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Forum Review

Free Radicals and Lipid Signaling in Endothelial Cells

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ABSTRACT

Lipid mediators generated by oxidative pathways play essential roles in vascular homeostasis and disease through activating signal transduction pathways that control a variety of cellular functions, including vascular tone, gene expression, and leukocyte and platelet activation. Several enzyme families generate oxidized lipids, and a number of these are either constitutively expressed or inducible in the endothelium, including prostaglandin H synthases, lipoxygenases, and cytochrome P450 isoforms. Mediators generated by these enzymes are predominantly arachidonate-derived and include lipid hydroxides, epoxides, hydroperoxides, and prostanoids. These enzymes may also generate low levels of lipid-derived radicals in the vasculature following escape of substrate radicals from the active site. Lipid oxidation enzymes are often up-regulated in atherosclerosis and hypertension, with several lines of evidence suggesting that they play a central role in the pathogenesis of the disease process itself. This review will describe the isoforms of lipid oxidation enzymes present in endothelial cells focusing on their physiological functions and proposed roles in initiation and progression of vascular disease. *Antioxid. Redox Signal.* 5, 195–203.

ENDOTHELIUM

THE ENDOTHELIUM comprises a single cell layer separating the lumen of blood vessels from their underlying smooth muscle and extracellular matrix. The major function of the healthy endothelium is to maintain vascular homeostasis through provision of an antiadhesive surface and generation of vascular protective signaling mediators. These include the vasodilator free radical, nitric oxide (NO), and oxidized lipid mediators such as prostacyclin (PGI_2) and endothelium-derived hyperpolarizing factor (EDHF), which may be an epoxyeicosatetraenoic acid (EET). Following an inflammatory challenge, the properties of the endothelium alter with a switch in generation of vasoprotective mediators, to formation of factors that can potentiate the inflammatory response through enhancing recruitment, adhesion, and migration of leukocytes and platelets. These include a variety of cytokines and chemokines, but also additional lipid mediators that are proinflammatory, such as cysteinyl leukotrienes (111).

Endothelial cells (EC) express several enzymes that oxidize unsaturated lipid to signaling mediators. These include both constitutive and inducible isoforms of prostaglandin H synthases (PGHS), lipoxygenases (LOX), and cytochrome P450 (CYP), with the levels of expression and isoform type being dependent on the inflammatory state of the cells. The predominant substrate utilized by all these pathways is arachidonate, hydrolyzed from the *sn*2 position of phospholipids by phospholipase A_2, in response to agonist activation. Following release, it undergoes enzymatic oxidation and isomerization forming a complex variety of signaling mediators that are released either to signal in adjacent cells or to signal intracellularly in the endothelium itself.

The following sections will describe each signaling pathway focusing in particular on their expression and function in the endothelium and biological actions of their lipid products on EC themselves.

PGHS–1 AND –2 IN EC

Enzymology of PGHS-1 and –2

Prostaglandins are predominantly generated through the action of PGHS, of which there are both constitutive (PGHS-

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1; stomach, gut, kidney, platelets) and inducible (PGHS-2: fibroblasts, macrophages) isoforms. Synthesis involves a two-step conversion of arachidonic acid. First, the enzyme oxidizes arachidonic acid to a cyclic endoperoxide, prostaglandin G_2 (PGG_2), by a cyclooxygenase activity, then a peroxidase reduces the peroxide to a hydroxide, yielding the endoperoxide, prostaglandin H_2 (PGH_2) (67, 74, 96, 97) (Scheme 1).

The peroxidase and cyclooxygenase activities of PGHS are located on opposite sides of the protein, separated by the heme prosthetic group, and function independently of each other. Activation of PGHS by hydroperoxide results in formation of a tyrosyl radical, proposed to be the oxidant responsible for cyclooxygenase activity (32, 54). In this mechanism, ferric PGHS is oxidized to an oxyferryl porphyrin π cation radical intermediate (PGHS compound 1) by hydroperoxide. Compound 1 then oxidizes a tyrosine residue, forming a tyrosyl radical, and is in turn reduced to PGHS compound 2 ($Fe^{4+}{=}O$). Following this, the tyrosyl radical oxidizes arachidonate, forming a carbon-centered radical (105) (Scheme 1).

Biochemically, PGHS-1 and –2 are very similar, sharing 60% sequence homology, similar or identical reaction mechanisms, superimposable x-ray crystal structures, and the same subcellular localization at the endoplasmic reticulum and nuclear membrane (31, 60, 67, 84, 98). However, despite these similarities, PGHS isoforms function as two independent prostaglandin synthesis systems utilizing different cellular arachidonate pools in the same cell type, and with very different patterns of expression control. This predominantly results from different activation kinetics and different rates of negative allosteric regulation by substrate concentrations.

