

Prostanoids in health and disease

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Abstract The prostanoids are a family of lipid mediators generated by the action of cyclooxygenase on a 20-carbon unsaturated fatty acid, arachidonic acid. Prostanoids are generated widely in response to diverse stimuli and, acting in a paracrine or autocrine manner, play important roles in normal physiology and disease. This review summarizes the current knowledge on prostanoid generation and the roles of individual mediators, their biosynthetic pathways, and their receptors in health and disease.—Smyth, E. M., T. Grosser, M. Wang, Y. Yu, and G. A. FitzGerald. **Prostanoids in health and disease.** *J. Lipid Res.* 2009. S423–S428.

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Arachidonic acid (AA), a 20-carbon unsaturated fatty acid, is the predominant precursor for a family of lipid mediators, the eicosanoids. Eicosanoid biosynthesis begins with release of AA, esterified in the sn-2 domain of membrane phospholipids, by the action of phospholipase A₂, particularly group IVA cytosolic cPLA₂. Three major groups of enzymes, prostaglandin G/H synthases, lipoxygenases, or epoxygenases, then catalyze the formation of the prostaglandins (PGs) and thromboxane A₂ (TxA₂), the leukotrienes, or the epoxyeicosatrienoic acids, respectively. A parallel family of free radical catalyzed isomers, the iso-eicosanoids, is formed by nonenzymatic peroxidation of AA in situ (1). This review will focus on the PGs and TxA₂, collectively termed the prostanoids (Fig. 1), in normal physiology and disease.

PROSTANOID BIOSYNTHESIS

Prostanoids are formed by the action of prostaglandin G/H synthase, or cyclooxygenase (COX), on AA. COX, an evolutionarily conserved (2) bisfunctional enzyme, exists as two distinct isoforms, COX-1 or COX-2. COX-1, ex-

pressed constitutively in most cells, is the dominant (but not exclusive) source of prostanoids for housekeeping functions, such as gastric epithelial cytoprotection and hemostasis. COX-2, induced by cytokines, shear stress, and tumor promoters, is the more important source of prostanoid formation in inflammation and perhaps cancer. However, both enzymes contribute to the generation of autoregulatory and homeostatic prostanoids, and both can contribute to prostanoid formation during inflammation.

COX-1 or COX-2 function as homodimers, and perhaps heterodimers (3), inserted into the endoplasmic reticular membrane, to transform AA into the unstable cyclic endoperoxides PGG₂ and PGH₂ (Fig. 1). Downstream isomerases and synthases complete the biosynthesis of TxA₂ and D, E, F, and I series PGs. COX-1 and COX-2 are closely related in their amino acid sequence and crystal structure (4). Isoform-specific preference for downstream enzymes has been reported in heterologous expression systems, although the biological relevance is unknown. COX-1 couples preferentially, but not exclusively, with thromboxane synthase, prostaglandin F synthase, and the cytosolic prostaglandin E synthase (PGES) isozymes. COX-2 prefers prostaglandin I synthase (PGIS) and the microsomal (m) PGES isozymes, both of which are induced by cytokines and tumor promoters. Two forms of prostaglandin D and F synthase have been identified, underscoring the diversity of the isomerases and synthases.

PROSTANOID RECEPTORS

Prostanoids activate membrane receptors at, or close to, the site of their formation. Specific G-protein-coupled receptors have been cloned for all the prostanoids (5). A single gene product has been identified for prostacyclin [the I prostanoid (IP) receptor], PGF_{2α} [the F prostanoid receptor (FP)], and TxA₂ [the T prostanoid receptor (TP)], while four distinct PGE₂ receptors (the EP_{1–4}) and two PGD₂ receptors (DP₁ and DP₂) have been cloned. Two additional

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Abbreviations: AA, arachidonic acid; AAA, abdominal aortic aneurysm; Ang, angiotensin; COX, cyclooxygenase; IP, I prostanoid; NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin; TxA₂, thromboxane A₂.

