Abstract—Prostaglandins are lipid autacoids derived from arachidonic acid. They both sustain homeostatic functions and mediate pathogenic mechanisms, including the inflammatory response. They are generated from arachidonate by the action of cyclooxygenase isoenzymes, and their biosynthesis is blocked by nonsteroidal antiinflammatory drugs, including those selective for inhibition of cyclooxygenase-2. Despite the clinical efficacy of nonsteroidal antiinflammatory drugs, prostaglandins may function in both the promotion and resolution of inflammation. This review summarizes insights into the mechanisms of prostaglandin generation and the roles of individual mediators and their receptors in modulating the inflammatory response. Prostaglandin biology has potential clinical relevance for atherosclerosis, the response to vascular injury and aortic aneurysm. (Arterioscler Thromb Vasc Biol. 2011;31:986-1000.)

Key Words: eicosanoids ■ prostacyclin ■ prostaglandins ■ thromboxanes

Inflammation is the immune system’s response to infection and injury and has been implicated in the pathogeneses of arthritis, cancer, and stroke, as well as in neurodegenerative and cardiovascular disease. Inflammation is an intrinsically beneficial event that leads to removal of offending factors and restoration of tissue structure and physiological function. The acute phase of inflammation is characterized by the rapid influx of blood granulocytes, typically neutrophils, followed swiftly by monocytes that mature into inflammatory macrophages that subsequently proliferate and thereby affect the functions of resident tissue macrophages. This process causes the cardinal signs of acute inflammation: rubor (redness), calor (heat), tumor (swelling), and dolor (pain). Once the initiating noxious stimulus is removed via phagocytosis, the inflammatory reaction can decrease and resolve. During the resolution of inflammation, granulocytes are eliminated, and macrophages and lymphocytes return to normal preinflammatory numbers and phenotypes. The usual outcome of the acute inflammatory program is successful resolution and repair of tissue damage, rather than persistence and dysfunction of the inflammatory response, which can lead to scarring and loss of organ function. It may be anticipated, therefore, that failure of acute inflammation to resolve may predispose to autoimmunity, chronic dysplastic inflammation, and excessive tissue damage.¹

Prostaglandins (PGs) play a key role in the generation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue, and they contribute to the development of the cardinal signs of acute inflammation. Although the proinflammatory properties of individual PGs during the acute inflammatory response are well established, their role in the resolution of inflammation is more controversial.

In this review, we discuss the biosynthesis of and response to PGs and the pharmacology of their blockade in orchestrating the inflammatory response, with particular regard to cardiovascular disease.

Biosynthesis of PGs

PGs and thromboxane A₂ (TXA₂), collectively termed prostanoids, are formed when arachidonic acid (AA), a 20-carbon unsaturated fatty acid, is released from the plasma membrane by phospholipases and metabolized by the sequential actions of PGG/H synthase or by cyclooxygenase (COX) and their respective synthases.

There are 4 principal bioactive PGs generated in vivo: prostaglandin E₂ (PGE₂), prostacyclin (PGI₂), prostaglandin D₂ (PGD₂), and prostaglandin F₂₀ (PGF₂₀).

They are ubiquitously produced—usually each cell type generates 1 or 2 dominant products—and act as autocrine and paracrine lipid mediators to maintain local homeostasis in the body. During an inflammatory response, both the level and the profile of PG production change dramatically. PG production is generally very low in uninflamed tissues but increases immediately in acute inflammation before the recruitment of leukocytes and the infiltration of immune cells.

PG production (Figure 1) depends on the activity of PGG/H synthases, colloquially known as COXs, bifunctional enzymes that contain both COX and peroxidase activity and that exist as distinct isoforms referred to as COX-1 and COX-2.²

COX-1, expressed constitutively in most cells, is the dominant source of prostanoids that subserve housekeeping...
functions, such as gastric epithelial cytoprotection and homeostasis. COX-2, induced by inflammatory stimuli, hormones, and growth factors, is the more important source of prostanoid formation in inflammation and in proliferative diseases, such as cancer. However, both enzymes contribute to the generation of autoregulatory and homeostatic prostanoids, and both can contribute to prostanoid release during inflammation.

PGH₂ is produced by both COX isoforms, and it is the common substrate for a series of specific isomerase and synthase enzymes that produce PGE₂, PGF₂α, PGD₂, and TXA₂. COX-1 couples preferentially, but not exclusively, with thromboxane synthase, PGF synthase, and the cytosol (c) PGE synthase (PGES) isozymes. COX-2 prefers prostaglandin I synthase (PGIS) and the microsomal (m) PGES isozymes, both of which are often coinduced along with COX-2 by cytokines and tumor promoters.

The profile of prostanoid production is determined by the differential expression of these enzymes within cells present at sites of inflammation. For example, mast cells predominantly generate PGD₂, whereas macrophages produce PGE₂ and TXA₂. In addition, alterations in the profile of prostanoid synthesis can occur on cellular activation. Although resting macrophages produce TXA₂ in excess of PGE₂, this ratio changes to favor PGE₂ production after bacterial lipo polysaccharide (LPS) activation.

**PG Receptors**

PGs exert their effects by activating rhodopsin-like 7-transmembrane-spanning G protein-coupled receptors (Table). The prostanoid receptor subfamily is composed of 8 members: E prostanoid receptor (EP) 1, EP2, EP3, and EP4 subtypes of the PGE receptor; PGD receptor (DP1); PGF receptor (FP); PGI receptor (IP); and thromboxane receptor (TP). Two additional isoforms of the human TP (TPα, TPβ) and FP (FPα, FPβ) and 8 EP3 variants are generated through alternative splicing, which differ only in their C-terminal tails. In addition, there is another G protein-coupled receptor termed chemoattractant receptor-homologous molecule ex-

