglandin D₂ (PGD₂), prostaglandin E₂ (PGE₂), prostaglandin F_{2α} (PGF_{2α}), prostacyclin (PGI₂), and thromboxane A₂ (TxA₂) by the action of various cell-specific terminal synthases.⁸

Among these PGs, PGE₂ is the major inflammatory mediator and its biological actions are mediated by signaling via various G-protein coupled receptors, which include EP₁ (405 aa), EP₂ (362 aa), EP₃, and EP₄ (513 aa). EP₃ has multiple splicing isoforms such as EP_{3α} (366 aa), EP_{3β} (362 aa), and EP_{3γ} (365 aa). The distribution and relative abundance of these receptors vary, for example, in mouse EP₂ is the least abundant receptor, while EP₃ and EP₄ are the most dominant (widely distributed) receptors, and EP₁ mRNA is restricted to organs such as the kidneys, stomach, and lungs.^{9,10} Their signaling mechanism involves G-protein mediated activation of downstream targets such as kinases via second messengers such as cAMP, Ca²⁺, and inositol phosphates. EP₁ induces Ca²⁺ elevation with activation by agonist via unidentified G protein, whereas EP₂ and EP₄ receptors couple G_s for their biological action by a raise in cAMP levels. EP₃, which exists in multiple splicing isoforms,⁹ inhibits adenylyl cyclase by coupling with G_i, leading to a decrease in cAMP levels. In humans, PGs are important physiological mediators, hence the dysregulation of its synthesis has links with inflammation, pain, cancer, cardiovascular disease, asthma, osteoporosis, male sexual dysfunction, etc.¹¹ As a result, the COX, catalyzing the first step in the

biosynthesis of PGs, has become the target for developing anti-inflammatory drugs.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Their Targets

Many of the available anti-inflammatory drugs are non-steroidal in nature (NSAIDs) and target COX isoforms as part of their therapeutic action. The Greek physician Hippocrates used an extract of willow bark and leaves in the treatment of fever and inflammation for the first time about 3,500 years ago. Later on, the active compound of the extract was identified as salicylic acid in the 17th century. Acetylsalicylic acid, the acetyl derivative of salicylic acid (aspirin), was introduced in 1869 by Bayer,¹² but the mode of action was unknown when the drug was out in the market. After almost a century, the molecular mechanistic role of aspirin was studied by Vane¹³ and colleagues, and the findings that all these NSAIDs inhibit the COX enzyme have now become a platform for developing novel NSAIDs. The most common side-effects associated with these NSAIDs, the extent of which varies depending on the type of NSAID, are gastrointestinal symptoms such as stomach pain, constipation, diarrhea, stomach ulcers, etc. In addition, kidney and liver problems have also been reported.¹⁴ Though these classical NSAIDs such as aspirin, indomethacin, ibuprofen, etc. have been in use for more than a century, it is not clear how these therapeutic and side-effects are being mediated by NSAIDs simultaneously.

With the discovery of an inducible isoform of COX, COX-2,^{15,16} it became very clear that there are two isoforms of COX, the constitutive isoform, COX-1, which is cytoprotective and mediates various physiological functions while the inducible isoform; and COX-2, which is the mediator of inflammation. The classical NSAIDs inhibit both the isoforms of COX – COX-1 and COX-2. This discovery of COX-2 has led to the development of selective COX-2 inhibitors (COXIBs); celecoxib, co-developed by G. D. Searle and Pfizer in 1999, followed by rofecoxib by Merck, and many others subsequently, which became the block buster drugs.

Current Targets and Their Limitations

As pointed out above the NSAIDs in general have gastric and renal side-effects. Aspirin was shown to cause damage in the gastric system in a rat model by decreasing the

plasma membrane protein of tight junctions, occludin expression, which was reversed by pretreatment with another drug mosapride.¹⁷ High-dose of ibuprofen caused jejunal perforations even in short-courses.¹⁸ Another anti-inflammatory drug, naproxen, causes gastric antral ulcerations, and an increase of lipid peroxide levels, but the effect was reversed with curcumin.¹⁹ Similarly perforated jejunal ulcers²⁰ and small bowel ulcerations²¹ have been reported with the usage of NSAIDs. The simultaneous use of proton pump inhibitors and non-selective short-course NSAIDs increases the risk of bowel injury.²² Similarly a combination of ibuprofen and acetaminophen causes kidney and liver problems even at a therapeutic dosage.^{23,24} Another drug, rofecoxib, is associated with increased renal and arrhythmia risks.²⁵ Diclofenac, an NSAID, has also been found to increase the risk of heart attacks and strokes by 50% within days of ingestion. This study, performed in around 6.3 million cases over a period of 20 years from 1996–2016,²⁶ also reported that the drug causes a lot of acidity and gastric intolerance in Indian patients. The adverse reactions with NSAIDs are high in patients who are under long-term medication and these adverse effects were attributed due to the targeting COX-1 enzyme, which is cytoprotective.