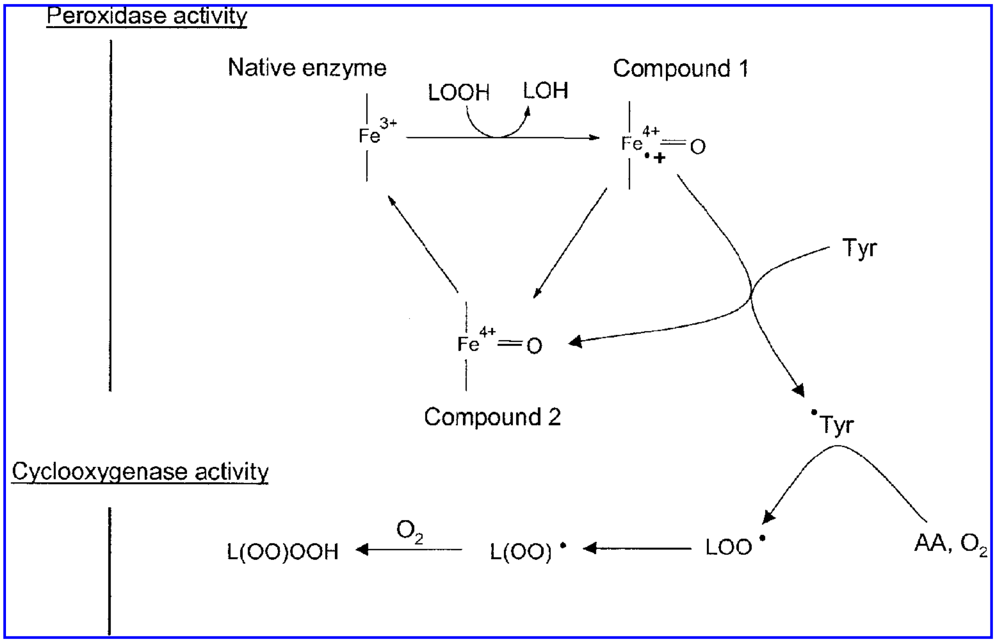
PGHS in vascular disease

In the vasculature, PGHS isoforms are centrally involved in regulating vascular homeostasis through generation of PGH_2, which is the precursor for either PGI_2 (endothelial) or thromboxane A_2 (TXA_2; platelets). PGHS is transiently activated in platelets or endothelial cells following stimulation by agonists such as thrombin, collagen (platelets), bradykinin, or acetycholine (endothelium). Following this, the PGH_2 is rapidly converted into PGI_2 or TXA_2 by the CYP enzymes, prostacyclin synthase (PGI synthase) or thromboxane synthase (TXS), respectively. Platelet PGHS-1 is the primary source of plasma TXA_2 in healthy humans, whereas endothelial PGHS-2 is the major source of PGI_2 (~80%) (16, 23, 25, 70). These eicosanoids have opposing effects with PGI_2 being vasodilatory and an inhibitor of platelet activation via elevating cyclic AMP, and TXA_2 causing vasoconstriction and platelet activation.

The formation of PGHS-derived prostaglandins, including TXA_2, PGI_2, and isoprostanes, is markedly elevated in vascular disease (28, 29, 36, 38, 100). For example, urinary 8-epi-prostaglandin $F_{2\alpha}$ is increased 130% in hypercholesterolemia (29). Also, isoprostanes are present in human atherosclerotic lesions along with PGHS-1 and -2 (3, 38, 100). In a recent study of patients with atherosclerosis, the selective PGHS-2 inhibitor, nimesulide, reduced PGI_2 generation by 46%, with no effect on TXA_2 (3). This indicates that both isoforms contribute to the raised generation of PGI_2, but that TXA_2 is formed exclusively by PGHS-1 in patients with vascular disease, as well as normal controls (70).