### Table. Signal Transduction of Prostanoid Receptors

<table>
<thead>
<tr>
<th>Class</th>
<th>Subtype</th>
<th>G-Protein Coupled</th>
<th>Second Messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE₂</td>
<td>EP1</td>
<td>G₉, G₁₂, G₁₅</td>
<td>↑ IP₃</td>
</tr>
<tr>
<td></td>
<td>EP2</td>
<td>G₉, G₂</td>
<td>↑ cAMP</td>
</tr>
<tr>
<td></td>
<td>EP3</td>
<td>G₉, G₁₂, G₁₅</td>
<td>↓ cAMP, ↑ Ca²⁺²</td>
</tr>
<tr>
<td></td>
<td>EP4</td>
<td>G₂</td>
<td>↑ cAMP</td>
</tr>
<tr>
<td></td>
<td>CRTH2</td>
<td>G₁₂</td>
<td>↓ cAMP, ↑ Ca²⁺²</td>
</tr>
<tr>
<td>PGD₂</td>
<td>DP</td>
<td>G₁₂</td>
<td>↑ cAMP</td>
</tr>
<tr>
<td></td>
<td>CRTH2</td>
<td>G₁₂</td>
<td>↓ cAMP, ↑ Ca²⁺²</td>
</tr>
<tr>
<td>PGF₂ω</td>
<td>FPₐ, FP₉</td>
<td>G₉, G₁₅</td>
<td>↑ IP₃</td>
</tr>
<tr>
<td>PGI₂</td>
<td>IP-IP</td>
<td>G₂, G₉, G₁₁, G₁₅</td>
<td>↑ cAMP, ↑ IP₃</td>
</tr>
<tr>
<td></td>
<td>IP-TP</td>
<td>G₂, G₁₅</td>
<td>↑ cAMP</td>
</tr>
<tr>
<td>TXA₂</td>
<td>TPα, TPβ</td>
<td>G₂, G₂, G₁₅</td>
<td>↑ IP₃, ↑ ↓ cAMP, ↑ Ca²⁺²</td>
</tr>
</tbody>
</table>
pressed on T helper 2 cells (CRTH2 or DP2) that responds to PGD₂ but belongs to the family of chemokine receptors. CRTH2 is a member of the N-formyl-methionyl-leucyl-phenylalanine chemoattractant receptor superfamily (Figure 2).

Prostanoid receptors couple to a range of intracellular signaling pathways that mediate the effects of receptor activation on cell function. EP2, EP4, IP, and DP1 receptors activate adenylyl cyclase via Gₛ, increasing intracellular cAMP. EP1 and FP activate phosphatidylinositol metabolism via Gq, leading to the formation of inositol trisphosphate with mobilization of intracellular free calcium. In addition to signaling through Gq, the FP receptor couples to the small G-protein Rho via a Gq-independent mechanism. TP couples mainly to 2 types of G-proteins, the G₉ (G₁₁, G₁₂, G₁₅, G₁₆) and the G₁₃ (G₁₂, G₁₃) families, resulting in the activation of phospholipase C and guanine nucleotide exchange factor of the small G protein Rho, respectively. In addition, TP can also be coupled via G₉ to phospholipase C, as well as via G₁ and G₁₀ to adenylyl cyclase. Both TP isoforms are coupled to phospholipase C activation, but TPα stimulates adenylyl cyclase, whereas TPβ inhibits it. EP3 isoforms can couple via G₁₁ or G₁₂ to elevation of intracellular Ca²⁺, inhibition of cAMP generation, and activation of the small G protein Rho. The DP2/CRTH2 couples to a G₁₃-type G protein to inhibit cAMP synthesis and elevate intracellular Ca²⁺. However, the effects of prostanoids on these G protein–coupled signaling pathways may change as a function of ligand concentration or structure.

Some but not all prostanoid receptors exhibit the capacity to dimerize, which may alter ligand affinity or preference for downstream signaling pathways. Thus, although DP1/DP2 dimers appear not to form, under similar conditions, IP and TP receptors can associate to form homo- and heterodimers. TPα-TPβ heterodimers enhance the response to activation by free radical–catalyzed isoprostanes. Furthermore, dimerization of IP and TPα enables cAMP formation through TP receptor activation, a cellular outcome typically observed with IP activity. Moreover, EP1 receptor activation has been shown to modulate β2-adrenoreceptor function in bronchial airways via formation of a heterodimeric complex.

**Figure 2.** Phylogenetic tree of lipid G protein–coupled receptors. Figure modified with permission from Shimizu.

**COXs and Inflammation**

The 2 COX isoforms, COX-1 and COX-2, are targets of nonsteroidal antiinflammatory drugs (NSAIDs). These drugs are competitive active site inhibitors of both COXs. Although both COXs exist as homodimers, only 1 partner is used at a time for substrate binding. COX-1/COX-2 heterodimers may also exist, but their role in biology remains to be established. NSAIDs bind to and inactivate the COX site at only 1 of the monomers of the COX dimer, and this is sufficient to shut down prostanoid formation. The other monomer appears to play an allosteric function. The peroxidase capacity of both proteins is unaltered by NSAIDs.

The clinical efficacy of structurally distinct NSAIDs, all of which share this capacity for prostanoid inhibition, points to the importance of these mediators in the promotion of pain, fever, and inflammation. The dramatic increase of COX-2 expression on provocation of inflammatory cells, its expression in inflamed tissues, and the assumption that inhibition of COX-1-derived prostanoids in platelets and gastric epithelium explain NSAID-evoked gastrointestinal adverse effects and provide a rationale for development of NSAIDs designed to be selective for inhibition of COX-2 for treating arthritis and other chronic inflammatory diseases.
Although COX-2 appears to be the dominant source of PG formation in inflammation, there is some suggestion that both isoforms of the human enzyme may contribute to the acute inflammatory response. COX-1 is constitutively expressed in resident inflammatory cells, and there is evidence for induction of COX-1 during LPS-mediated inflammatory response and cellular differentiation. Both COX isoforms are coexpressed in circulating inflammatory cells ex vivo and in both inflamed rheumatoid arthritis (RA) synovial and atherosclerotic plaques obtained from patients. Human data are compatible with COX-1-derived products driving the initial phase of an acute inflammation, with COX-2 upregulation occurring within several hours. However, controlled clinical trials to test the comparative efficacy of NSAIDs that inhibited both COXs versus COX-2 alone were never performed at scale. Such trials were designed to seek divergence in the incidence of gastrointestinal adverse effects rather than to assess comparative clinical efficacy.

Studies in both COX-1- and COX-2-knockout (KO) mice reveal impaired inflammatory responses, although the impacts of gene deletion diverge in time course and intensity. Mice deficient in COX-1 but not COX-2 exhibit a reduction in AA-induced ear edema, although AA induces an equivalent inflammatory response in wild-type (WT) and COX-2-deficient mice. By contrast, the level of edema induced by the tumor promoter tetradecanoil phorbol acetate was not significantly different among WT, COX-1-deficient, and COX-2-deficient mice. The ear inflammation studies indicate that COX-1, as well as COX-2, may contribute to inflammatory responses, and the isoform responsible for the inflammation may depend on the type of inflammatory stimulus or the relative levels of each isoform in the target tissue.

