Eicosanoids in Regulation of Arterial Smooth Muscle Cell Phenotype, Proliferative Capacity, and Cholesterol Metabolism

Kenneth B. Pomerantz and David P. Hajjar

Eicosanoids, particularly prostacyclin (PGI₂) and thromboxane A₂ (TXA₂), have been implicated in the regulation of vascular homeostasis from the point of view of platelet-vessel wall interactions and in the regulation of blood vessel tone and hemostasis (for reviews, see references 1 and 2). However, subsequent investigations have revealed that PGI₂ and other eicosanoids may also have an important role in the regulation of arterial smooth muscle cell phenotype and cellular cholesterol metabolism. The purpose of this review is to summarize recent findings on the role of eicosanoids in the regulation of smooth muscle cell proliferative capacity and cellular cholesterol content under normal physiological conditions and in an "atherogenic" environment.

Evidence Implicating Eicosanoids in Atherosclerosis

It is now well established that oxygenated metabolites of arachidonic acid (a polyunsaturated fatty acid derived from chain elongation and delta-9 desaturation of linoleic acid), namely prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids (HETEs), may play a role in vascular homeostasis. PGI₂ is the principal arachidonic acid metabolite synthesized by arterial tissue principally by endothelium and, to a lesser extent, by underlying medial smooth muscle cells. Prostaglandin E₂ (PGE₂) and prostaglandin F₂α (PGF₂α) are also synthesized by vascular endothelium and smooth muscle cells, but to a much lesser extent. On the other hand, platelets synthesize predominantly TXA₂ and 12-HETE, which are potent vasoconstrictors and platelet-aggregators. Moncada and Vane⁴ hypothesized that the balance of TXA₂ and PGI₂ maintained "vascular integrity" consistent with maintenance of the anticoagulated state. This hypothesis also implied that derangements in vascular eicosanoid metabolism could predispose to thrombosis and vasoospasm due to the release of procoagulant and vasoactive constituents from platelets and potentially other inflammatory cells. However, it is becoming increasingly apparent that vascular eicosanoids may be implicated in the atherogenic process.

The metabolic derangements leading to smooth muscle cell migration, proliferation, cholesteryl ester deposition, foam cell formation, and eventual plaque development are incompletely understood. Early studies on the pathogenesis of atherosclerosis were carried out by Virchow,⁵ who suggested that atherosclerotic lesions form as a consequence of vascular injury. This concept was further extended by Ross et al.,⁶ who proposed that endothelial denudation elicited mural platelet deposition and secretion of platelet mitogens, which in turn stimulated arterial smooth muscle cell proliferation and accretion of lipid. These pathologic events were postulated to occur in response to a variety of injurious stimuli.⁶ Since endothelial denudation and platelet deposition do not normally take place in blood vessels, the response-to-injury hypothesis has now been modified to suggest that alterations in endothelial cell function, perhaps as a result of inflammatory stimuli or other factors, may initiate and mediate the subintimal changes leading to plaque development.⁶,⁷,⁸

Evidence implicating eicosanoids in the pathophysiology of atherosclerosis relates to observations that altered eicosanoid metabolism accompanies atherosclerosis. It appears that either a relative deficiency in arachidonic acid or defects in arachidonic acid metabolism may occur in atherosclerosis. Patients at risk for myocardial infarction have less arachidonic acid in plasma and tissue than normal.⁹ Furthermore, numerous studies¹⁰⁻¹⁴ have determined that the PGI₂ synthesis is reduced in human, rabbit, and rat atherosclerotic blood vessels during the disease process. Cholesterol feeding also impairs the regeneration of PGI₂ synthetic capacity by neointima (comprised of proliferating endothelial and smooth muscle cells) after balloon catheterization in rabbits.¹⁵,¹⁶ Diets enriched in polyunsaturated fatty acids (principally linoleic and arachi-
donic acids) have been shown to reduce the clinical sequelae of atherosclerotic lesion formation in humans and in animal models.\textsuperscript{17,18} However, others have shown increased urinary\textsuperscript{19} and vascular\textsuperscript{20,21} PGI\textsubscript{2} production in human and animal atherosclerosis. A number of factors may explain this discrepancy. First, there may be a time-dependent effect of hypercholesterolemia on PGI\textsubscript{2} production, where the onset of cholesterol feeding initially increases, then progressively decreases, vascular PGI\textsubscript{2} production ex vivo.\textsuperscript{22} Second, there may be a distinction between tissue capacity to synthesize eicosanoids and actual eicosanoid biosynthetic rates.\textsuperscript{23,24} Thus, although total eicosanoid synthetic capacity may be reduced in atherosclerotic disease, a possible state of activation as a result of ischemia or interactions with other cell types, including platelets, as a result of vessel injury may result in increased eicosanoid generation by the diseased tissue. This explanation is also compatible with the temporal effects of hypercholesterolemia on vascular eicosanoid metabolism.

Furthermore, known positive risk factors for atherosclerosis are associated with altered eicosanoid metabolism. Overwhelming evidence suggest that diabetes, a disorder associated with accelerated atherosclerosis, reduces PGI\textsubscript{2} synthesis in rats and other species.\textsuperscript{25-36} Although urinary production of PGI\textsubscript{2} and its metabolites may be unchanged or increased and subsequently normalized by insulin treatment,\textsuperscript{37} The mechanism by which diabetes inhibits vascular PGI\textsubscript{2} generation may be due to reduction in arachidonate availability to eicosanoid synthetic enzymes,\textsuperscript{32,34} with no alteration in the activity of PGI\textsubscript{2} synthetase.\textsuperscript{36,40} Elevations in urinary PGI\textsubscript{2} metabolites in diabetes may be due to increased PGI\textsubscript{2} production by hypertrophied urinary bladder as a result of the diabetic condition,\textsuperscript{41} suggesting that measurements of urinary metabolites of PGI\textsubscript{2} may not reflect an accurate estimate of vascular PGI\textsubscript{2} synthesis. In addition, the effects of diabetes are additive with hypercholesterolemia in inhibiting PGI\textsubscript{2} synthesis from rat aorta.\textsuperscript{42}

Smoking, a major risk factor for development of atherosclerosis,\textsuperscript{43-49} causes reduced vascular eicosanoid synthesis.\textsuperscript{44}

Aging, which is temporally associated with the incidence and severity of atherosclerosis, is also associated with decreased arterial eicosanoid synthetic capacity\textsuperscript{49,50} and increased smooth muscle proliferation.\textsuperscript{51,52}

Viral infection has been implicated as a potential causative factor of atherosclerosis. Viral infection of avian,\textsuperscript{53,54} bovine,\textsuperscript{55} and human\textsuperscript{55} arterial smooth muscle cells reduces eicosanoid synthetic capacity and decreases cholesterol ester hydrolytic activities concomitant with deposition of cholesterol ester.