Endothelial expression of PGHS isoforms

It has long been considered that PGI_2 is the main prostanoid synthesized by EC, and TXA_2 the main prostanoid from platelets. However, cultured human umbilical vein EC (HUVEC) express PGHS-1 constitutively, with this enzyme being the major source of EC-derived PGH_2 precursor for low-level TXA_2 synthesis (18). Basal expression of PGHS-2 is low or absent in most EC, but following stimulation with



Scheme 1. Peroxidase and cyclooxygenase activities of PGHS. AA, arachidonate; LOH, lipid hydroxide; LOOH, lipid hydroperoxide; Tyr, tyrosine.

laminar flow, platelet-derived TXA_2, hypoxia, interleukin-1β (IL-1β), tumor necrosis factor-α, fibroblast growth factor, phorbol ester, lipopolysaccharide (LPS), or vascular endothelial growth factor (VEGF), its up-regulation through an immediate early gene leads to generation of PGI_2 and PGE_2 (17–19, 34, 52, 66, 72, 93, 104). Interestingly, IL-1β induces PGI synthase and PGE synthase in tandem with PGHS-2, but not TXS (18). It is therefore likely that the PGHS-2-dependent generation of PGI_2 *in vivo* in both healthy people and patients with vascular disease requires continuous stimulation of gene expression, for example, by laminar flow or proinflammatory cytokines. In contrast to HUVEC, PGHS-2 is a significant source of TXA_2 generated by human microvascular EC, which can inhibit migration and angiogenesis *in vitro* (27). The *in vivo* importance of this is unclear, however, because platelet PGHS-1 is the major source of TXA_2 in healthy people (70). PGHS-2 is also negatively regulated at the transcriptional level in EC. For example, aspirin, sodium salicylate, or NO inhibits IL-1β-, phorbol-, or LPS-induced PGHS-2 expression in HUVEC and bovine pulmonary artery EC (19, 110).

Although PGHS-1 is expressed constitutively by EC, its expression is also controlled by transcriptional regulation. For example, up-regulation of PGI_2 synthesis in intrapulmonary arteries rises markedly during late fetal life, due to a developmental increase in PGHS-1 expression that occurs via estrogen stimulation of the estrogen receptor (5, 51). This may also have implications for PGHS-1 expression in pre- and post-menopausal females, where risk of vascular disease increases with decreased estrogen levels, and estrogen replacement is associated with decreased cardiovascular risk (2, 11).

In addition to generation of endogenous TXA_2 and PGI_2, EC-derived PGH_2 can serve as a source of substrate for prostaglandin synthesis by other cell types. Aspirin-treated platelets synthesize TXA_2 *in vitro* when incubated with EC that are secreting PGH_2 following thrombin activation (53). However, selectively blocking platelet PGHS-1 by daily aspirin administration virtually abolishes generation of thromboxane metabolites *in vivo*. This suggests that EC are unlikely to be a significant source of precursors for synthesis of platelet TXA_2 in the vasculature.

Regulation of EC function by PGHS products

EC function is regulated in several ways through PGHS signaling. In particular, recent data have implicated the prostaglandin 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) in mediating multiple responses through activating peroxisome proliferator-activated receptors (PPARs). These are members of the nuclear receptor superfamily of transcription factors that are important mediators of the inflammatory response. Through this pathway, 15d-PGJ_2 activation of endothelial PPARs inhibits leukocyte–endothelial interactions, interferon-γ-induced expression of CXC chemokines, and tumor necrosis factor-induced oxidized low-density lipoprotein receptor (LOX-1) and induces stress proteins, including heme oxygenase and plasminogen activator inhibitor type-1 (20, 49, 55, 56, 66, 69). 15d-PGJ_2 also signals in a PPAR-independent manner in EC, inducing apoptosis and synthesis of GSH and IL-8 (4, 50, 63).

In addition to 15d-PGJ_2, additional prostaglandins that signal in EC include PGE_2, which induces expression of P-selectin, VEGF, and endothelial nitric oxide synthase (eNOS) through activation of ERK/JNK2 signaling pathways, and PGD_2, which can relax vessels through stimulation of eNOS activity in bovine coronary arteries (6, 33, 39, 43, 80).

In summary, PGHS isoforms expressed in EC regulate normal vascular function and participate in the pathophysiology of vascular disease. In addition, PGHS products generated by adjacent cells are important in regulating numerous EC functions, including apoptosis, integrin expression, and eNOS activity.