The COX-2 selective drugs, COXIBs, became the most preferred anti-inflammatory drugs as they have good anti-inflammatory activity, and some exhibited reduced gastrointestinal toxicity.^{27,28} However, very soon it became clear that COXIBs are associated with cardiac side-effects on long-term use in arthritic patients.^{29,30} As a result, some of the COXIBs such as rofecoxib were withdrawn from the market while others like celecoxib are still on the market with a warning label for use in patients with cardiovascular problems.³¹ Though COX-2 was originally identified in inflammatory tissues, it is now evident that it is also expressed constitutively in tissues like kidney, brain, and testis.^{32,33}

The side-effects associated with COXIBs were attributed to the simultaneous reduction of prostacyclin, also a product of COX-2, which is a natural inhibitor of platelet aggregation and also involved in renal hemodynamics, and the control of blood pressure.³⁰ Also the inhibition of COX was shown to shunt the arachidonic acid metabolism towards the 5-LOX pathway, leading to increased levels of leukotrienes, which were also a contributing factor for the side-effects of COX inhibitors.^{34–36} With these developments the search has begun for anti-inflammatory drugs without gastric and cardiac side-effects. The new era of

anti-inflammatory agents that have emerged include NO-NSAIDs, Biologicals, cytokine inhibitors, etc, which are out of the scope of the present review. This review will focus particularly on the targets of eicosanoid pathways, which are at different stages of development.³⁷

COX-2/5-LOX Dual Inhibitors Spare Gastrointestinal and Cardiac Side-Effects?

In addition to the key role of biologically active prostaglandins formed through the cyclooxygenase pathway in inflammation, there is a growing body of information on the involvement of other arachidonic acid metabolites such as leukotrienes formed via the 5-lipoxygenase pathway.³⁸ Though several molecules have been developed with the objective of COX/LOX dual inhibitors, none of them reached the market in view of their unfavorable toxicity.^{34,39}

In this direction the German pharmaceutical company, Merckle GmbH, together with Euro Alliance partners Alfa Wassermann and Lacer, developed licofelone (ML3000), which is a COX/LOX dual inhibitor, the first member of this new class of analgesic and anti-inflammatory drugs.⁴⁰ It was shown to decrease the production of proinflammatory PGs and LTs with the potential to combine good analgesic and anti-inflammatory effects with excellent gastrointestinal tolerability.⁴¹ It is currently under evaluation for the treatment for osteoarthritis (OA), the most common form of arthritis. Although Phase III trials have been successfully completed in OA patients no dates for regulatory submission have been given (<https://www.clinicaltrialsarena.com/projects/licofelone/>).⁴² Later studies indicate that licofelone suppresses PGE₂ formation by inhibiting mPGES-1, in addition to inhibition of COX-1 and COX-2.⁴³ Our studies in this direction have resulted in the isolation of a natural product, chebulagic acid isolated from *Terminalia chebula* and 6-hydroxy salvinolone isolated from the roots of *Premna integrifolia* with COX-2/5-LOX dual inhibition and with potent anti-inflammatory and anticancer effects.^{44–46} However, further well-designed pre-clinical and clinical trials are required for evaluation of their efficacy and safety and further development.

Thus, the evolution of anti-inflammatory drugs, targeting COX and/or LOX enzymes, ie, from NSAIDs to COXIBs to CLOXIBs, have not resulted in the development of anti-inflammatory drugs without side-effects.⁴⁷

Hence there is a need to explore novel targets for the development of anti-inflammatory drugs without side-effects.

Prostaglandins and Inflammation: Search for Novel Anti-Inflammatory Drug Targets

In view of several complications reported with anti-inflammatory drugs targeting COX and LOX enzymes, there is a need for alternate target(s) for treatment of inflammatory disorders. The COX enzyme is responsible for the formation of a stable intermediate, PGH₂, which forms the precursor for the formation of prostaglandins (PGE₂, PGF_{2α}, PGD₂, TXB₂, PGI₂, etc.) by tissue-specific enzymes.⁸ By targeting COX and/or LOX pathways, as seen in NSAIDs, COXIBs, and CLOXIBs, they not only block the formation of PGE₂, the major mediator of inflammation, but also block the formation of other downstream metabolites, which are essential for homeostatic functions.^{48,49} Also targeting these PLA2 or COX pathways is known to affect the production of histamine.⁵⁰ Hence, the selection of a target and its validation in terms of other linked functions is very essential to come up with safe and effective drugs.