Thrombosis, another complication of atherosclerosis, has also been studied in animal models by using inhibitors of cyclooxygenase, such as aspirin. Unfortunately, the results of these studies are contradictory. In some studies, aspirin inhibited the progression of atherosclerosis,\textsuperscript{56,57} while in another study, aspirin had no beneficial effect.\textsuperscript{58} This differential response to cyclooxygenase inhibition may be related to the dose of aspirin, since platelet cyclooxygenase is more sensitive to aspirin inhibition than arterial cyclooxygenase; higher doses of aspirin abrogated the beneficial effect of aspirin seen at lower doses.\textsuperscript{59-62} Aspirin also ameliorates the recurrence of myocardial infarction in men who have suffered previous myocardial damage.\textsuperscript{63} The beneficial effect of aspirin in this setting may be due to stabilization of platelets.\textsuperscript{1,20}

Hypertension, which is a major predisposing factor for atherosclerosis,\textsuperscript{64,65} is associated with increased vascular PGI\textsubscript{2} production,\textsuperscript{66-72} possibly due to increased phospholipase\textsuperscript{73,74,75} or PGI\textsubscript{2} synthetase\textsuperscript{76} activities. It has been postulated that increased PGI\textsubscript{2} synthesis in hypertension may serve as a compensatory mechanism for the maintenance of arterial tone secondary to increased arterial pressure.\textsuperscript{76} However, in spite of increased vascular prostacyclin generation by vascular tissue, the effects of hypertension on plasma prostacyclin are equivocal, with both decreased\textsuperscript{77} and increased\textsuperscript{79} levels of 6-keto-PGF\textsubscript{1a} reported in human hypertensive disease. Such observations suggest that eicosanoids may not have an important role in mediating blood pressure regulation in hypertensive disease. This conclusion is reinforced by observations that aspirin does not exacerbate hypertension. It is also important to note that lipid accumulation does not typically occur in hypertension unless there is superimposed hyperlipidemia.\textsuperscript{90}

It is, therefore, possible that mural eicosanoids may be involved in the atherogenic process, although a cause-effect relationship between these two parallel events has yet to be established. Accordingly, the influence of eicosanoids on the ontogeny of the development of the secondary lesion has been an area of extensive study. Eicosanoids have now been implicated in the regulation of the differentiated state of the smooth muscle cells, the migration of medial smooth muscle cells into the subintimal space, and the subsequent proliferation and accumulation of intracellular lipid. The involvement of eicosanoids in these cellular processes is reviewed here.

**Role of Eicosanoids in Arterial Smooth Muscle Cell Function**

**Smooth Muscle Cell Phenotype**

Although the process by which arterial smooth muscle cells change from the contractile to the synthetic phenotype has been reviewed,\textsuperscript{81-94} the cellular mechanisms causing de-differentiation in vascular smooth muscle cells remain obscure. Components of plasma and connective tissue matrix have been implicated\textsuperscript{85,86,87} in normally differentiated arterial smooth muscle cells have abundant thick and thin fibers containing dense bodies, possess little endoplasmatic reticulum or Golgi apparatus,\textsuperscript{87} and do not respond to mitogens (contractile phenotype).\textsuperscript{86} However, de-differentiated (or "modulated") cells have disagggregated actin/myosin filaments, possess an abundant and hypertrophic perinuclear microsomal compartment, secrete connective tissue matrix,\textsuperscript{92,93,89,90,91} and respond to mitogens.\textsuperscript{90} These cells, which were originally described in vitro,\textsuperscript{9} have in vivo counterparts in the atherosclerotic lesion.\textsuperscript{92,93} Indeed, these may be the cells that have been described histologically as progenitor cells in the athero-
sclerotic lesion.94 Since the process of de-differentiation is a major, but insufficient, requirement for cell proliferation,95 loss of differentiation may be one of the initial events in atherogenesis.96 Unfortunately, there is relative paucity of data on the role of eicosanoids in mediating the transition in smooth muscle cells from the contractile to the synthetic phenotype. In one carefully done study, modulated arterial smooth muscle cells synthesized more PGI2 de novo than did contractile smooth muscle cells.97 In another study, exogenously added prostaglandin E1 (PGE1), which has biological properties similar to PGI2, stimulated the transition from contractile to synthetic phenotype.98 However, the cause-effect relationship between eicosanoids and the differentiated state in smooth muscle cells remains obscure.

**Smooth Muscle Cell Proliferation**

In one study, arachidonic acid inhibited smooth muscle cell proliferation independent of PGI2 biosynthesis, suggesting that inhibition of smooth muscle cell growth was due to other fatty acid components or to lipid peroxides.103 However, in a later study, the same group reported that arachidonate stimulated the proliferation of smooth muscle cells that was correlated with and dependent upon PGI2 biosynthesis.104 Thus, the initial study must be confirmed. These findings suggest that oxidized metabolites of arachidonate or other fatty acids can affect cell proliferation105; however, the conflicting results concerning the effects of arachidonate on smooth muscle cell proliferation may be a function of the dose used in each study or of the nonspecific detergent effects of the fatty acid.