Similarly, arthritis models exhibit a significant reliance on either the COX-1 or COX-2 isoforms for the development of clinical synovitis. This varies, depending on the experimental model used. Thus, in the K/BxN serum-transfer model of arthritis, COX-1-derived PGs, in particular PGI2, make a model used. Thus, in the K/BxN serum–transfer model of clinical synovitis. This varies, depending on the experimental setting of inflammation are sufficient and necessary to mediate resolution.

In the case of atherosclerosis, deletion or inhibition of COX-2 has been shown variously to retard, accelerate, or leave unaltered atherogenesis in mouse models. This may reflect an impact postnatally of disruption of the many roles of the enzyme in development in COX-2 KOs, differences in timing of interventions with COX-2 inhibitors, or a failure in most cases to define biochemically the selectivity for inhibition of COX-2 of the drug regimen deployed. In contrast, COX-1 deletion markedly attenuated lesion development in the apolipoprotein E–KO mouse, as does inhibition of COX-1 and COX-2 together in low-density lipoprotein receptor–KO model. Thus, products of COX-1, such as TXA2, promote atherogenesis, whereas there is more ambiguity around the role of COX-2. Nevertheless, deletion of the IP, the receptor for the major COX-2 product, PGL2, fosters the initiation and early development of atherosclerosis in hyperlipidemic mice.

### PGE2 and Inflammation

PGE2 is one of the most abundant PGs produced in the body, is most widely characterized in animal species, and exhibits
versatile biological activities. Under physiological conditions, PGE₂ is an important mediator of many biological functions, such as regulation of immune responses, blood pressure, gastrointestinal integrity, and fertility. Dysregulated PGE₂ synthesis or degradation has been associated with a wide range of pathological conditions. In inflammation, PGE₂ is of particular interest because it is involved in all processes leading to the classic signs of inflammation: redness, swelling, and pain. Redness and edema result from increased blood flow into the inflamed tissue through PGE₂-mediated augmentation of arterial dilatation and increased microvascular permeability. Pain results from the action of PGE₂ on peripheral sensory neurons and on central sites within the spinal cord and the brain.

PGE₂ is synthesized from PGH₂ by cPGES or mPGES-1 and mPGES-2. cPGES is constitutively and abundantly expressed in the cytosol of various tissues and cells and it requires glutathione as a cofactor. The role of cPGES and even its ability to form PGE₂ is controversial. cPGES seems capable of converting COX-1-derived but not COX-2-derived PGH₂ to PGE₂ in cells, particularly during the immediate PGE₁-biosynthetic response elicited by Ca²⁺-evoked stimuli. Localization of cPGES in the cytosol may allow coupling with proximal COX-1 in the endoplasmic reticulum in preference to distal COX-2 in the perinuclear envelope. Functional coupling of cPGES with COX-1 suggests that the functions of cPGES in vivo overlap significantly, if not entirely, with COX-1. cPGES-deficient mice were developed, but they have not been particularly informative in addressing the importance of cPGES-derived PGE₂, because deletion of this enzyme results in perinatal lethality.

mPGES-1 is a member of the membrane-associated proteins involved in eicosanoid and glutathione metabolism superfamily, and like cPGES, it requires glutathione as cofactor. mPGES-1 is a perinuclear protein that is markedly induced by cytokines and growth factors and downregulated by antiinflammatory glucocorticoids, as in the case of COX-2. It is functionally coupled with COX-2 in marked preference to COX-1. Constitutive expression of mPGES-1 in certain tissues and cell types was also reported.

The generation of mPGES-1-deficient mice has revealed the dominant role of this enzyme in PGE₂ generation relevant to promotion of inflammation. In collagen-induced arthritis, a disease model of human RA, mPGES-1-null mice exhibited a reduced incidence and severity of disease compared with WT controls. This difference was not associated with alterations in interleukin (IL)-6 production by peritoneal macrophages or significant differences in circulating IgG2a anticollagen antibodies. Likewise, in collagen antibody–induced arthritis, another model of RA that does not involve the activation of the immune system, mPGES-1-null mice had a similar incidence but a lesser severity of arthritis than WT mice, as well as a 50% reduction in paw levels of PGE₂. In the same study, it was also observed that the migration of macrophages following peritoneal injection of thioglycollate was strikingly reduced in mPGES-1-null mice relative to WT mice.

The formation of inflammatory granulation tissue and attendant angiogenesis in the dorsum induced by subcutaneous implantation on the paw of a cotton thread was significantly reduced in mPGES-1-KO mice as compared with WT mice. In this model, mPGES-1 deficiency was also associated with reduced induction of vascular endothelial cell growth factor in the granulation tissue. These results indicate that mPGES-1-derived PGE₂, in cooperation with vascular endothelial growth factor, may play a critical role in the development of inflammatory granulation and angiogenesis, thus eventually contributing to tissue remodeling.

Together, these findings illustrate that deletion or inhibition of mPGES-1 markedly reduces inflammatory response, in several mouse models. The proinflammatory effect of mPGES-1-derived PGE₂ was also observed in atherosclerosis. Deletion of mPGES-1 retarded atherogenesis in fat-fed hyperlipidemic mice, in both sexes. Interestingly, in addition to the expected depression of PGE₂ production, deletion of mPGES-1 permits redirevension of the PGH₂ substrate to other PG synthases, with, for example, augmented formation of PGI₂ and PGD₂. This complicates the selection of mPGES-1 as a drug target. Thus, elevated PGI₂ may contribute to the more benign cardiovascular profile of mPGES-1 deletion compared with COX-2 deletion or inhibition: less predisposition to hypertension and thrombogenesis. However, this same effect may attenuate relief of pain, in the case of augmented PGI₂, or may mediate adverse effects on bronchial tone, allergic inflammatory disease, or the sleep-wakefulness cycle, in case of elevated PGD₂. This may account for the less impressive effectiveness of disrupting mPGES-1 versus COX-2 in some models of pain. Recently, Brenneis et al have provided evidence that mPGES-1-deficient mice may contribute both to promotion and resolution of neuroinflammation in mice. Finally, the major substrate products of redirevision will be influenced by the dominant cell type in a particular setting. For example, augmented PGI₂ may contribute to the restraint of atherogenesis in hyperlipidemic mice consequent to mPGES-1 deletion. However, it remains to be seen whether mPGES-1 inhibition in the setting of established atherosclerosis causes regression or possibly accelerates further progression of disease because of endoperoxide redirevision to TXA₂ in macrophage-rich plaques.