Targeting PGE₂: The Possible Effects and Limitations

It is recognized that the key lipid mediator that is involved in chronic inflammation is PGE₂, which has been implicated in tumor development.⁵¹ Also, PGE₂ is a key PG that mediates several biological functions, such as blood pressure, fertility, immune responses, etc. Its action is mediated through the G-protein-coupled receptors, EP₁₋₄.⁵² Dysregulation of PGE₂ production is also linked with several complications.⁵³ As a result, PGE₂ metabolism and signaling formed as one of the areas being investigated actively so as to identify the most ideal therapeutic target (Figure 1). The significant elevation in microsomal PGE Synthase (mPGES) level has been observed in patients with myositis⁵⁴ and gastric ulcers.⁵⁵ Based on these studies, it is very clear that PGE₂ is the major mediator of inflammation and hence the enzymes involved in PGE synthesis are being explored for development of anti-inflammatory drugs.⁵⁶

The synthesis of PGE₂ from endoperoxide PGH₂ is mediated by prostaglandin E synthases (PGES). There are three different PGE synthases such as cytosolic PGE

synthase (cPGES) and two membrane-bound PGE synthases, mPGES-1 and mPGES-2. Of these, mPGES-2 and cPGES are constitutive enzymes, whereas mPGES-1 is an inducible enzyme. While mPGES-2 and cPGES are responsible for maintenance of constitutive levels of PGE₂, mPGES-1 is mainly responsible for the synthesis of enhanced levels of PGE₂ during inflammation. While COX-1 and cPGES function in coordination to maintain constitutive levels of PGE₂, COX-2 and mPGES-1 are responsible for elevated levels of PGE₂ under inflammatory conditions.⁵⁷ Unlike NSAIDs, inhibitors of mPGES-1, which reduces the PGE₂ production without affecting the synthesis of other PGs, may form better anti-inflammatory drug candidates without side-effects. Especially, mPGES-1 is the only inducible enzyme and in many pathological conditions it is co-induced with COX-2.⁵⁸ Also, mPGES-1 is having an association in other inflammatory diseases of the brain such as ischemic stroke, Alzheimer's disease, Parkinson's disease, epilepsy, brain cancer, etc.⁵⁸

Overexpression of mPGES-1 was reported in several types of cancers such as colorectal, gastric adenoma, gastric cancer, breast cancer, pancreatic cancer, papillary thyroid, ovarian cancer, head and neck cancer, lung cancer, etc.⁵⁹ The in vitro/in vivo models with mPGES-1 knockout, RNA interference with siRNA or genetic deletion have a negative effect on tumor growth, which collectively indicates a role for mPGES-1 in cancer.⁵⁹ The rest of the PGE synthases are constitutively expressing enzymes and may not form good targets for anti-inflammatory drug development. Bergqvist et al⁶⁰ reported recently how selective inhibitors of mPGES-1 are beneficial. They have shown that mPGES-1 inhibitor, CIII, decreased PGE₂ production and increased PGF_{2α} and TXB₂ whereas NS-398 (COX-2 inhibitor) blocked the entire PGs production in A549 lung cancer cells. Hence, the selective inhibitors of mPGES-1, reducing the production of only PGE₂ with no effects on other PGs, may form a better target for the development of anti-inflammatory drugs without side-effects.

mPGES-1: A Better Target?

The mPGES-1, the terminal enzyme involved in the production of inducible prostaglandin E₂, has become an attractive target for development of anti-inflammatory drugs. It is a homo trimer with three subunits of 16 kDa each with 152 amino acids. Microsomal prostaglandin E synthase-1, a membrane associated protein, is a member of the Membrane Associated Proteins in Eicosanoid and