There have been studies which have shown that PGI2 inhibits the proliferation of arterial smooth muscle cells in vivo,106 presumably by inhibiting platelet activation and secretion of platelet products known to stimulate endothelial and smooth muscle cell PGI2 generation (see below) and in vitro by inhibiting DNA synthesis.107 However, proliferating cells also synthesize more PGI2 than quiescent cells.97 PGE1 (an eicosanoid synthesized from d-homogamma-linoleic acid) inhibits smooth muscle cell growth directly but only at the G-1 phase of the cell cycle via stimulation of cyclic 3',5'-adenosine monophosphate (cAMP).108 Once cells progressed into the S-phase, PGE1 no longer had an inhibitory effect.109 These data were corroborated by Nilsson and Olsson,110 who demonstrated that PGE1 more than PGE2 but not PGF2α, inhibited proliferation induced by the platelet-derived growth factor (PDGF) (see below). These data support the concept that endothelial- and smooth muscle cell-derived eicosanoids antagonize and therefore modulate the response to growth factors.111 These data further suggest that reduction of arterial eicosanoid synthetic capacity may predispose to increased smooth muscle cell proliferation. This hypothesis is supported by observations that aging smooth muscle cells not only synthesize less PGI2 than do young cells,48,49 but also become more responsive to mitogenic agents such as PDGF.51

The inhibition of cell proliferation appears to be due to increased intracellular cAMP.108 PGI2 and PGE1 potently stimulate cAMP synthesis in vascular tissue.112,113,114Dipyridamole also increases cAMP and reduces the development of atherosclerosis in rabbits by undefined mechanisms.115 Since PGI2 synthetase antigen has been localized in both plasma and nuclear membrane,116 the ability of PGI2 to inhibit smooth muscle cell proliferation may be a direct nuclear event. This concept has yet to be developed experimentally.

The effects of lipooxygenase products on cell proliferation are contradictory. In an in vivo study, dexamethasone, but not indomethacin, prevented chemotaxis and proliferation of smooth muscle cell into the intima in "cuff"-induced atherosclerosis in rabbits.109 In parallel in vitro studies, LTα2, but not 5- or 12-HETE, stimulated arterial cell proliferation, suggesting that LTα2 is important in mediating the vascular inflammatory response to injury.102 In contrast, 12-HETE inhibited smooth muscle cell proliferation, 5-HETE and LTα2 were weakly inhibitory, and TxA2 and PGF2α were inactive.117 These data support the concept that neutrophil or monocyte infiltration predisposes to smooth muscle cell proliferation due not only to macrophage-derived peptide growth factors such as PDGF (see below) but also to LTα2.

**Arterial Cholesterol Metabolism**

The concept that eicosanoids may modulate cholesterol metabolism was based on original observations that eicosanoid production was reduced in atherosclerotic...
vessels concomitant with an increase in mural cholesteryl ester content.\textsuperscript{11,118,119} Although a causal relationship between these two metabolic pathways has been suggested, it has not been proven. Before discussing the role of eicosanoids on cellular cholesterol metabolism, we will describe the cholesteryl ester cycle as it exists in vascular smooth muscle cells.

Briefly, low density lipoprotein (LDL) cholesteryl esters are degraded in the lysosomal compartment after receptor-mediated endocytosis via acid cholesteryl ester hydrolase (ACEH), and the liberated free cholesterol enters into a cytoplasmic pool. This serves to down-regulate the activity of 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA)-reductase (the committed step in cholesterol biosynthesis from mevalonate). Cytoplasmic free cholesterol also reduces synthesis of the LDL receptor at the level of transcription. Cellular free cholesterol is metabolically active, and its concentration in the cell is rigidly controlled. Excess free cholesterol is stored within the cell as cytoplasmic cholesteryl esters via the enzyme acyl CoA: cholesteryl acyltransferase (ACAT); these cytoplasmic cholesteryl esters may subsequently be hydrolyzed by the cytoplasmic (neutral) cholesteryl ester hydrolase. Free cholesterol may also be translocated to the cell membrane, where it becomes available for removal by high density lipoprotein (HDL) or other plasma (or interstitial) acceptors. This subject has been extensively reviewed.\textsuperscript{\textsuperscript{5,6}}

Early studies\textsuperscript{119} demonstrated that PGE\textsubscript{2} inhibits cholesteryl esterification via ACAT in the skin of rats subjected to a diet deficient in essential fatty acids, suggesting for the first time that eicosanoids may modulate cholesteryl ester metabolism. Purified ACAT from either skin or aorta was inhibited dose-dependently by PGE\textsubscript{2}, independent of diet (normal vs. cholesterol-supplemented diet)\textsuperscript{120,121,122}. In spite of the observation that PGE\textsubscript{2} biosynthesis also increased after exposure to an atherogenic diet,\textsuperscript{121} in similar studies, PGE\textsubscript{2} inhibited ACAT activity in the aortas of atherosclerosis-resistant Show Racer pigeons but not in the atherosclerosis-susceptible White Carneau pigeons.\textsuperscript{123} The mechanism of this apparent sensitivity of the enzyme to inhibition by PGE\textsubscript{2} was not investigated.\textsuperscript{123} Similar findings were also reported: arachidonic acid conversion to PGE\textsubscript{2} was greater in atherosclerosis-susceptible White Carneau pigeons.\textsuperscript{122} These studies are in contrast to later studies by this group, which demonstrated that PGI\textsubscript{2} synthesis is reduced in other models of atherosclerosis.\textsuperscript{114,115} Cholesteryl ester hydrolase activity was unaffected by PGE\textsubscript{2} treatment;\textsuperscript{122} however, PGE\textsubscript{2}, slightly inhibited cholesteryl ester hydrolase and ACAT activity.\textsuperscript{124}

These early experiments, which demonstrated that PGE\textsubscript{2} inhibited cholesteryl deposition, although performed by using cellular homogenates or subcellular fractions, provided the background for future research in our laboratory to define the role of eicosanoids in mediating cholesterol metabolism in intact cells. Using intact rabbit aortic smooth muscle cells, we discovered that PGI\textsubscript{2} stimulated lysosomal (acid) cholesteryl ester hydrolase activity by enhancing cAMP levels in these intact arterial smooth muscle cells. This activity was also increased by providing exogenous arachidonic acid (suggesting that endogenously synthesized eicosanoids may mediate the effect) and dibutyryl cAMP.\textsuperscript{125,126} Importantly, the cytoplasmic (neutral) cholesteryl ester hydrolase was also stimulated by PGI\textsubscript{2} via a cAMP-dependent protein kinase mechanism, demonstrating that activation of the cytoplasmic enzyme may occur by covalent phosphorylation.\textsuperscript{127,128,129} PGI\textsubscript{2} could also enhance the efflux of the liberated cholesterol from the cell through a cAMP-dependent mechanism.\textsuperscript{125,128} Ettingin et al.\textsuperscript{130} extended these studies and demonstrated that other metabolites of PGI\textsubscript{2}, including the dinor and 13,14-dihydro-6,15-diketo-, and 6-15-diketo-PGF\textsubscript{1α}, derivatives, could stimulate both the acid and neutral cholesteryl ester hydrolases.