mPGES-2 is synthesized as a Golgi membrane–associated protein, and the proteolytic removal of the N-terminal hydrophobic domain leads to the formation of a mature cytosolic enzyme. This enzyme is constitutively expressed in various cells and tissues and is functionally coupled with both COX-1 and COX-2. mPGES-2-deficient mice showed no specific phenotype and no alteration in PGE₂ levels in several tissues or in LPS-stimulated macrophages. Studies with PGES-null mice have revealed that cross-regulation between the different PGES isofoms may function, on occasion, as a compensatory mechanism. For example, mPGES-1-null mice exhibit a delayed increase in urinary PGE₂ excretion in response to acute water loading, coincident with enhanced renal medullary expression of cPGES but not of mPGES-2. Similar evidence suggestive of cross-regulation was observed with the COXs. Thus, deletion of COX-2 in macrophages is associated with upregulated expression of COX-2 in vascular smooth muscle cells (VSMCs) in atherosclerotic plaque.
protein-4 or diffuses across the plasma membrane to act at or near its site of secretion.53

PGE2 then acts locally through binding of 1 or more of its 4 cognate receptors (Table), termed EP1–EP4.44 Among the 4 EPs, EP3 and EP4 receptors are the most widely distributed, with their mRNAs being expressed in almost all mouse tissues, and have the highest affinity for binding PGE2. In contrast, the distribution of EP1 mRNA is restricted to several organs, such as the kidney, lung, and stomach, and EP2 is the least abundant of the EP receptors. Both EP1 and EP2 bind PGE2 with lower affinity.54 Each EP subtype shows a distinct cellular localization within tissues.54

One of the lessons learned from the KO mouse studies is that PGE2 can exert both proinflammatory and antiinflammatory responses, and these actions are often produced through regulation of receptor gene expression in relevant tissues. For example, hyperalgesia, a classic sign of inflammation, is mediated mainly by PGE2 through EP1 receptor signaling that acts on peripheral sensory neurons at the site of inflammation, as well as on central neuronal sites.55 Other studies have also implicated the EP3 receptor in the inflammatory pain response mediated by low doses of PGE2.56

EP2 and EP4 redundantly mediate development of paw swelling associated with collagen-induced arthritis.57 Likewise, studies of carrageenan-induced paw edema and carrageenan-induced pleurisy both revealed participation of EP2 and EP3 in inflammatory exudation.58 The EP4 receptor also appears to play a proinflammatory role in the pathogenesis of RA. PGE2 produced by rheumatoid synovium has been implicated in IL-6 production and joint destruction.59,60 Mice deficient in the EP4 but not in the EP1, EP2, or EP3 receptors exhibit an attenuated response in the collagen antibody–induced arthritis model, with significantly lower levels of the inflammatory cytokines IL-6 and IL-1 and a phenotype permitting their homing to draining lymph nodes.65,66 Simultaneously, PGE2 stimulation early during maturation induces the expression of costimulatory molecules of the tumor necrosis factor superfamily on DCs resulting in an enhanced T-cell activation.67 In contrast, PGE2 has also been demonstrated to suppress Th1 differentiation, B-cell functions, and allergic reactions.68 Moreover, PGE2 can exert antiinflammatory actions on innate immune cells, such as neutrophils, monocytes, and natural killer cells.69

PGE2 can thus modulate various steps of inflammation in a context-dependent manner and coordinate the whole process in both proinflammatory and antiinflammatory directions.

This dual role of PGE2 and its receptors in modulating the inflammatory response has been observed in several disorders. In atherosclerosis, EP4 deficiency promotes macrophage apoptosis and suppresses early atherosclerosis in low-density lipoprotein receptor–/– mice chimeric for EP4+/– in hematopoietic cells after 8 weeks on a Western diet.69 EP2 deficiency in hematopoietic cells revealed a trend for similar, but modest, effects on atherosclerosis.69 In the same study macrophage EP4 appeared to play a proinflammatory role in the early stages of atherosclerosis by regulating production of inflammatory cytokines, such as IL-1β, IL-6, and monocyte chemotactic protein-1.69 In contrast, EP4 deletion in bone marrow-derived cells enhanced local inflammation (increased expression of chemotactic proteins, including monocyte chemotactic protein-1 and IL-10, and increased inflammatory cells, such as macrophages and T cells) and altered lesion composition (increased smooth muscle cells within plaque) but did not alter plaque size or morphology in established atherosclerosis (after 10 weeks of high-fat diet).70

PGE2 also plays contrasting roles during neuroinflammation. LPS-induced PGE2 synthesis causes deleterious effects in neurons resulting in lesions or enhanced pain transmission.71–73

However, PGE2 also has antiinflammatory properties. It mediates bradykinin-induced neuroprotection and blocks LPS and ATP-induced cytokine synthesis in cultured microglia and in neuron-glia cocultures.74,75 The antiinflammatory and neuroprotective effects of PGE2 are mediated via microglial EP2 and EP4 receptors. Recently, it has been reported that PGE2 limits cytokine and PG synthesis mainly through EP2 activation in a model of LPS-induced neuroinflammation and that mPGES-1 is a critical enzyme in this negative feedback regulation.49

PGI2 and Inflammation

PGI2 is one of the most important prostanoids that regulates cardiovascular homeostasis. Vascular cells, including endothelial cells, VSMCs, and endothelial progenitor cells, are the major source of PGI2.76

PGI2 is generated by the sequential action of COX and PGIS, a member of the cytochrome P450 superfamily that specifically converts PGH2 to PGI2. PGIS colocalizes with COX in the endoplasmic reticulum, plasma membrane, and nuclear membrane.77 PGIS is constitutively expressed in endothelial cells, where it couples with COX-1,78 although COX-2-dependent PGI2 production by endothelial cells has been reported to be modulated in vitro by thrombin, shear stress, oxidized low-density lipoprotein, hypoxia, and inflammatory cytokines, and it is synchronized by upregulation of COX-2.79,80 In vivo studies in mice and humans showed that COX-2 was the dominant source of PGI2.81

Once generated, PGI2 is released to act on neighboring VSMCs, as well as circulating platelets. Indeed, PGI2 exerts
its effects locally, is not stored, and is rapidly converted by nonenzymatic processes to an inactive hydrolysis product, 6-keto-PGF1α.82

PGI₂ is a potent vasodilator and an inhibitor of platelet aggregation, leukocyte adhesion, and VSMC proliferation.75 PGI₂ is also antimitogenic and inhibits DNA synthesis in VSMC.83