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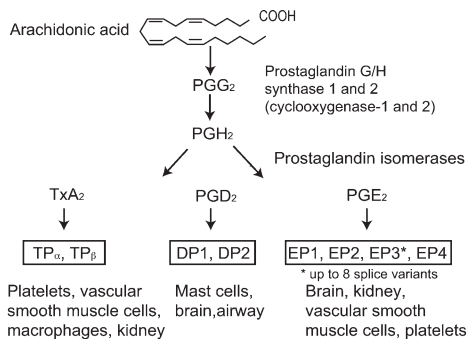


Fig. 1. The prostanoid biosynthesis response pathway.

isoforms of the human TP and FP and eight EP₃ variants are generated through differential splicing. EP₂, EP₄, IP, and DP₁ receptors activate adenylyl cyclase via G_s, increasing intracellular cAMP. EP₁, FP, and TP activate phosphatidylinositol metabolism, leading to the formation of inositol trisphosphate with mobilization of intracellular Ca²⁺ stores. TP couples to multiple G proteins, including G_{12/13} and G₁₆, to stimulate small G protein signaling pathways and may activate or inhibit adenylyl cyclase. EP₃ isoforms can couple via G_i or G₁₂ to elevation of intracellular Ca²⁺, inhibition of cAMP generation, and activation of the small G protein Rho. The DP₂ (also known as the chemoattractant receptor homologous molecule expressed on Th2 cells) couples to a G_i-type G protein to inhibit cAMP synthesis and elevate intracellular Ca²⁺.

PROSTANOIDS IN HEALTH AND DISEASE

Inflammation

Prostanoid biosynthesis is significantly increased in inflamed tissue. Nonselective COX-1/COX-2 inhibitors, aspirin and the traditional (t) nonsteroidal anti-inflammatory drugs (NSAIDs), are widely used anti-inflammatory agents, highlighting the pro-inflammatory role of the prostanoids. The marked induction of COX-2 in inflammatory cells and tissues provided a rationale for development of selective COX-2 inhibitors. However, although COX-2 is a major source of pro-inflammatory prostanoids, an inflammatory role for COX-1 is also evident (6). Indeed, COX-1 accounts for ~10–15% of the prostanoid formation induced by lipopolysaccharide in humans, and both isozymes are expressed in circulating inflammatory cells *ex vivo*. Impaired inflammatory responses have been reported in both COX-1- and COX-2- deficient mice, although they diverge in time course and intensity. Human data indicate that COX-1-derived products drive the initial phase of an acute inflammation, with COX-2 upregulation occurring within several hours.

PGE₂ and PGI₂ are the predominant pro-inflammatory prostanoids. Both markedly enhance edema formation and leukocyte infiltration by promoting blood flow. PGE₂ and PGI₂, through activation of the EP₂ and IP, respectively, also increase vascular permeability and leukocyte infiltration (5). The chemotactic function of PGD₂, a major product of mast cells, contributes to inflammation in allergic responses, particularly in the lung. Activation of DP₁ increases blood flow and vascular permeability and pro-

motes T-cell polarization to the Th2 phenotype. PGD₂ can also promote inflammation via DP₂ through activation of Th2 cells and eosinophils (7). DP₂ antagonists may prove useful in treatment of airway inflammation; however, conflicting results with respect to airway function in DP₂-deficient mice suggest a complex context- and tissue-dependent inflammatory role for PGD₂.

Cyclooxygenase inhibitors have a long history as anti-pyretic drugs. The early phase of the pyretic response to IL-1β, an endogenous pyrogen that mediates the febrile response to a variety of exogenous stimuli, is likely mediated by ceramide, but the late response is mediated by central induction of PGE₂ synthesis. IL-1β and other cytokines induce the coordinate expression of COX-2 and mPGES-1 in endothelial cells of the highly vascularized midline of the preoptic area. PGE₂ can cross the blood-brain barrier to act on the EP₃, and perhaps EP₁, expressed on thermosensitive neurons (8).

Pain

PGE₂ and PGI₂ reduce the threshold of nociceptor sensory neurons to stimulation. This “peripheral sensitization” potentiates the pain-producing activity of bradykinin and other autocooids. COX-1 and COX-2, expressed in the spinal cord, release PGs in response to peripheral pain stimuli. PGE₂, and perhaps also PGD₂, PGI₂, and PGF_{2α}, contribute to “central sensitization” (9), an increase in spinal dorsal horn neuron excitability that augments pain intensity, widens the perception area, and results in pain from innocuous stimuli.