Recently our laboratory demonstrated that 12-HETE and 12,20-diHETE also stimulated smooth muscle cell ACEH activity. These eicosanoids did not affect ACAT activity. This reaction resulted in a concomitant reduction in cellular free and esterified cholesterol content.\textsuperscript{130} PGE\textsubscript{2} also inhibited ACAT activity (corroborating the above data), but not PGI\textsubscript{2}, 6-keto-PGF\textsubscript{1α}, or 6-keto-PGF\textsubscript{1α}.\textsuperscript{127} PGE\textsubscript{2} has also been shown to inhibit cholesteryl ester accumulation in macrophages, presumably by inhibiting ACAT activity.\textsuperscript{131} The above data suggest that endogenously synthesized eicosanoids may mediate cholesterol metabolism in intact vessels and also imply that eicosanoids derived from adjacent endothelial cells may mediate alterations in smooth muscle cell cholesteryl ester hydrolytic activities in vivo.

Several years ago, this laboratory showed that cholesteryl esters can accumulate in reendothelialized aortic intima in rabbits fed a normocholesterolemic or hypercholesterolemic diet.\textsuperscript{122,133} These results suggested that endothelial cells could modulate cholesteryl ester deposition in smooth muscle cells that were present in the adjacent neointima.\textsuperscript{122,133} Cholesterol feeding also retarded recovery of neointimal PGI\textsubscript{2} synthetic capacity after balloon endoendothelialization in rabbits.\textsuperscript{15,16} This was corroborated by several in vitro studies, where endothelial cells in co-culture, but not endothelial cell-conditioned media, influenced smooth muscle cell cholesteryl ester hydrolysis in a time-dependent manner.\textsuperscript{124,135} The stimulation of lysosomal cholesteryl ester hydrolase activity in smooth muscle cells when co-cultured with endothelial cells was eicosanoid dependent. We observed that endothelial cells initially treated with eicosatetraynoic acid (ETYA, a dual cyclooxygenase and lipooxygenase inhibitor) or aspirin (a cyclooxygenase inhibitor) inhibited the stimulatory effect on the hydrolase by the endothelial cell. Conditioned media from 48-hour cultures of endothelial cells also stimulated cholesteryl ester hydrolytic activity in the smooth muscle cell, an effect which was inhibited by ETYA, suggesting that lysosomal cholesteryl ester hydrolytic activity was mediated at least in part by stable endothelial cell-derived eicosanoids (6-keto-PGF\textsubscript{1α}, PGE\textsubscript{2}, 12-KETE, and 12,20-dihETE).\textsuperscript{135} In contrast to these observations in smooth muscle cells, lipooxygenase inhibitors will prevent cholesterol accumulation in macrophages exposed to acetylated LDL, suggesting that macrophage HETE or leukotriene production may promote cholesterol deposition.\textsuperscript{136} The effects of eicosanoids on smooth muscle cell cholesterol metabolism are summarized in Figure 1.
Articular Eicosanoids in Atherosclerosis

Pomerantz and Hajjar

Arterial Smooth Muscle Cell

Figure 1. Eicosanoids and the regulation of arterial cholesterol metabolism. Prostacyclin (PGI₂) and 12-hydroxy-eicosatetraenoic acids (HETE) derived from endothelial and smooth muscle cells stimulate smooth muscle cell lysosomal acid cholesteryl ester hydrolase (ACEH) and cytoplasmic neutral cholesteryl ester hydrolase (NCEH) by cyclic 3',5'-adenosine monophosphate (cAMP) and cAMP-dependent protein kinase, respectively. The increase in the activities of these enzymes increases the degradation of cholesteryl esters (CE) derived from low density lipoprotein (LDL), as well as CE in neutral lipid droplets. Prostaglandin E₂ (PGE₂) decreases the activity of acyl-CoA: cholesterol acyltransferase (ACAT), thus facilitating net cholesteryl ester hydrolysis. CHOL=cholesterol, FA=fatty acid.

In summary, the above data provide a reasonable understanding of the role of eicosanoids (PGI₂ and PGE₂) in the promotion of cholesterol efflux by initially hydrolyzing cellular esterified cholesterol to its free form, thereby rendering it accessible to removal from the cell by plasma acceptor particles such as HDL. HETEs may have both a positive and a negative influence on this effect by promoting arachidonate release from membrane phospholipids and by inhibiting cyclooxygenase activity.

Summary

There are experimental data that demonstrate that eicosanoids derived from the arterial wall serve to maintain the cell in a contractile, quiescent, phenotypic state, which is responsive to vasoactive stimuli and not responsive to mitogens. Furthermore, endogenously synthesized eicosanoids help to maintain cellular cholesterol content at a low level. However, eicosanoids derived from monocytes and neutrophils may promote the inflammatory response by promoting smooth muscle cell modulation to the synthetic phenotype and promoting smooth muscle cell migration, proliferation, and cholesteryl ester deposition. This raises the possibility that mural eicosanoids are antiatherogenic, while eicosanoids derived from inflammatory cells may initiate or mediate the processes leading to plaque development. The data are summarized in Table 1.