These actions of PGI₂ are mediated through specific IP receptors (Table). This receptor is expressed in kidney, liver, lung, platelets, heart, and aorta.84 There is inconclusive evidence that some effects of PGI₂ on the vasculature might be mediated by the PPARδ pathway, in addition to the classical IP-cAMP signaling pathway.85 PGI₂ can indeed activate PPARδ; however, just as with 15d-PGD₂ and PPARγ, it is unclear that it represents a biological target at concentrations of the ligand attained in vivo.86

Although IP-deficient mice mature normally without experiencing spontaneous thrombosis, both the response to thrombogenic stimuli and VSMC proliferation in response to vascular injury are enhanced compared with control littersmates.87 Mice lacking IP are also sensitive to dietary salt induced hypertension88 and exhibit accelerated atherogenesis with enhanced platelet activation and increased adhesion of leukocytes on the vessel walls in both the low-density lipoprotein receptor and apolipoprotein E KO models.35,89

In addition to its cardiovascular effects, PGI₂ is an important mediator of the edema and pain that accompany acute inflammation. PGI₂ is rapidly produced following tissue injury or inflammation and it is present at high concentrations in inflammatory milieu.90 PGI₂ is the most abundant prostanooid in synovial fluid in human arthritic knee joints, as well as in peritoneal cavity fluid from mice injected with irritants.91,92 In IP receptor–deficient mice, potentiation of bradykinin-induced microvascular permeability by PGI₂ is abolished; in addition, these mice have substantially reduced carrageenan-induced paw edema.93 The level of paw edema observed was equivalent to that of indomethacin-treated controls, and indomethacin treatment of IP-deficient animals did not induce a further decrease in swelling, indicating that PGI₂-IP receptor signaling is the major prostanooid pathway that mediates the acute inflammatory response in this model. It has also been suggested that bradykinin induces PGI₂ formation leading to enhancement of microvascular permeability and edema.94 The IP receptor has been shown to mediate nociceptive pain during acute inflammation. IP receptor mRNA is present in dorsal root ganglion neurons including those that express substance P, a marker for nociceptive sensory neurons.95 IP receptor-deficient mice have an attenuated writhing response following intraperitoneal injection of either acetice acid or PGI₂, indicating that the IP receptor plays a role in mediating peripheral nociceptive sensitization to inflammatory stimuli.96 The IP receptor is also expressed in the spinal cord and has been implicated in spinal pain transmission in response to peripheral inflammation.97 IP antagonists were shown to reduce pain responses in several models, including acetice acid–induced abdominal constriction, mechanical hyperalgesia produced by carrageenan, and pain associated with models of osteoarthritis and inflammatory arthritis.97,98 In contrast to the proinflammatory effects of IP receptor activation in nonallergic acute inflammation, some studies have suggested that IP receptor signaling suppresses Th2-mediated allergic inflammatory responses.99 IP receptor mRNA is upregulated in CD4+ Th2 cells, and inhibition of PGI₂ formation by the COX-2 inhibitor NS-398 during antigen-induced airway inflammation results in greater lung Th2-mediated lung inflammation.99 PGI₂ has been suggested to exert this effect in part by enhancing Th2 cell production of the antiinflammatory cytokine IL-10. This immunosuppressive role for the IP receptor in Th2-mediated inflammation is supported by the observation that in ovalbumin (OVA)-induced asthma, IP deletion results in increased antigen-induced leukocyte accumulation in bronchoaveolar lavage fluid and peribronchiolar and perivascular inflammatory infiltration.100 Thus, PGI₂ may shift the balance within the immune system away from a Th2 dominant response and inhibit allergic inflammation.

**PGD₂ and Inflammation**

PGD₂ is a major eicosanoid that is synthesized in both the central nervous system and peripheral tissues and appears to function in both an inflammatory and homeostatic capacity.101 In the brain, PGD₂ is involved in the regulation of sleep and other central nervous system activities, including pain perception.102,103 In peripheral tissues, PGD₂ is produced mainly by mast cells but also by other leukocytes, such as DCs and Th₂ cells.104–106 Two genetically distinct PGD₂-synthesizing enzymes have been identified, including hematopoietic- and lipocalin-type PGD synthases (H-PGDS and L-PGDS, respectively). H-PGDS is generally localized to the cytosol of immune and inflammatory cells, whereas L-PGDS is more restrained to tissue-based expression.107

PGD₂ can be further metabolized to PGF₂α, 9α,11β-PGF₂ (the stereoisomer of PGF₂α) and the J series of cyclopentanone PGs, including PGJ₁, Δ12-PGJ₁, and 15d-PGJ₂.108 Synthesis of J series PGs involves PGD₂ undergoing an initial dehydration reaction to produce PGJ₁ and 15d-PGJ₂, after which PGJ₁ is converted to 15d-PGJ₂ and Δ12-PGJ₂ via albumin-dependent and albumin-independent reactions, respectively.109

PGD₂ activity is principally mediated through DP or DP₁ and CRTH2 or DP₂, as described previously (Table). Also, 15d-PGJ₂ binds with low affinity the nuclear PPARγ.110 PGD₂ has long been associated with inflammatory and atopic conditions, although it might exert an array of immunologically relevant antiinflammatory functions as well.

PGD₂ is the predominant prostanooid produced by activated mast cells, which initiate IgE-mediated type I acute allergic responses.104,111 It is well established that the presence of an allergen triggers the production of PGD₂ in sensitized individuals. In asthmatics, PGD₂, which can be detected in the bronchoaveolar lavage fluid within minutes, reaches biologically active levels at least 150-fold higher than preallergen levels.112 PGD₂ is produced also by other immune cells, such as antigen-presenting DCs and Th₂ cells, suggesting a modulatory role for PGD₂ in the development of antigen-specific immune system responses.104,105 PGD₂ challenge elicits several hallmarks of allergic asthma, such as bronchoconstriction and airway eosinophil infiltration,113,114 and mice that over-
express L-PGDS have elevated PGD$_2$ levels and an increased allergic response in the OVA-induced model of airway hyperreactivity.\textsuperscript{115}

The proinflammatory effects of PGD$_2$ appear to be mediated by both DP1 and DP2/CRTH2 receptors. Because both receptors bind PGD$_2$ with similar high affinity, PGD$_2$ produced by activated mast cells or T cells would be capable of activating multiple signaling pathways leading to different effects, depending on whether the DP1 or DP2/CRTH2 receptors or both are locally expressed.