COX-1-deficient mice show increased tolerance to pain stimuli. COX-1 is the predominant isoform expressed in neurons of dorsal root ganglia, and prolonged expression has been observed in spinal microglia during central sensitization (10). COX-2, expressed basally in both neurons and glia, contributes to central sensitization in the early phase of peripheral inflammation. Within a few hours, it is upregulated widely in the spinal chord, contributing to prolonged central sensitization. Activation of EP₁ and IP play a more pronounced role during early phases of inflammatory pain, while activation of EP₂ may be more relevant in chronic events (11).

Renal function

Renal PGs, especially PGE₂ and PGI₂, but also PGF_{2α} and TxA₂, perform complex and intricate functions in the kidney (12, 13). Both COXs are expressed in renal tissue;

COX-1 mainly in the cortical and medullary collecting ducts, mesangial cells, arteriolar endothelium, and the epithelium of Bowman's capsule and COX-2 in medullary interstitial cells, the macula densa, and the cortical thick ascending limb.

COX inhibition is associated with an increased risk of peripheral edema and sodium retention (14). COX-2-derived prostanoids increase medullary blood flow and inhibit tubular sodium reabsorption. Indeed, expression of medullary COX-2 and mPGES-1 is increased by high salt intake, and COX-1-derived products promote salt excretion in the collecting ducts. Loss of these effects may underlie the systemic or salt-sensitive hypertension often associated with COX inhibition. However, COX-1 and COX-2 products may have contrasting renal effects; COX-1 deletion or inhibition reduces the hypertensive response to angiotensin (Ang) II in rodents, while COX-2 deletion or inhibition reduces medullary blood flow and enhances the hypertensive response to Ang II. Therefore, the renal side effects of selective and nonselective NSAIDs may not be identical, a notion that is supported by a large meta-analysis showing that selective inhibition of COX-2 elevates blood pressure more than nonselective inhibition (15).

Renal-cortex-derived prostanoids modulate systemic blood pressure in a manner that is distinct from the medullary enzyme. Cortical COX-2-derived PGE₂ and PGI₂ increase renal blood flow and glomerular filtration by local vasodilation, actions that may be particularly relevant in marginally functioning kidneys and volume-contracted states. Cortical COX-2 expression is increased by low dietary salt intake, which, through the action of PGE₂, and possibly PGI₂, increases renin release, leading to sodium retention and elevated blood pressure. Concordantly, COX-2 inhibition or disruption decreases plasma renin following administration of a low-salt diet (12).

The regulated expression patterns of renal prostanoid receptors, particularly the EPs, contributes substantially to this complexity (12). EP₁, expressed exclusively in collecting ducts, mediates PGE₂-dependent inhibition of salt and water absorption. EP₁-deficient mice have a urine concentration defect due to decreased vasopressin release, resulting in hypotension (16). EP₂ mRNA is present at low levels in the descending thin limb of Henle and the vasa recta of the outer medulla; mice deficient in EP₂ develop salt-sensitive hypertension. EP₃ is abundant in the thick ascending limb and collecting ducts and also in glomeruli. EP₄ is expressed primarily in the glomerulus and outer medullary vasa recta, mediating PGE₂-dependent dilation of the renal microcirculation as well as renin release. TP is localized to glomeruli and the renal vasculature, corresponding to TxA₂'s potent vasoconstrictor effects that reduce renal blood flow and glomerular filtration rate. The FP is highly expressed in the distal convoluted tubules and the cortical collecting duct. In vitro studies suggest that activation of the FP modulates water absorption through inhibition of vasopressin action (17), while infusion of PGF_{2α} causes both natriuresis and diuresis. Mice with FP deficiency exhibit hypotension, probably due to decreased renin-angiotensin activity (unpublished observations). The

IP is predominantly expressed in renal interlobular, vasa recta, and glomerular afferent arterioles. Similar to PGE₂, PGI₂ dilates the glomerular microvasculature and can regulate renin release.