Factors Modulating Arterial Smooth Muscle Cell Proliferation, Cholesterol Metabolism, and Eicosanoid Biosynthesis

Plasma Lipoproteins

The effects of LDL on eicosanoid metabolism in vascular tissue are undefined. Early studies by Nordoy et al. demonstrated that high concentrations of LDL inhibited the platelet-antiaggregatory activity derived from human umbilical venous endothelial cells. The major source of this activity was thought to be PGI₂. However, in subsequent studies the same group found that very low density lipoprotein (VLDL) and LDL had no effect on PGI₂ generation. Even though eicosanoid metabolism was not augmented in these experiments, these lipoproteins did stimulate endothelial cell synthesis of apolipoprotein (apo) A-1, the principal apoprotein of HDL. However, in subsequent research, native LDL was shown to stimulate eicosanoid production in endothelial and smooth muscle cells. The mechanism(s) by which LDL induced eicosanoid production are unclear, but may be due to enhanced substrate availability. This is in accord with the observations by Hartung et al., who demonstrated that acute stimulation of the scavenger receptor by acetylated or malondialdehyde-modified LDL promotes eicosanoid generation in monocyte/macrophage populations. These results suggest that activation of phospholipase A₂ may also be a feature of LDL-induced PGI₂ generation in the absence of cholesterol enrichment. It has been further proposed that the mechanism by which LDL decreases eicosanoid production involves free radical-mediated destruction of eicosanoid-synthetic enzymes by lipid peroxides artifactually generated during purification of LDL from plasma. This is based on observations that LDL oxidized by exposure to agents such as copper or by exposure to either endothelial cells or macrophages contains lipids peroxides, which are thought to decrease eicosanoid production. This is a significant finding, since 15-HPETE is a major HETE...
product of the atherosclerotic vessel wall\(^{154}\) and inhibits vascular PGL\(_2\) synthetase.\(^{155}\) In any case, the role of LDL on cellular eicosanoid generation remains to be completely elucidated.

In contrast, plasma HDL is the most active of the cholesterol acceptor molecules in plasma.\(^{156,157,158}\) HDL actually promotes net cholesterol efflux from all cells studied, including vascular smooth muscle cells,\(^{157-161}\) fibroblasts,\(^{158,161-165}\) macrophages,\(^{166,167,168}\) and endothelium.\(^{160}\) HDL is thought to be the major carrier of cholesterol from peripheral tissue to the liver for ultimate excretion (i.e., "reverse cholesterol transport"\(^{163,170}\)).

Importantly, these findings may have clinical relevance, since high plasma LDL levels are inversely related to the incidence and severity of atherosclerosis.\(^{171,172}\) This is supported by additional studies. We and others have demonstrated that HDL stimulates eicosanoid production from a variety of cell types in several model systems. HDL induces PGI\(_2\) production in vascular endothelial cells,\(^{140,142,173,174}\) smooth muscle cells,\(^{141}\) and isolated perfused rabbit hearts.\(^{175,176}\) HDL-induced eicosanoid production originates from arachidonate of HDL cholesteryl esters or phospholipid pools that are phospholipase-sensitive and accessible to cyclooxygenase.\(^{141,142}\) In addition, HDL stimulates the mobilization of cellular arachidonic acid. This suggests that HDL increases turnover of arachidonic acid in cellular phospholipid pools.\(^{141,142,175,178}\)

The requirement of HDL for endothelial and smooth muscle viability\(^{177}\) may, in part, be mediated through its ability to remove excess cellular cholesterol. In fact, HDL-induced cholesterol efflux may be mediated, at least in part, by endogenous eicosanoid production.

Studies with cultured cells have been performed to elucidate mechanisms of altered eicosanoid metabolism induced by cholesterol enrichment. These have been derived either from cholesterol-fed animals or by enrichment with cholesterol in vitro. Eicosanoid metabolism is a function of substrate availability from plasma,\(^{178,179,180}\) activity of high affinity uptake mechanisms for arachidonic acid,\(^{181}\) intracellular substrate availability to cellular phospholipases,\(^{23,106}\) and the activity of phospholipases and "distal" enzymes from the rate-limiting step in the metabolic cascade, such as PGI\(_2\) synthetase. Conceivably, alterations in any of the above could result in altered eicosanoid metabolism after cholesterol enrichment. In fact, cultured smooth muscle cells and endothelial cells derived from human atherosclerotic aortas demonstrate reduced capacity for synthesis of PGI\(_2\) and PGE\(_2\) from either exogenous or endogenous arachidonic acid.\(^{13,182,183,184}\) However, the mechanism of this phenomenon is not known.

Cholesterol-enriched smooth muscle cells synthesize less eicosanoids, but again the mechanism is unclear.\(^{185}\) Our laboratory has demonstrated that cholesterol-enriched cells synthesize less eicosanoids by at least two mechanisms. The first is inhibition of phospholipase A\(_2\) by linoleate in LDL cholesteryl esters. The latter is hydrolyzed in the lysosomal compartment of the cell and becomes incorporated into the phospholipid compartment. As phospholipid, it competes at the level of phospholipase A\(_2\) for release and conversion to eicosanoids. This finding is reinforced by data demonstrating that linoleate and other fatty acids can compete with arachidonate for incorporation into cell phospholipids and can inhibit endothelial and smooth muscle cell eicosanoid metabolism.\(^{186-189}\) The second mechanism is direct inhibition of phospholipase A\(_2\) by cholesterol.\(^{190}\) This finding supports previous observations that cholesterol can directly inhibit phospholipase A\(_2\) in fibroblasts,\(^{191}\) presumably by altering membrane fluidity.