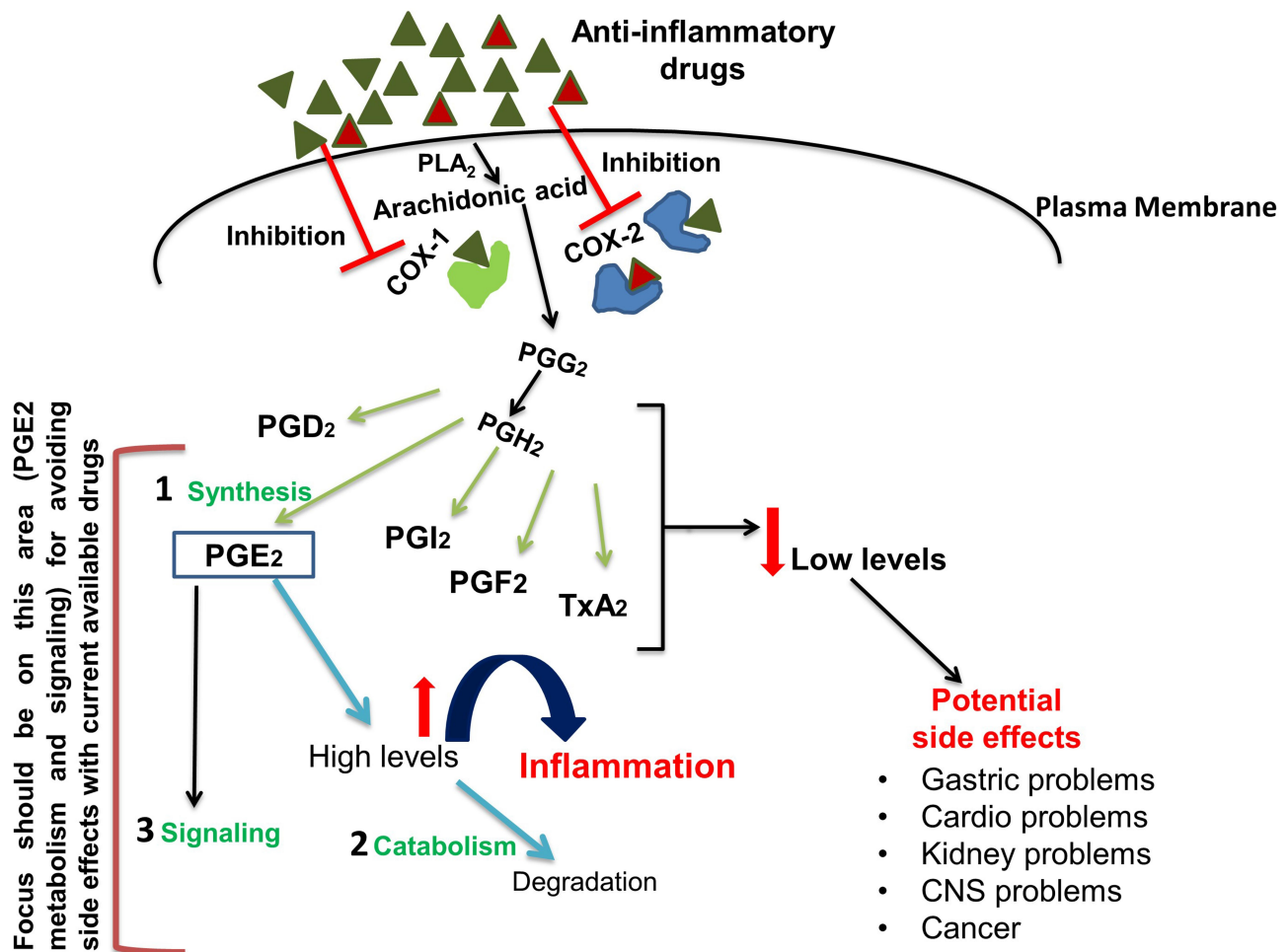


Figure 1 Cyclooxygenase pathway showing the formation of PGE₂ and other metabolites. Inhibition of both COX-1 and COX-2 non-selectively by NSAIDs (green triangles) and selective inhibition of COX-2 by COXIBs (red triangles) is also shown. The potential targets in the COX pathway at various levels – Synthesis (1), Catabolism (2) and Signaling (3) are also indicated.

Abbreviations: COX, cyclooxygenase; PGG₂, prostaglandin G₂; PGD₂, prostaglandin D₂; PGE₂, prostaglandin E₂; PGI₂, prostacyclin; PGF₂, prostaglandin F₂ α ; TxA₂, thromboxane A₂.