The DP1 receptor is expressed on bronchial epithelium and has been proposed to mediate production of chemokines and cytokines that recruit inflammatory lymphocytes and eosinophils, leading to airway inflammation and hyperreactivity seen in asthma.\textsuperscript{116} Mice deficient in DP1 exhibit reduced airway hypersensitivity and Th2-mediated lung inflammation in the OVA-induced asthma model, suggesting that the DP1 plays a key role in mediating the effects of PGD$_2$ released by mast cells during an asthmatic response.\textsuperscript{62} Furthermore, PGD$_2$ may inhibit eosinophil apoptosis via the DP1 receptor.\textsuperscript{117}

DP1 antagonists exert antiinflammatory properties in several experimental models, including inhibition of antigen-induced conjunctival microvascular permeability in guinea pigs and OVA-induced airway hyperreactivity in mice.\textsuperscript{118,119}

DP2/CRTH2 receptors contribute largely to pathogenic responses by mediating inflammatory cell trafficking and by modulating effector functions. PGD$_2$ released from mast cells may mediate recruitment of Th2 lymphocytes and eosinophils directly via the DP2/CRTH2 receptor. In humans, the DP2/CRTH2 receptor is expressed on Th2 lymphocytes, eosinophils, and basophils,\textsuperscript{8,120,121} and an increase in DP2/CRTH2+ T cells has been positively associated with certain forms of atopic dermatitis.\textsuperscript{122} The DP2/CRTH2 receptor has been demonstrated to mediate PGD$_2$-stimulated chemotaxis of these cells in vitro and leukocyte mobilization in vivo.\textsuperscript{123}

In contrast to the proinflammatory role of PGD$_2$ in allergic inflammation, PGD$_2$ may act to inhibit inflammation in other contexts. The DP1 receptor is expressed on DCS that play a key role in initiating an adaptive immune response to foreign antigens. PGD$_2$ activation of the DP1 receptor inhibits DC migration from lung to lymph nodes following OVA challenge, leading to reduced proliferation and cytokine production by antigen-specific T cells.\textsuperscript{124} DP1 activation also reduces eosinophilia in allergic inflammation in mice and mediates inhibition of antigen-presenting Langerhans cell function by PGD$_2$.\textsuperscript{125,126} As mentioned, PGD$_2$ and its degradation product 15d-PGJ$_2$ have been suggested as the COX-2 products involved in the resolution of inflammation.\textsuperscript{28,127} Administration of a COX-2 inhibitor during the resolution phase exacerbated inflammation in a carrageenan-induced pleurisy model.\textsuperscript{28} In a zymosan-induced peritonitis model, deletion of H-PGDS induced a more aggressive inflammatory response and compromised resolution, findings that were moderated by addition of a DP1 agonist or 15d-PGJ$_2$.\textsuperscript{123} Although these data appear to implicate PGD$_2$ and 15d-PGJ$_2$ in resolution, there is a large disparity between the nanomolar to picomolar amounts of 15d-PGJ$_2$ detected by physicochemical methodology in vivo settings and the amount needed to have a biological effect in vitro on PPAR$\gamma$ or nuclear factor-$\kappa$B (micromolar amounts).\textsuperscript{32,128,129} This discrepancy is supported by recent data reported in zymosan-induced peritonitis, where we observed evoked biosynthesis of PGD$_2$ only during the proinflammatory phase and not during resolution. Consistent with this observation, DP2/CRTH2 deletion reduced the severity of acute inflammation, but neither DP1 or DP2/CRTH2 deletion affected resolution. Although 15d-PGJ$_2$ is readily detected when synthetic PGD$_2$ is infused into rodents,\textsuperscript{130} endogenous biosynthesis of 15d-PGJ$_2$ was not detected during promotion or resolution of inflammation (J. Mehta et al, unpublished data, 2010).

PGD$_2$ may play a role in the evolution of atherosclerosis. In the context of inflamed intima, PGD$_2$ in part derives from H-PGDS-producing inflammatory cells that are chemotactically compelled to permeate the vasculature.\textsuperscript{131,132} Additionally, L-PGDS expression is induced by laminar shear stress in vascular endothelial cells and is actively expressed in synthetic smooth muscle cells of atherosclerotic intima and coronary plaques of arteries with severe stenosis.\textsuperscript{133–135} PGD$_2$ has been shown to inhibit expression of proinflammatory genes, such as inducible nitric oxide synthase and plasminogen activator inhibitor.\textsuperscript{136,137} Indeed, L-PGDS deficiency accelerates atherogenesis.\textsuperscript{138}

In summary, studies with COX-2 inhibitors suggest that products of this enzyme may play a role in resolution in several models of inflammation. However, the identity of such products, whether formed directly by COX-2 or because of substrate diversion consequent to COX-2 inhibition, remains, in many cases, to be established.

**PGF$_{2\alpha}$ and Inflammation**

PGF$_{2\alpha}$ is synthesized from PGH$_3$ via PGF synthase, and it acts via the FP, which couples with $G_q$ protein to elevate the intracellular free calcium concentration (Table). Two differentially spliced variants of the sheep FP receptor ortholog have been reported: FP$\alpha$ and FP$\beta$, which differ from each other in the length of their C-terminal tails.\textsuperscript{139} The FP receptor is the least selective of the prostanoid receptors in binding the principal endogenous PGs; both PGD$_2$ and PGE$_2$ ligate the FP with EC$_{50}$ values in the nanomolar range.\textsuperscript{140} PGF$_{2\alpha}$ ring compounds can be formed as minor products from other PGs. For example, enzymatic reduction of 9-keto group of PGE$_2$ compounds by 9-ketoreductases results in either 9a-hydroxyl, yielding PGF$_{2\alpha}$ compounds, or more rarely a 9b-hydroxyl, yielding PGF$_{2\beta}$ compounds.\textsuperscript{141} PGF$_{2\alpha}$ ring metabolites may also be formed from PGD$_2$ ring compounds by 11-keto reductases.\textsuperscript{142}

15-Keto-dihydro-PGF$_{2\alpha}$, a major stable metabolite of PGF$_{2\alpha}$ that reflects in vivo PGF$_{2\alpha}$ biosynthesis, is found in larger quantities first in the peripheral plasma and later on in the urine both in basal physiological conditions and in certain physiological and pathophysiological situations, such as acute and chronic inflammation.\textsuperscript{143}

PGF$_{2\alpha}$, derived mainly from COX-1 in the female reproductive system, plays an important role in ovulation, luteolysis, contraction of uterine smooth muscle, and initiation of parturition.\textsuperscript{144,145} Recent studies have shown that PGF$_{2\alpha}$ also plays a significant role in renal function.\textsuperscript{146}
arteries, myocardial dysfunction, brain injury, and pain. Analogs of PGF \(_{2\alpha}\) have previously been developed for estrus synchronization and abortion in domestic animals and to influence human reproductive function. FP agonists are being widely used worldwide to reduce intraocular pressure in the treatment of glaucoma.