The effects of cholesterol enrichment on macrophage eicosanoid metabolism are not yet clarified. Oxidized LDL augments arachidonic acid metabolism by stimulation of phospholipase A\(_2\) in macrophages, but not in fibroblasts.\(^{192}\) Similarly, Mathur and Field\(^{193}\) demonstrated that cholesterol enrichment increased release of arachidonate and its metabolism to 12-HETE and thence to di-HETEs. In contrast, Saito et al.\(^{194}\) have shown that peripheral blood monocytes from cholesterol-fed rabbits exhibited reduced eicosanoid biosynthesis. One explanation for this discrepancy may relate to the time frame of the study. We suggest that linoleate from LDL cholesteryl esters is incorporated into cellular phospholipids, which initially increases eicosanoid biosynthesis as arachidonate is mobilized into eicosanoid biosynthesis, but again the mechanism is unclear.\(^{185}\)

### Table 1. Effect of Eicosanoids on Smooth Muscle Cell Function

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<tr>
<th>Phenotype (con—&gt;syn)</th>
<th>PGI(_2)</th>
<th>mPGI(_2)*</th>
<th>PGE(_2)</th>
<th>PGE(_1)</th>
<th>PGF(_{2\alpha})</th>
<th>HETEs</th>
<th>LTB(_4)</th>
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<tr>
<td>Migration/chemotaxis</td>
<td>NA†</td>
<td>NA</td>
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* mPGI\(_2\) includes metabolites of PGI\(_2\), including 6-keto-PGF\(_{2\alpha}\), 6-keto-PGE\(_2\), and 15-0H-PGD\(_2\) derivatives.
† NA = no data available, I = increase, D = decrease, 0 = no effect.

ACAT = acyl-CoA: cholesterol acyltransferase, cAMP = cyclic 3',5'-adenosine monophosphate.

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LTB\(_4\) = leukotriene B\(_4\), ACEH = acid cholesteryl ester hydrolase, NCEH = neutral cholesterol ester hydrolase, ACAT = acyl-CoA: cholesterol acyltransferase, cAMP = cyclic 3',5'-adenosine monophosphate.

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<td></td>
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* mPGI\(_2\) includes metabolites of PGI\(_2\), including 6-keto-PGF\(_{2\alpha}\), 6-keto-PGE\(_2\), and 15-0H-PGD\(_2\) derivatives.
† NA = no data available, I = increase, D = decrease, 0 = no effect.

ACAT = acyl-CoA: cholesterol acyltransferase, cAMP = cyclic 3',5'-adenosine monophosphate.

LTB\(_4\) = leukotriene B\(_4\), ACEH = acid cholesteryl ester hydrolase, NCEH = neutral cholesterol ester hydrolase, ACAT = acyl-CoA: cholesterol acyltransferase, cAMP = cyclic 3',5'-adenosine monophosphate.

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Aspirin pretreatment inhibited both the increase in lysosomal cholesteryl ester hydrolase activity and PGI₂ release 135.

Highly purified PDGF can stimulate cholesteryl ester hydrolase production in smooth muscle cells. The latter phenomenon may be mediated by endothelial cells, smooth muscle cells, and macrophages after vascular injury. 206 In fact, RNA transcripts of PDGF are not performed in the presence of a cholesterol acceptor such as HDL. Also, it has previously been demonstrated that PGE₂ does not stimulate lysosomal or cytoplasmic cholesteryl ester hydrolytic activities. 128,129 Our laboratory has found that cholesterol enrichment abolishes eicosanoid-dependent cholesterol efflux by reducing eicosanoid stimulation of lysosomal cholesteryl ester hydrolase. Van Sickle and Nasjletti 196 have demonstrated that in cholesteryl ester-enriched macrophages, only a minor component (10% to 15%) of HDL-induced cholesterol efflux is eicosanoid dependent. The data suggest that in pathological states in which there is significant cholesteryl ester accumulation, eicosanoid-dependent mechanisms of cholesterol removal may be less important than the effects of cholesterol substrate for removal by cholesterol acceptors in plasma and esterification by ACAT activity. In addition, the experiments were not performed in the presence of a cholesterol acceptor such as HDL. Also, it has previously been demonstrated that PGE₂ does not stimulate lysosomal or cytoplasmic cholesteryl ester hydrolytic activities. 128,129 Our laboratory has found that cholesterol enrichment abolishes eicosanoid-dependent cholesterol efflux by reducing eicosanoid stimulation of lysosomal cholesteryl ester hydrolase. Van Sickle and Nasjletti 196 have demonstrated that in cholesteryl ester-enriched macrophages, only a minor component (10% to 15%) of HDL-induced cholesterol efflux is eicosanoid dependent. The data suggest that in pathological states in which there is significant cholesteryl ester accumulation, eicosanoid-dependent mechanisms of cholesterol removal may be less important than the effects of cholesterol substrate for removal by cholesterol acceptors in plasma and esterification by ACAT activity.

Platelet-derived Growth Factor

There is accumulating evidence that the chemotactic and chemokinetic properties of growth factors may depend upon endogenously synthesized eicosanoids. Platelets, endothelial cells, smooth muscle cells, and macrophages secrete PDGF,7,197–204 which, in turn, stimulates smooth muscle cell proliferation.4,205 There is also increased production of PDGF by proliferative smooth muscle cells after vascular injury.206 In fact, RNA transcripts of PDGF are increased in atheromatous207 but not in normal regions of aorta.208 Smooth muscle cells derived from atheromatous lesions are also more proliferative,209 possibly due to increased PDGF in that location. PDGF is both chemotactic210 and chemokinetic211 for smooth muscle cells. The latter phenomenon may be mediated by endogenously synthesized lipoxigenase, but not cyclooxygenase products of arachidonic acid, since ETYA, but not indomethacin, inhibited PDGF-induced cell migration.211 In addition, while serotonin alone stimulates PGI₂ release by smooth muscle cells, PDGF is synergistic with serotonin in stimulating smooth muscle cell PGI₂ synthesis.212 Therefore, at sites of platelet deposition or monocyte infiltration, eicosanoids may mediate the effect of PDGF on smooth muscle cell chemotaxis. Exogenously added, highly purified PDGF can stimulate cholesteryl ester hydrolysis and PGI₂ production in smooth muscle cells.135 Aspirin pretreatment inhibited both the increase in lysosomal cholesteryl ester hydrolase activity and PGI₂ release in these smooth muscle cells. 136 These data suggest that endothelial cells may mediate cholesteryl ester hydrolysis in smooth muscle cells by elaboration of other soluble factors, including PDGF, which augment eicosanoid metabolism in these cells. 135

However, the ability of PDGF to stimulate eicosanoid production is controversial. In some studies, PDGF stimulated cellular eicosanoid production,212–214 whereas in others, PDGF had no effect.216,217 Callahan et al. 217 attribute the ability of PDGF to alter eicosanoid production in some mesenchymal cells to impurities in the preparations, thus accounting for discrepancies in the literature involving PDGF and eicosanoid production. Collectively, these data become even more controversial, since PDGF has been shown to up-regulate activity of the LDL receptor,218,219,220 to increase fluid phase pinocytosis in the absence of a storage pool of cellular cholesterol,202,221 and to possibly render the cell dependent upon cholesterol synthesis to effect the proliferative response to PDGF.222 This is in contrast to fibroblasts, where PDGF stimulates cholesteryl ester deposition in NIH 3T3 cells.223 Thus, the role of eicosanoids as second messengers in response to PDGF at the cellular level remains unresolved and requires further elucidation because of the involvement of this arterial cytokine in the promotion of intimal hyperplasia during atherosclerosis.