Glutathione metabolism (MAPEG) super family.⁵⁹ MAPEG proteins are small proteins of 14–18 kDa and have a similar 3D structure. mPGES-1 is the terminal enzyme in the biosynthesis of PGE₂. The first report on selective inhibitors of mPGES-1 came from the group of Riendeau et al⁶¹ in 2005, where they have shown a reduction in levels of PGE₂ in IL-1 β induced A549 cells.⁶¹ In contrast to COX-2 inhibition, mPGES-1 inhibition was associated with lower risk of cardiovascular side-effects, as it results in increasing PGI₂ levels.⁶² Recently, Eli Lilly developed a compound inhibiting mPGES-1, LY3031207, but the study was terminated after in Phase I trial in view of drug induced liver injury.⁶³ Glenmark Pharmaceuticals molecule, GRC 27864, a potent, selective, and orally bioavailable inhibitor of mPGES-1, is currently in Phase II clinical trials for evaluation of efficacy and safety in patients with moderate osteoarthritic pain ([https://www.](https://www.pnnewswire.com/in/news-releases/glenmark-initiates-phase-iib-dose-range-finding-study-for-novel-molecule-grc-27864-669501853.html)

[pnnewswire.com/in/news-releases/glenmark-initiates-phase-iib-dose-range-finding-study-for-novel-molecule-grc-27864-669501853.html](https://www.pnnewswire.com/in/news-releases/glenmark-initiates-phase-iib-dose-range-finding-study-for-novel-molecule-grc-27864-669501853.html)).⁶⁴ These details and the progress in the development of mPGES-1 inhibitors over time have been reviewed recently.⁶⁵

As of today there are no approved inhibitors of mPGES-1 in clinical practice due to different issues with the compounds themselves.⁶⁶ In another study, Ding et al⁶⁷ have developed a molecule based on a structure-based design of mPGES-1 inhibitors, which was found to be orally bioavailable and effective against both human and mouse mPGESs. Also, DREAM-in-CDM (Drug Repurposing Effort Applying Integrated Modeling-in vitro/in vivo-Clinical Data Mining), is another novel approach for structure-based screening of FDA-approved drugs against mPGES-1 drug repurposing.⁶⁸ For example, lapatinib, a known anti-cancer drug, was

identified as a potent inhibitor of mPGES-1, using this novel approach, and it can be used in treatment of inflammation, pain, and inflammation-related diseases.⁶⁸ Design and development of a specific inhibitor of mPGES-1 is a challenging task as there are interspecies differences in the structure of mPGES-1 in humans and rodents. Also, the structural similarity of the mPGES-1 with others like Huntingtin interacting protein 12, microsomal glutathione-S-transferase (GST)-1-like 1 and protein tyrosine kinase 2 beta (PTK2B),⁵⁹ makes the task much more challenging.

mPGES-1/5-LOX Dual Inhibitors

As discussed, the NSAIDs, COXIBs, and COX/5-LOX dual inhibitors (CLOXIBs), being used in the treatment of many inflammatory diseases, are associated with gastrointestinal, renal, and cardiovascular problems, as they are involved in blocking not only the PGE₂ formation but also are inhibiting the formation of cytoprotective prostacyclin and other eicosanoids. In light of the above, attempts are being made to target microsomal prostaglandin E synthase-1 (mPGES-1) and 5-LOX, so as to spare COXs and thus the cytoprotective PGs. Several mPGES-1 inhibitors are being developed as potential candidates for the treatment of inflammatory disorders, including cancer.^{59,69,70} Licoferone, originally identified as a dual inhibitor blocking both COX and 5-LOX pathways, has also been shown to inhibit mPGES-1 activity with an IC₅₀ value of 6 μM.⁴³ Compared to licoferone, which inhibits both COXs and 5-LOX, mPGES-1/5-LOX dual inhibitors spare COX1/2 and thus may form better candidates for the development of next generation anti-inflammatory drugs. Further in-depth studies, however, are required to evaluate their efficacy in treating various inflammatory disorders and their safety.

Limiting the PGE₂ Levels: Role of 15-Hydroxyprostaglandin Dehydrogenase (15-PGDH)

As pointed above, PGE₂ has been identified as the key mediator of inflammation and as a result the enzymes limiting the formation of PGE₂ have been exploited as the targets for the discovery and development of anti-inflammatory drugs: at PLA₂ level, steroidal; COX-1 and/or -2 -non-steroidal/COX-2 specific; mPGES level. However, the effective level of PGE₂ in the tissues ultimately depends on its rate of formation or anabolism and its rate of degradation or catabolism. The key enzyme involved in the catabolism of PGE₂ has been identified as 15-PGDH (15-Hydroxyprostaglandin