Administration of PGF \(_{2\alpha}\) leads to acute inflammation, and NSAIDs inhibit PGF \(_{2\alpha}\) biosynthesis both in vitro and in vivo. In models of acute inflammation, evoked biosynthesis of PGF \(_{2\alpha}\) may coincide with free radical catalyzed generation of F ring isoprostanes, indices of lipid peroxidation.

The tachycardia induced in WT mice by injection of LPS is greatly attenuated in FP-deficient or TP-deficient mice and is completely absent in mice lacking both of these receptors. A recent study reported that deletion of FP selectively attenuates pulmonary fibrosis without a change in alveolar inflammation after microbial invasion.

Elevated biosynthesis of PGF \(_{2\alpha}\) has been reported in patients experiencing RA, psoriatic arthritis, reactive arthritis, and osteoarthritis.

Cardiovascular risk factors, such as diabetes, obesity, smoking, and thickening of intima-media ratio in the carotid artery, have been variably associated with elevations in PGF \(_{2\alpha}\) metabolites, together with IL-6 and acute phase proteins in body fluids. Deletion of the FP reduces the risk of hyperlipidemic mice despite the absence of detectable FP in large blood vessels and their atherosclerotic plaques.

PGF \(_{2\alpha}\) is the most abundant prostanooid formed by human umbilical cord endothelial cells in response to laminar shear stress that upregulates expression of COX-2.

The emerging role of PGF \(_{2\alpha}\) in acute and chronic inflammation opens opportunities for the design of new antiinflammatory drugs.

**Thromboxane and Inflammation**

TXA\(_{2}\), an unstable AA metabolite with a half-life of about 30 seconds, is synthesized from PGH\(_{2}\) via thromboxane synthase, and it is nonenzymatically degraded into biologically inactive TXB\(_{2}\). TXA\(_{2}\) is predominantly derived from platelet COX-1, but it can also be produced by other cell types, including macrophage COX-2.

TXA\(_{2}\) activity is principally mediated through the TP, which couples with G\(_{i}\), G\(_{12/13}\), and multiple small G proteins, which in turn regulate several effectors, including phospholipase C, small G protein Rho, and adenyl cyclase (Table). TP\(_{\alpha}\) and TP\(_{\beta}\), 2 spliced isoforms of TP in humans, communicate with different G proteins and undergo heterodimerization, resulting in changes in intracellular traffic and receptor protein conformations. Only the TP\(_{\alpha}\) protein is expressed in mice.

TP activation mediates several physiological and pathophysiological responses, including platelet adhesion and aggregation, smooth muscle contraction and proliferation, and activation of endothelial inflammatory responses. TP function is regulated by several factors, such as oligomerization, desensitization and internalization, glycosylation, and cross-talk with receptor tyrosine kinases.

Although TXA\(_{2}\) is the preferential physiological ligand of the TP receptor, PGH\(_{2}\), in particular, can also activate this receptor. In addition, isoprostanes (nonenzymatic free radical-catalyzed peroxidative products of polyunsaturated fatty acids) and hydroxyeicosatetraenoic acids (generated by lipoxygenases and cytochrome P450 monoxygenases or formed by nonenzymatic lipid peroxidation) are also potent agonists at TP receptors. Epoxyeicosatrienoic acid (cytochrome P450 metabolites of AA) dihydro derivatives, in contrast, are selective endogenous antagonists of TP. However, whether PGH\(_{2}\), isoprostanes, or hydroxyeicosatetraenoic acids significantly contribute to the responses attributed to TP activation in vivo is still to be investigated. For example, TP activation by isoprostanes may play an important role in clinical settings of oxidative stress, such as during reperfusion after organ transplant.

TP-deficient mice are normotensive but have blunted vascular responses to TP agonists and show a tendency to bleeding.

The deletion of TP decreases vascular proliferation and platelet activation in response to vascular injury, delays atherogenesis, and prevents angiotensin II- and 1-NAME-induced hypertension and the associated cardiac hypertrophy.

In septic shock models, TP deletion or TP antagonism protected against various LPS-induced responses, such as the increase in inducible nitric oxide synthase expression, acute renal failure, and inflammatory tachycardia, suggesting a potential role of TXA\(_{2}\) as proinflammatory mediator.

The phenotype of thromboxane synthase-deficient mice is much less pronounced, perhaps because TXA\(_{2}\) is only 1 of the endogenous ligands of TP and more likely because the deletion of this enzyme may redirect the PGH\(_{2}\) toward other countervailing synthases.

**Prostanoids in Translation**

This review has described a stunning complexity of evidence about the role of prostanoids in inflammation. Different products have conflicting effects on both the promotion and resolution of inflammation. The same product formed by different enzymes—COX-1 or COX-2—may either promote or resolve inflammation. Products of the same enzyme may promote or resolve inflammation in different models.

These observations prompt several questions.

First, given this complex array of biological effects mediated by prostanoids, how does their general inhibition, high up in the cascade, result in drugs that are reasonably well tolerated and reasonably effective? Aspirin and the myriad NSAIDs, including acetaminophen and those developed to inhibit selectively COX-2, are among the most commonly consumed drugs on the planet. Hard evidence with which to address this question is in short supply, but let us speculate. Aspirin at doses less than 100 mg per day or greater than 1 g per day have equivalent effects on platelet COX-1-derived TXA\(_{2}\). They both suppress it completely.
ing daily doses of aspirin increasingly inhibit PG\textsubscript{I}\textsubscript{2} coincidently with this effect. We do not have direct randomized comparisons across doses, but indirect comparisons suggest that the cardioprotective efficacy of aspirin may be progressively attenuated as the dose is increased. Similarly, locally formed, COX-1-derived PGE\textsubscript{2} and PG\textsubscript{I}\textsubscript{2} are protective of gastroduodenal epithelial integrity, and platelet COX-1-derived TXA\textsubscript{2} contributes to hemostatic competence. Disruption of these pathways by NSAIDs that inhibit COX-1 is thought to account for NSAID induced ulcers. However, NSAIDs selective for inhibition of COX-2 only halve the comparative incidence of serious gastrointestinal events. This may in part reflect their impact on gastroduodenal epithelial COX-2-dependent prostanoids that accelerate ulcer healing.

In these examples, inhibitors high up in the pathway confer benefit, but it is a net benefit, and of course the margin of that benefit may vary substantially between individuals. We only poorly understand interindividual differences in antiinflammatory efficacy among the reversibly acting NSAIDs.