Cardiovascular

The importance of prostanoids in maintaining cardiovascular homeostasis is highlighted by clinical experience with NSAIDs. Despite their superior gastrointestinal safety, compared with nonselective tNSAIDs, COX-2 selective inhibitors increase the risks of myocardial infarction, stroke, systemic and pulmonary hypertension, thrombosis, congestive heart failure, and sudden cardiac death (18). Seven randomized controlled trials, involving three structurally distinct COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib), provide compelling evidence for this cardiovascular hazard (18, 19). This extends to some older drugs, such as diclofenac, meloxicam, and nimesulide, which also show some COX-2 selectivity.

Because of their short half-life, prostanoids do not circulate and do not impact directly systemic vascular tone. However, they may modulate local vascular tone at the site of their formation and affect systemic blood pressure through the kidney. Upon infusion, PGE₂, PGD₂, and PGI₂ elicit vasodilation in most vascular beds. Vasoconstriction can result from activation of EP₁ and EP₃ by PGE₂. We and others reported that, unlike interruption of COX-2 activity, deletion of mPGES-1, which substantially reduced PGE₂ biosynthesis, fails to alter blood pressure in mice fed a normal or high-salt diet (20). Hypertension induced by Ang II infusion in hyperlipidemic mice is also uninfluenced (21), although the hypertensive response to a more intensive salt load, and to Ang II infusion, in normolipidemic mice was augmented (22). This discrepancy may reflect differences in mouse strain genetic background and/or dosing regimen.

Polymorphisms in PGIS and the IP have been associated with essential hypertension (23), although studies argue against a role for PGI₂ in the homeostatic maintenance of vascular tone. PGI₂ limits pulmonary hypertension induced by hypoxia and systemic hypertension induced by Ang II. PGI₂, and its stable analogs, have been used successfully to treat pulmonary arterial hypertension (24). Local subcutaneous release of PGD₂ causes dilation of skin vasculature contributing to the facial flushing associated with niacin treatment in humans. PGF_{2α} is a potent constrictor of both pulmonary arteries and veins in humans, while TxA₂ is a vasoconstrictor in the whole animal and in isolated vascular beds.

Hypertension and congestive cardiac failure have been observed in placebo-controlled trials of NSAIDs (18). We recently found that selective deletion of cardiomyocyte COX-2 resulted in heart failure and cardiac fibrosis in mice (unpublished observations), demonstrating a direct role of COX-2-derived prostanoids in cardiac function. Acting on the IP or the EP₃, respectively, PGI₂ and PGE₂ protect against oxidative injury in cardiac tissue. Global deletion of the IP augments ischemia/reperfusion injury (25), while both global deletion of mPGES-1 (26) and cardiomyocyte-specific deletion of the EP₄ (27) exacerbate

the decline in cardiac function after myocardial infarction. In an alternative heart failure model, COX-2-derived TXA₂ contributed to oxidant stress and isoprostane generation to increase cardiomyocyte apoptosis and fibrosis (28). A compensatory rise in PGI₂ biosynthesis reflects the apparent role of this PG in subserving a homeostatic cardioprotective function.

Platelets

Activated platelets synthesize TxA₂, amplifying further platelet activation and recruitment (29). The total biosynthesis of TxA₂ is augmented in clinical syndromes of platelet activation, including unstable angina, myocardial infarction and stroke. Mature platelets express only COX-1, although megakaryocytes and immature platelet forms also express COX-2 (30). While most NSAIDs inhibit COX reversibly, aspirin acetylates Ser-529 in COX-1 (Ser-516 in COX-2) covalently, inhibiting its enzymatic activity irreversibly. This unique feature, which sustains inhibition of platelet TxA₂ biosynthesis, together with the limited capacity of platelets for de novo protein synthesis, underlies aspirin's position as the only COX inhibitor with proven cardioprotective activity (31).

In platelets, the TP couples predominantly to G_q and G_{12/13}. G_q activates protein kinase C-dependent pathways, which facilitate platelet aggregation, whereas G_{12/13}-mediated Rho/Rho-kinase-dependent regulation of myosin light chain phosphorylation contributes to platelet shape change. Endogenous inhibitors of platelet function, including nitric oxide and prostacyclin (PGI₂), serve to limit platelet activation in vivo (18).