dehydrogenase). In fact, recent reports indicate the importance of PGE₂ catabolism, on various inflammatory disorders, including cancer.⁷¹ 15-hydroxy prostaglandin dehydrogenase (15-PGDH), a dimer with a molecular weight of 25–29 kDa, catalyzes the reversible oxidation of the 15-hydroxyl group of prostaglandins to produce a 15-keto metabolite with reduced biological activity.⁷² It exists in two isoforms, PGDH-1 and 15-PGDH-2. PGDH-1, NAD⁺ dependent enzyme, catalyzes the conversion of PGE₂ to 15-keto-PGE₂. 15-PGDH-2, on the other hand, is NADP⁺ dependent and has a much broader range of substrates and can also use NAD⁺ as a cofactor.⁷² Contrary to COX-2 which is being overexpressed in lung and many other tumors, 15-PGDH was found to be under-expressed. In inflammation associated human colon cancer upregulation of PGE₂ is considered as a key event.⁷³ 15-PGDH a PGE₂ catabolizing enzyme is downregulated in colon cancer.⁷⁴ 15d-PGJ₂, a peroxisome proliferator activated receptor-γ ligand, which has anticarcinogenic activities, upregulates the expression of 15-PGDH in the HCT119 human colon cancer cell line.⁷⁵ 15-PGDH and miR-21 are inversely correlated in colorectal cancer (CRC) patients. It has been reported that dysregulated expression of miR-21 contributes to the loss of PGDH expression and promotes CRC progression via accumulation of PGE₂.⁷⁶ miR-21 also induces loss of 15-PGDH in early gastric tubular adenocarcinoma.⁷⁷ It was shown that inhibition of 15-PGDH enhances KRAS-driven tumor progression via all *-trans* retinoic acid (ATRA) depletion in the pancreas.⁷⁸ Thus, downregulation of 15-PGDH expression in lung and other tumors suggest that this enzyme is a tumor suppressor. Docosahexaenoic acid (DHA), a polyunsaturated fatty acid of omega 3 class, significantly reduces PGE₂ levels in line with upregulation of 15-PGDH in endothelial cells.⁷⁹ It was revealed that NAD⁺ triggered reactive oxygen species (ROS) mediate degradation of 15-PGDH and drove cells to undergo EMT transition.⁸⁰ It was shown that 15-PGDH-derived 15-keto-PGE₂ from hepatocytes is able to activate PPAR-γ and inhibit inflammatory cytokine production in Kupffer cells and that this paracrine mechanism negatively regulates the LPS-induced necro-inflammatory response in the liver.⁸¹

In addition to its pro-inflammatory and pathogenic role, PGE₂ is an important mediator for bone formation, gastric ulcer healing, and dermal wound healing. Elevation of PGE₂ using a 15-PGDH inhibitor was proved to be valuable for the management of diseases that require elevated PGE₂.⁸² Inhibitors of 15-PGDH are anticipated to elevate the *in vivo* levels of PGE₂ and promote healing and tissue regeneration.⁸³ PGDH inhibition attenuated acute

inflammation and weight loss and decreased mortality in murine pulmonary fibrosis.⁸⁴ 7,3',4'-Trimethoxyflavone (TMF), a potent inhibitor of 15-PGDH, facilitated *in vitro* wound healing in a HaCaT cell scratch model, which was completely inhibited by adding both 15-PGDH and NAD⁺ as a cofactor, confirming the involvement of PGE₂ in its wound healing effect.⁸⁵ Recently it was shown that inhibition of 15-PGDH could alleviate LPS-induced acute kidney injury by regulating the apoptosis, autophagy, and oxidative stress rather than inflammation in mice.⁸⁶

The foregoing studies clearly indicate that 15-PGDH is weakly expressed in many types of inflammatory disorders and cancers, where COX-2 and mPGES-1 are overexpressed. Such a situation eventually leads to accumulation of PGE₂ levels and disease manifestation. As a result, the pharmacological inhibition of 15-PGDH, which elevates PGE₂ levels, may not be a right choice for treating inflammatory disorders. On the contrary agents which induce 15-PGDH could be explored for the treatment of inflammatory disorders. This in fact appears to be the mechanism by which many of the disease modifying anti-rheumatic drugs (DMARDs) like hydroxychloroquine bring in therapeutic efficacy in osteoarthritis and rheumatoid arthritis, where 15-Hydroxyprostaglandin dehydrogenase is upregulated.⁸⁷ Similarly, the beneficial effects of hydroxychloroquine in the case of COVID-19 patients may also be mediated through similar induction of 15-PGDH and decreased PGE₂ levels. However, the impact of long-term use of such DMARDs on normal physiological functions requiring high levels of PGE₂ such as bone formation, gastric ulcer healing, and dermal wound healing needs to be assessed. In such a scenario the alternative target which will not affect other normal functions could be the specific receptors of PGE₂, which mediate inflammatory responses.