Prostanoids tend to be relatively weak agonists in systems where their blockade has resulted in clinical efficacy. For example, TXA\textsubscript{2} is a relatively weak platelet agonist compared with thrombin, and there is a considerable amount of redundancy in the system.

Why does blockade of just 1 of the many pathways of platelet activation result in an effect so great that its impact can be detected by as crude and instrument as a randomized clinical trial? Similarly, why does blockade of sulfidopeptide leukotrienes alone among many bronchoconstrictors result in clinical efficacy in asthma, or why do other mediators, such as NO, not substitute for the cardioprotective effects of PG\textsubscript{I}\textsubscript{2}, suppressed by NSAIDs selective for inhibition of COX-2? Perhaps drug efficacy is realized because eicosanoids often tend to function as amplifying signals for other, more potent agonists. Activate platelets with thrombin, ADP, or collagen and release of TXA\textsubscript{2} amplifies and sustains the aggregation response. Perhaps this is why aspirin is so effective in the secondary prevention of myocardial infarction or stroke. As for why other mediators do not step in to substitute for suppressed prostanoids, this may speak to their singular importance in circumstances of phenotypic perturbations, as discussed next.

Given the myriad biological effects of these compounds, how are drugs that shut down their synthesis even tolerated? NSAIDs may indeed result in life-threatening gastrointestinal or cardiovascular adverse events, but only in a small minority (perhaps 1% to 2%) of patients exposed. This may reflect the fact that prostanooid formation is a homeostatic response system. Under physiological conditions, trivial amounts of these compounds are formed, and their biological importance is, in many cases, marginal. However, when a system is stressed, they may become pivotal. Examples include their essential role in the maintenance of renal blood flow under renoprival conditions, their antihypertensive effects in patients infused with vasopressors, or their anti-thrombotic effects in patients at increased risk of thrombogenesis. For example, deletion of the IP does not result in spontaneous thrombosis but rather accentuates the response to thrombogenic stimuli. Similarly, although preexisting cardiovascular disease was often used to dilute the legal liability of the sponsor in cases where patients experienced myocardial infarctions while taking coxibs, the relative risk of myocardial infarctions on celecoxib relates to the underlying burden of cardiovascular disease, an expected consequence of suppression of COX-2 derived PG\textsubscript{I}\textsubscript{2}.\textsuperscript{164}

Given the contrasting effects of prostanoids, should we move down the pathway to get a more targeted and safer response? Presently, we have almost no data that address this question. In the case of downstream PG synthase versus COX-2 inhibition, the experience with mPGES-1 deletion highlights the complexity of the comparison. Here, substrate rediversion to PGIS may attenuate the cardiovascular risk of COX-2 inhibition but dilute analgesic efficacy. Another example is the comparison between low-dose aspirin for cardioprotection and TP antagonism. The latter strategy avoids PG\textsubscript{I}\textsubscript{2} suppression, but this is very modest, on average \textcirca{15%}, with low-dose aspirin. One would need an enormous clinical trial to detect that theoretical benefit. Alternatively, the antagonist, unlike aspirin, might block TP activation by unconventional ligands, such as isoprostanes and hydroxyeicosatetraenoic acids. However, although these compounds can activate the TP, their relevance in vivo, even in settings of tissue reperfusion where they are formed in excess, remains speculative. One might of course model this comparison and use COX-1 knockdown mice, which mimic the asymmetrical impact on platelet COX-1 of low-dose aspirin, to address the question. Finally, as the overlap in the biological consequences of activating several prostanoid receptors—the IP, EP2, EP4, and DP1 group or the FP, TP, and EP1 group, for example—hint at the possibility that efficacy might be diluted as one moves downstream to target just 1 prostanoind in the pathway. Our poor understanding of such potential functional redundancy at the receptor level, never mind insight into the implications of receptor dimerization, leave these as open questions for drug development.

Surely, this complexity suggests that experiments in animals are going to be of virtually no value when it comes to predicting drug effects in vivo. Certainly the limitations of standard experimental paradigms apply in this pathway, as in others. We study mouse models of atherosclerosis that fail to undergo spontaneous plaque fissure and thrombotic occlusion of vital arteries to reach conclusions about prevention or provocation of myocardial infarction. We extrapolate from drug action on murine tolerance of a hotplate to patients undergoing molar extraction in an effort to divine therapies for elderly women with osteoarthritis of the knees. These and many such examples inspire caution in the field of translational therapeutics. However, consistency of evidence from different model systems across multiple species can, especially when integrated with independent lines of evidence, predict with some confidence the outcome in randomized clinical trials of drug action in this pathway. Such was the case in the prediction and mechanistic elucidation of the cardiovascular hazard from NSAIDs.\textsuperscript{178}

Finally, is it likely that this pathway will yield more therapeutic opportunities? Besides drugs already approved for various indications (like aspirin and the myriad NSAIDs; analogues of PGE\textsubscript{2}, PGF\textsubscript{2a}, and PG\textsubscript{I}\textsubscript{2}; TP and leukotriene
antagonists) currently inhibitors of mPGES-1, 5–lipoxygenase and its activating factor (five lipoxygenase activating protein) and antagonists of DP1, DP2, and EP4 are all undergoing clinical evaluation. Many other targets in the eicosanoid pathway are undergoing preclinical evaluation, just as others, such as the multiple secretory phospholipases and the soluble epoxide hydrolase, emerge. This coincides with new information about old targets.

Why do we need to inhibit both COXs, not just COX-1, to see gastrointestinal injury in model systems? Why is a form of aspirin confined to platelet inhibition in the presystemic circulation associated with a reduction in the incidence of colon cancer? Much remains to be discovered about the biology of the eicosanoids, and from this is likely to come new therapeutic opportunity.

Conclusion
Prostanoids can promote or restrain acute inflammation. Products of COX-2 in particular may also contribute to resolution of inflammation in certain settings. Presently, we have little information on which products of COX-2 might subserve this role or indeed whether the dominant factors reflect redirection of the AA substrate to other metabolic pathways consequent to deletion or inhibition of COX-2. As with cyclopentanone prostanoids, many arachidonate derivatives, including transcellular products, when synthesized and administered as exogenous compounds, can promote resolution in models of inflammation. However, rigorous physicochemical evidence for the formation of the endogenous species in relevant quantities to subserve this role in vivo is limited. Elucidation of whether and how prostanoids might restrain inflammation and how substrate modification, such as with fish oils, might exploit this understanding is currently a focus of much research from which novel therapeutic strategies are likely to emerge.

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