Procoagulant Activities

Normally endothelial cells maintain a characteristic nonthrombotic surface; secretory products from nonactivated cells include PGI₂ and tissue plasminogen activator and little, if any, plasminogen activator inhibitor. However, in response to inflammatory and coagulant stimuli such as lipopolysaccharide, endothelial cells proliferate224 and synthesize pro-inflammatory cytokines, such as interleukin-1 (IL-1) (see below). In these activated endothelial cells, the balance between plasminogen activator and plasminogen activator inhibitor favors net procoagulant characteristics.225–228 This shift from anticoagulant to procoagulant activity allows more local thrombin generation at the site of thrombus generation. Thrombin promotes proliferation by endothelial cells by activation of c-sis gene expression198; agents that elevate CAMP formation also inhibit thrombin induced c-sis gene expression200 and expression of the B-chain for PDGF.202 In addition to activating endothelial cells, thrombin also stimulates endothelial cell eicosanoid generation.201,202 Since endothelial cell-derived eicosanoids are antiproliferative, this activity may represent a mechanism by which these eicosanoids modulate procoagulant activity and endothelial mitogenic response to thrombin. However, thrombin has different effects on arterial smooth muscle cells. Thrombin does not promote smooth muscle cell proliferation231 or stimulate smooth muscle cell eicosanoid synthesis. The direct effects of thrombin on smooth muscle cell cholesterol metabolism are unknown. However, thrombin may regulate these processes in smooth muscle cells indirectly by promoting endothelial cell eicosanoid generation.

Host Defense Mediators

Endothelial cells synthesize PGE₃ in response to, and potentiate the effect of, a variety of host defense mediators. These include bradykinin, LTC₄, complement, kallikrein, immune complexes, complement complexes, and...
These agents may, therefore, indirectly modulate smooth muscle proliferative capacity and regulation of the cholesteryl ester cycle via endothelial cell-derived eicosanoids. In addition, serotonin, bradykinin, and angiotensin II may also directly stimulate smooth muscle cell eicosanoid generation. These agents have not been thought to be involved in processes controlling arterial cholesterol metabolism. However, it is now known that eicosanoids clearly influence arterial cholesterol metabolism, the concept that host defense mediators may influence vascular cholesterol metabolism via endogenously synthesized eicosanoids should be considered, since atherogenesis is considered to be an inflammatory/proliferative response to injury.

**Interleukin-1**

IL-1 is a pro-inflammatory cytokine elaborated by endothelial cells in response to lipopolysaccharide and other stimuli. IL-1 promotes monocyte and neutrophil chemotaxis and diapedesis into the vessel wall and stimulates monocyte eicosanoid generation. Monocyte adhesion and diapedesis is associated with increased endothelial cell permeability to plasma components, including LDL and β-VLDL into the vascular interstitium. This may be partly due to production of monocyte chemotactic agents. These data indicate that IL-1 could be involved in the atherogenic process. It has recently been demonstrated that IL-1 can directly stimulate PGE2, PGI2, and PGF2α synthesis as well as proliferation of human smooth muscle cells. Since IL-1-induced smooth muscle cell proliferation was augmented in the presence of cyclooxygenase inhibitors and inhibited by exogenous PGE2 and PGF2α, perhaps endogenously synthesized eicosanoids are antiproliferative or serve to control the proliferative effect of IL-1.

**Gonadal Steroids**

Although men are at a greater risk for cardiovascular morbidity and mortality than women before menopause, the influence of gender on arterial cholesterol deposition is unknown. In addition, the influence of gender and gonadal steroids in improving cardiovascular risk is equivocal. Indeed, no gender difference in human arterial eicosanoid synthesis has been identified; thus, further investigation in this area is required.

**Heparin**

Heparin is an endothelial cell and platelet product, which may maintain the smooth muscle cell contractile phenotype and inhibit smooth muscle cell proliferation. This property appears to be dissociated from heparin's anticoagulant activity. The mechanism of heparin's antiproliferative effect is not well understood, but may be due to its ability to maintain smooth muscle cells in the contractile phenotype, thus preventing smooth muscle cells to respond to mitogens and subsequently proliferate.

There may be numerous cellular mechanisms by which heparin inhibits the proliferation of arterial smooth muscle cells. Heparin decreases the number of epidermal growth factor (EGF) receptors on smooth muscle cells, suggesting that heparin reduces the ability of smooth muscle cells to respond to EGF stimulation. Heparin's ability to inhibit smooth muscle cell proliferation may also be mediated by activation of transforming growth factor-beta, a known inhibitor of smooth muscle cell proliferation. Heparin also inhibits 1,4,5-trisphosphate-induced calcium release from smooth muscle cells, suggesting that heparin may inhibit the effects of agonist-induced activation of the phosphoinositol pathway in smooth muscle cells. These data are significant since phospholipase C exists in arterial smooth muscle cells and appears to be important in the modulation of receptor-coupled PIP2 synthesis and calcium mobilization. Furthermore, eicosanoid lipids have been implicated in the regulation of cell proliferation via the phosphorylation of tyrosine kinases (for a review of this subject, see reference 261). However, no data are currently available on alterations of phospholipase C activity in hyperlipidemia or atherosclerosis. It is possible that the mitogenic effects of PIP2 are normally regulated by endogenous eicosanoid production, and that the loss of heparin effect during lipid-enrichment may favor cell proliferation.