PGE₂ (EP) Receptors as Potential Targets

The targets discussed so far, starting from PLA₂, COX, and/or LOX, mPGES-1, 15-PGDH, mediate not only inflammatory pathogenesis but also are involved in key homeostatic functions. As a result, it is quite expected to have therapeutic efficacy on one side and side-effects on the other. Hence there is a need to identify a target that is exclusively involved in mediating inflammatory pathologies. In this direction the PGE₂ receptor(s) mediating the inflammatory responses may form the right choice.

Prostaglandins mediate their effects through a class of G-protein-coupled receptors (GPCRs). PGE₂ also mediates its effects through GPCRs, EP 1–4, which are expressed tissue specifically.⁵² Among these four receptors, the EP₃ and EP₄ have high affinity towards PGE₂, while the EP₁ and EP₂ receptors are activated only by the high levels of PGE₂. In view of their pathogenic link with inflammation and cancer, the antagonists of EP receptors have become potential drug targets and constitute an intense area of research in anti-inflammatory drug discovery.⁸⁸

The developments on the therapeutic roles of EP receptor ligands have recently been reviewed¹⁰ in diseases such as Ulcerative colitis (EP₄ agonists: rivenprost, KAG-308, ONO-AE1-329), Glaucoma and intraocular hypertension (EP₂ agonist: taprenepag isopropyl), Solid tumors (EP₄ antagonists: grapiprant, ONO-AE3-208, GW627368X, AH23848), Colorectal cancer (EP₁ antagonist: ONO-8711 and EP₄ antagonist: ONO-AE-227), Cardiovascular diseases (EP₃ agonists: GR 63799X, MB-28767, ONO-AE-248, TEI-3356, and EP₄ agonists: EP4RAG), etc. From these studies it is observed that EP₄ receptor antagonists show greater potential in treating pain, inflammation, and solid tumors.¹⁰ Hence it is important to solve the EP receptors (even ligand-bound EP receptors) structures in high resolution for rational drug design. It is also important to develop antagonists specific to EP₄, which is the key receptor mediating inflammatory disorders, without affecting other receptors of PGE₂, which mediate homeostatic functions of PGE₂. Targeting EP receptors thus appear promising, but safety profiles of these targets have not been studied.⁸⁹ Further in-depth studies on the efficacy and safety of targeting EP receptors may form rewarding exercise for the Pharma companies.

Conclusions and Future Directions

In conclusion, the discovery and development of anti-inflammatory drugs is mostly based on targeting prostaglandin biosynthesis, to limit the formation of Prostaglandin E₂ via the cyclooxygenases. This approach though resulted in putting forth a number of drugs into the market, it has major limitations due to the undesirable side-effects. Hence there is now a shift in identifying the targets downstream of COXs, which limit the levels of PGE₂ or block its specific receptors. Also, efforts are being made for simultaneous targeting of the 5-LOX pathway which is involved in the formation of inflammatory leukotrienes. The efforts made so far in this direction include:

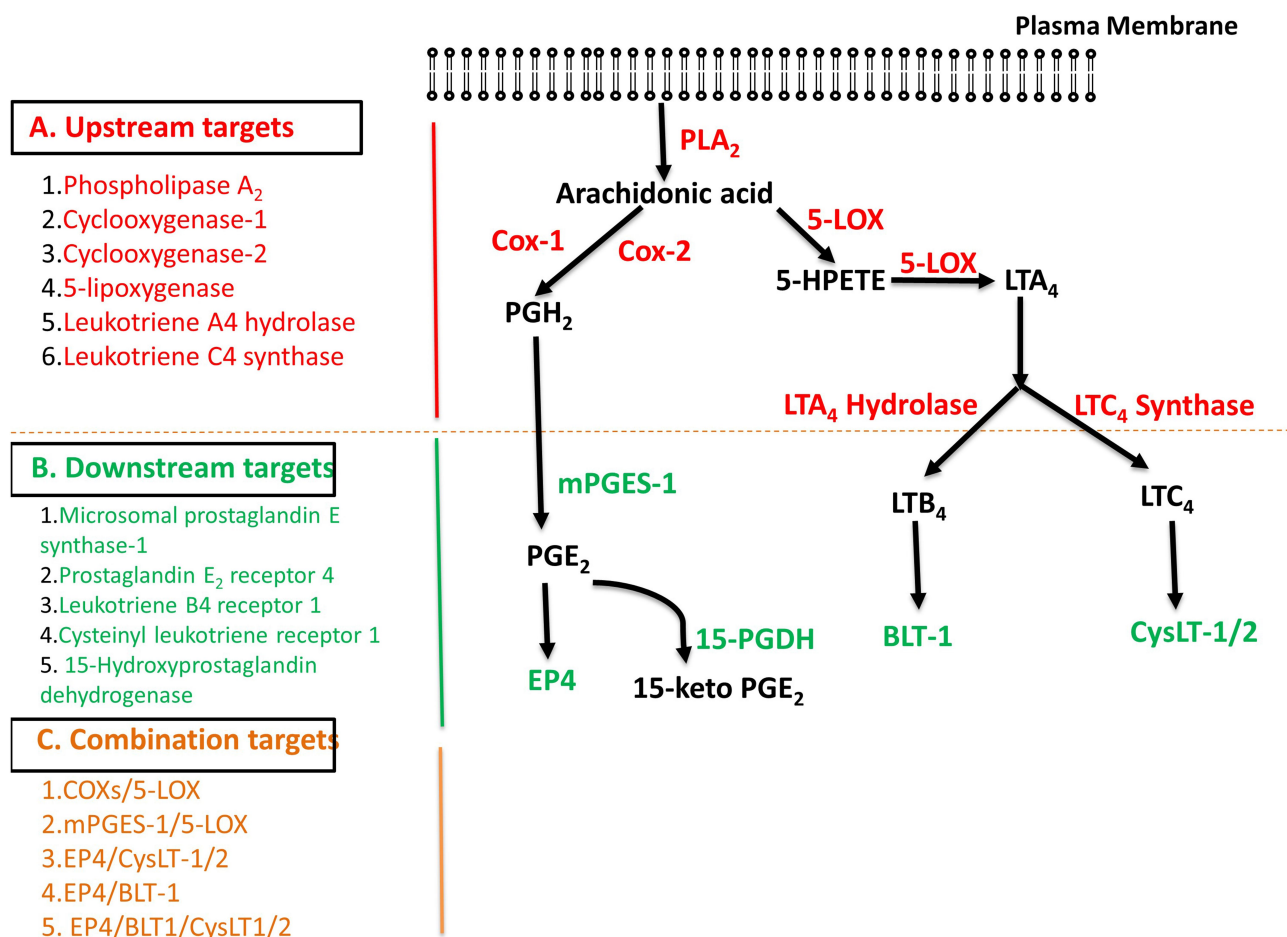


Figure 2 The metabolism of arachidonic acid via the cyclooxygenase and lipoxygenase pathways showing the possible up-stream (A), down-stream (B), and combination targets (C) for the discovery and development of anti-inflammatory drugs.

Abbreviations: COX1, cyclooxygenase 1; COX2, cyclooxygenase 2; NSAIDs, non-steroidal anti-inflammatory drugs; COXIBs, COX-2 inhibitors; mPGES, microsomal prostaglandin E synthase; cPGES, cytosolic prostaglandin E2 synthase; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; EP₄, prostaglandin E₂ (PGE₂) receptor-4.

a. Inhibitors of Phospholipases, which are involved in the release of arachidonic acid from membrane phospholipids.

b. Inhibitors of the COX enzymes – (NSAIDs).

c. Specific COX-2 (COXIBs) and COX-2 and 5-LOX dual inhibitors (CLOXIBs).

The drugs developed in this direction, though approved and in the market, have undesirable side-effects, as they affect the formation of other key metabolites mediating physiological functions. The focus, therefore, is now on downstream targets such as:

- (a) PGE synthases, specifically the inducible isoform – mPGES-1.
- (b) Enzymes involved in the metabolism of PGE₂, specifically 15-PGDH.
- (c) PGE receptors, specifically EP₄ which mediates inflammation.

Figure 2 summarizes the past, present, and future drug targets for the discovery and development of anti-inflammatory drugs. Hopefully, some of these novel approaches might lead to next generation anti-inflammatory drugs with enhanced efficacy and safety in the near future.

Abbreviations

AA, arachidonic acid; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; mPGES-1, microsomal prostaglandin E synthase-1; mPGES-2, microsomal prostaglandin E synthase-2; cPGES, cytosolic prostaglandin E₂ synthase; PGs, prostaglandins; PGE₂, prostaglandin E₂; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; LOX, lipoxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; COXIBs, cyclooxygenase-2 specific inhibitors; EP₁, EP₂, EP₃ & EP₄, E prostanoid receptor subtypes 1,2,3 and 4; PGG₂, prostaglandin G₂; PGH₂,

prostaglandin H₂; PGD₂, prostaglandin D₂; PGF_{2α}, prostaglandin F_{2α}; PGI₂, prostacyclin; TxA₂, thromboxane.

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Disclosure

The authors report no conflicts of interest for this work.

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