PGI₂ is the major platelet inhibitory prostanoid. It is synthesized by COX-2, and to a lesser degree by COX-1, in vascular endothelial and smooth muscle cells. Following activation of the IP-Gs-adenylyl cyclase pathway, cAMP activates PKA deactivating myosin light chain kinase to reduce myosin phosphorylation and decrease platelet aggregation (32). PKA also targets the vasodilator-stimulated phosphoprotein, which may regulate fibrinogen binding by modulating inside-out signaling of the integrin αIIbβ3. The IP may also modify specifically the response to TxA₂ through formation of an IPTP heterodimer (33). Augmented PGI₂ biosynthesis in syndromes of platelet activation serves to constrain the effects of platelet agonists, vasoconstrictors, and stimuli of platelet activation (34). The increased incidence of myocardial infarction and stroke associated with selective COX-2 inhibition, which is most parsimoniously explained by inhibition of COX-2-dependent PGI₂ formation (18), supports this concept.

The role of PGE₂ in platelet function in vivo remains less clear. In vitro, high PGE₂ concentrations (>10 mM), acting via the IP or, theoretically, the EP₂ or EP₄, inhibit platelet function (35). Low concentrations of PGE₂, acting via the EP₃, augment submaximal platelet stimulation by other agonists; mice lacking EP₃ have an increased bleeding tendency and decreased susceptibility to thromboembolism. Deletion of mPGES-1 does not affect thrombogenesis in mice, probably because of substrate redirection and augmented PGI₂ formation (20).

Atherothrombosis

In atherosclerosis, an inflammatory cardiovascular disease, unstable or ruptured plaques can result in intravascular thrombosis leading to severe clinical complications. Increased atherogenesis may be fundamental to evolution of a cardiovascular risk in patients taking COX-2-selective NSAIDs chronically (18). However, studies examining the impact of selective COX-2 inhibition on atherogenesis have yielded conflicting results. COX-2 inhibitors have been shown variously to retard, accelerate, or leave unaltered atherogenesis in mouse models (36). This may result from differences in drug specificity or dosing strategy but may also reflect the contrasting effect of local prostanoids, elaborated in a cell-specific manner, over the course of the disease.

Individual prostanoids are associated with contrasting effects in atherothrombosis. Suppression of TxA₂ biosynthesis, as well as TP antagonism or deletion, retards atherogenesis in mice (37, 38). Conversely, PGI₂ appears atheroprotective (38, 39). As mentioned above, the cardiovascular hazard associated with selective inhibition of COX-2 is mechanistically explicable by suppression of cardioprotective COX-2-derived prostanoids, especially PGI₂ (18, 23). In addition to its action as a general restraint on platelet activation (see platelet section, above) and its potential role in retarding atherogenesis, PGI₂ limits vascular proliferation, remodeling, and hypertension (20, 34, 38, 39). These mechanisms, primarily elucidated in rodents, would be expected to alter the cardiovascular risk of humans. Indeed, an Arg-212-to-Cys substitution in IP, which disrupts its signaling, cosegregated with increased cardiovascular risk in a recent study (23).

PGE₂ effects on atherothrombosis are more complex. mPGES-1 colocalizes, in some settings, with COX-2, and both enzymes are subject to regulation during inflammation. Deletion or inhibition of mPGES-1 markedly reduces inflammatory responses, in several mouse models, and mPGES-1 deletion reduces atherogenesis in fat fed hyperlipidemic mice (40). Interestingly, in addition to the expected depression of PGE₂ production, deletion of mPGES-1 augments biosynthesis of PGI₂, presumably through redirection of PGH₂ to PGIS. It is currently unclear, however, whether elevated PGI₂ contributes to the cardiovascular profile of mPGES-1 deletion and whether small molecule inhibitors of mPGES-1 will have the same metabolic and functional effects as gene deletion.