There is anecdotal, unpublished data suggesting that heparin's antiproliferative effect may also be mediated by its ability to stimulate eicosanoid production. However, the documented effect of heparin on smooth muscle cell eicosanoid generation is unknown, although the effects of heparin on smooth muscle cell proliferation are similar to those of PGF2α. Interestingly, postconfluent smooth muscle cells synthesize an antiproliferative heparan sulfate whose effect on smooth muscle cell eicosanoid generation is also unknown. These data suggest that endothelial cells may maintain smooth muscle cells in the contractile phenotype not only by synthesizing eicosanoids such as PGF2α, but also by synthesizing heparin and other heparin-like molecules. Thus, redundant systems appear to maintain smooth muscle cells in a physiologically quiescent state. These data also imply that reductions in heparin biosynthesis may predispose to smooth muscle cell modulation to the synthetic phenotype and increased responsiveness to mitogens. The fact that heparin and PDGF are found within platelets suggests that the smooth muscle response to mitogens delivered by platelets is regulated by the intrinsic antiproliferative effects of heparin as well as by endogenously synthesized eicosanoids.

In addition to affecting smooth muscle cell proliferative capacity, heparin may also affect cellular cholesterol metabolism. Heparin has the ability of binding to plasma lipoproteins, particularly LDL. Heparin-LDL complexes have been isolated from atheroma; such complexes in the presence of other connective tissue components, such as fibronectin and collagen, may promote cholesterol accumulation in macrophages by binding and internalization via the scavenger receptor. It has been postulated that such interactions are one potential mechanism of increased cholesteryl ester deposition in plaque areas. This phenomenon has not been evaluated in smooth muscle cells, nor has an eicosanoid-dependent component of this process been evaluated.

Thus, heparin has a multiplicity of effects that may be important in maintaining smooth muscle cell phenotype, and that may provide a potential mechanism for macro-
phage clearance of LDL lipid. Thus, the role of heparin in the atherogenic process is not complete, and the role of eicosanoids in mediating such effects requires further investigation.

**Dietary Modification of Eicosanoid Formation—Marine Lipids**

There is a developing substantive body of data on the effects of fish oils in altering the clinical sequelae of atherosclerosis. This information has been generated in part by observations that diets high in eicosapentaenoic (EPA) and docosahexaenoic acid (both found in relative abundance in fish oils), appear to be protective in coronary vascular disease in certain populations.268-270 See references 271 to 274 for reviews). The mechanism of this effect appears to be caused by reduced platelet function, such as decreases in platelet aggregation, PAF release, and PGDF release.275-278 This may be due to the fact that TxA2 (the EPA homolog of TXA2) possesses significantly less activity than TXA2, while PGI2 possesses similar biological properties to PGI2. In addition, these fatty acids may also inhibit arterial smooth muscle cell proliferation by inhibiting endothelial cell synthesis of PGDF.279 EPA may also reduce plasma lipids, principally triglycerides, with equivocal changes in LDL or HDL levels,280-283 and EPA may increase fecal excretion of neutral and acid sterols.284 However, the role of EPA and other marine lipids on arterial cholesterol metabolism is undefined since few laboratories are actively pursuing this area. Presently, we know that the accumulating results of EPA studies are equivocal. Adverse effects by EPA include alterations in serum lipids and increased dietary requirement for supplemental antioxidants, such as vitamins E and C. For this reason, it remains to be seen if marine lipids will modulate the interaction of lipoproteins within the vessel wall, as well as modulation of the cholesteryl ester cycle, to promote an antiatherogenic environment. It also remains to be established if this potential benefit is greater than the possible risks of free radical-mediated damage to membranes and other cell constituents.

**Conclusions**

Eicosanoids are thought to play a role in the maintenance of vessel wall homeostasis and to act either cooperatively or antagonistically to mediate or modulate external agonists. Endogenously synthesized eicosanoids can regulate the effects of vasodilators such as bradykinin and can antagonize the effects of vasoconstrictors, such as angiotensin.285 The data discussed in this article suggest that eicosanoids such as PGI2 synthesized by the blood vessel wall serve to restore smooth muscle cells to the differentiated, quiescent state. In addition, this eicosanoid can maintain a low, cell cholesterol content. This is accomplished by promoting net cellular cholesteryl ester hydrolysis by stimulation of the activities of the cholesteryl ester hydrolytic enzymes while inhibiting ACAT. Eicosanoids derived from adjacent endothelium as well as from inflammatory cells, such as neutrophils and macrophages, may also serve to stimulate smooth muscle cells into a proliferative state as a response to injury.286 Thus, reductions in eicosanoid synthetic capacity during the course of a chronic inflammatory state (induced by hyperlipidemia, viral infection, or hemodynamic stress) may also promote cholesterol accumulation superimposed upon cellular proliferation in response to growth factors and other cytokines. This could result in the eventual formation of atherosclerotic plaques. We have summarized this basic concept in Figure 2.

Thus, in addition to their possible use as vasodilators in vascular disorders such as pulmonary hypertension and the prolongation of allograft survival after cardiac and renal transplantation,288 it has been suggested that stable...
eicosanoid analogues that remain metabolically active can be used as a therapeutic modality to inhibit intimal smooth muscle cell proliferation and facilitate mobilization of cholesterol ester in smooth muscle cells in conditions of reduced endogenous eicosanoid generation during atherogenesis.\cite{1,2,3} It remains to be seen whether administration of such eicosanoid analogues (cyclooxygenase or lipooxygenase metabolites) can affect the progression of human coronary atherosclerosis or peripheral vascular disease under conditions of moderate to high blood lipid levels.

Acknowledgment
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Index Terms: atherosclerosis • eicosanoids • prostacyclin • prostaglandins • arterial smooth muscle cells • endothelial cells • phenotype • proliferation • cholesterol metabolism • lipoproteins • growth factors.
Eicosanoids in regulation of arterial smooth muscle cell phenotype, proliferative capacity, and cholesterol metabolism.

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