Aortic aneurysm

Abdominal aortic aneurysm (AAA), also an inflammatory cardiovascular disease, is a major cause of morbidity and mortality in humans. Nonsurgical treatments that retard aneurysm development, or induce its regression, remain to be identified. Human AAA biopsies stain strongly for COX-2, and there is evidence for the potential efficacy of NSAIDs, particularly COX-2 selective inhibitors, for treatment of aneurysmal growth. In mouse models, deletion or selective inhibition of COX-2 or mPGES-1, but not inhibition of COX-1, decreases AAA formation (21). Augmented biosynthesis of both PGI₂ and PGD₂ coincides with mPGES-1 deficiency, suggesting a contribution of sub-

strate redirection to reduced AAA formation and to the depression of attendant oxidant stress. These studies raise the possibility that specific mPGES-1 inhibitors might prevent or retard human AAA formation. However, mPGES-1 deletion is also associated with eccentric cardiac myocyte hypertrophy, left ventricular dilation, and impaired left ventricular contractile function, after myocardial infarction (26). The extent to which these observations may be translated to clinical indications of mPGES-1 inhibitors is unclear and necessitates further investigation.

Lung

COX-1- and COX-2-deficient mice, or mice treated with COX inhibitors, display exaggerated inflammatory airway responses and bronchoconstrictor hyperresponsiveness in murine models of asthma (41). PGE₂ can have anti-inflammatory and antiasthmatic effects via activation of EP₃ (42). IP deletion exaggerates features of acute and chronic experimental asthma, including increased bronchial hyperresponsiveness, while inhaled iloprost (a PGI₂ analog) suppresses the cardinal features of asthma in mice (43). The role of PGD₂ in allergic asthma is complicated (7). Deletion of DP₁ in mice sharply reduces allergen-induced infiltration of lymphocytes and eosinophils and airway hyperreactivity. However, activation of DP₁ on bone-marrow-derived cells inhibits airway inflammation, and activation of DP₁ on lung dendritic cells may also control the extent of airway inflammation (44). In vitro studies strongly support a pro-inflammatory role for PGD₂ acting at the DP₂. However, the surprising increase in the allergic asthmatic responses in DP₂-deficient mice suggests a more complex function for PGD₂ than previously thought.

Cancer

Pharmacological inhibition, or genetic deletion of COX-2, reduces tumor formation in experimental animal models of colon, breast, lung, and other cancers (45, 46). In mice, targeted overexpression of COX-2 in the mammary epithelium is sufficient to induce tumorigenesis. Large epidemiologic studies concur, reporting significant reductions in relative risk for developing these, and other, cancers with the incidental use of NSAIDs (47). COX inhibitors significantly decrease polyp formation, in patients with familial polyposis coli, while a polymorphism in COX-2 has been associated with increased risk of colon cancer. Three randomized controlled trials, the Adenoma Prevention with Celecoxib trial, the Prevention of Sporadic Adenomatous Polyps trial, and the Adenomatous Polyp Prevention on Vioxx trial, reported a significant reduction in the reoccurrence of adenomas in patients receiving either celecoxib or rofecoxib (48). However, this coincided with an increase in risk of cardiovascular events, undermining the risk-to-benefit ratio. Although celecoxib remains approved for use in patients with familial polyposis coli, none of these trials included the cheaper COX-1/COX-2 nonselective tNSAIDs as comparators, despite evidence in rodent models implicating both enzymes in polyp formation.

Most data indicate that PGE₂ is the a primary pro-oncogenic prostanoid, at least in part via transactivation

of epidermal growth factor receptor (46). PGE₂ facilitates tumor initiation, progression, and metastasis through multiple biological effects, including increased proliferation and angiogenesis, decreased apoptosis, augmented cellular invasiveness, and modified immunosuppression. Mice lacking EP₁, EP₂, or EP₄ display reduced disease in multiple carcinogenesis models. By contrast, EP₃ may play a protective role in some cancers. The pro- and anti-oncogenic roles of other prostanoids remain under investigation, with TxA₂ emerging as another likely COX-2-derived procarcinogenic mediator (45).

CONCLUSIONS

Deletion of prostanoid receptors in mice has revealed a remarkably diverse and contrasting biology mediated by this family of lipids. The therapeutic potential of this pathway is illustrated by the clinical efficacy of aspirin and the NSAIDs. Although NSAIDs selective for inhibition of COX-2 confer a risk of cardiovascular events, this appears to involve only 1–2% of exposed patients, and it would seem logical to investigate these drugs further to seek a scientific basis for risk management. In the meantime, other targets in the pathway, such as mPGES-1 and many of the receptors, have emerged as drug targets. It is likely that the harvest from this pathway will continue to yield therapeutic benefit in the years to come.

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