LOX IN EC

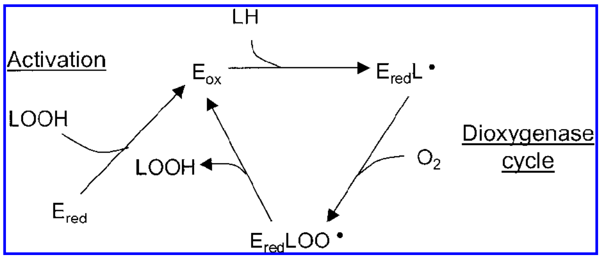
Enzymology of LOXs

LOX are non–heme iron-containing enzymes that catalyze arachidonate or linoleate oxidation to form a series of lipid hydroperoxides. In mammalian cells, several isoforms are known, named by their position of oxygen insertion into arachidonate. LOX contain a single non-heme iron that alternates between Fe^{2+} and Fe^{3+} during catalysis. Resting enzyme predominantly exists as the reduced form, requiring oxidation by hydroperoxides before dioxygenation can occur. Oxidation of arachidonate or linoleate by the ferric enzyme is shown (Scheme 2).

Vascular and endothelial expression of LOX isoforms

LOX enzymes are predominantly expressed by leukocytes (5- and 15-LOX in humans, rabbits, 12/15-LOX in mice, rats, pigs) and platelets (12-LOX). EC do not appear to express significant LOX protein, although several reports have suggested its presence in EC through (a) observations of 15- and 12-hydroxyeicosatetraenoic acid (HETE) synthesis and (b) effects of LOX inhibitors on a variety of EC functions, including angiogenesis, proliferation, and the glucose transporter GLUT-1 expression (1, 10, 13, 24, 45, 46, 75, 81, 82, 85, 108). However, detection of HETEs does not prove expression of LOX because these products can be generated by other metabolic pathways including PGHS also present in EC, and also nonenzymatically (62). In addition, inhibition of HETE synthesis by LOX inhibitors, such as nordihydroguaiaretic acid or eicosa-5,8,11,14-tetraynoic acid, is not conclusive due to the lack of specificity of these compounds.

Expression of mRNA encoding for several LOX isoforms has been described in EC, including leukocyte-type 12-LOX



Scheme. 2. Dioxygenase cycle of lipoxygenases. E_{red}, inactive native ferrous enzyme; E_{ox}, active ferric enzyme; LH, unsaturated lipid substrate; LOOH, lipid hydroperoxide product.

(porcine coronary EC), 5-LOX (human pulmonary artery EC), 15-LOX, and platelet 12-LOX (HUV EC) (37, 62, 111, 112). However, a recent study showed that for 15-LOX, the presence of mRNA does not necessarily imply the induction of protein or enzyme activity (62). In that study, IL-4 induced 15-LOX mRNA in HUVEC, but protein was not found, suggesting that additional posttranscriptional regulation was required for formation of active enzyme (62). Small amounts of the 5-LOX message and protein have been detected in human pulmonary artery EC using RT-PCR and western blotting (111). However, basal expression is too low to support A23187 stimulation of leukotriene synthesis, with only a small amount of 5-HETE being generated (111). Other studies have shown that functional 5-LOX protein is not expressed in either HUVEC or pig aortic EC, but that generation of leukotrienes in EC can occur following intercellular transfer of LOX products from associated granulocytes (22, 35). Increased protein expression of 5-LOX has been reported in pulmonary artery EC of patients with primary pulmonary hypertension, in hypoxic rats, and antigen-challenged mice (21, 107, 109). This suggests 5-LOX may be up-regulated in inflammatory-activated endothelium, although the mechanisms involved are unknown.

Regulation of EC function by LOX products

LOX products stimulate a variety of EC functions (44, 45, 83, 101–103, 108). In particular, an important role for platelet 12-LOX expressed by tumor cells in regulating EC functions in carcinogenesis is emerging. Several studies have shown that 12-LOX can stimulate proliferation, migration, and tube differentiation *in vitro* and angiogenesis *in vivo* (44, 75, 76, 103). In addition, 12-HETE up-regulates expression of alpha v beta 3 integrin on EC, which is required for angiogenesis of breast cancer, whereas biosynthesis of 12-HETE by B16 melanoma cells is a determinant of their metastatic potential (7–9, 64, 101, 103). Finally, 12-HETE can stimulate monocyte endothelial interactions following incubation of EC with high glucose or minimally oxidized low-density lipoprotein, suggesting a role for LOX activation of EC in inflammatory vascular disease (44, 45, 83).

In summary, expression of LOX in EC is low or absent under normal conditions. Up-regulation *in vivo* following inflammatory challenge may result in generation of low amounts of HETEs, but it is unclear whether this is of biological significance. In contrast, generation of LOX products by adjacent cells, including leukocytes and tumor cells, is centrally involved in regulating EC function under pathophysiological conditions.

CYP ENZYMES IN EC

CYP enzymes are a ubiquitously expressed family of heme enzymes that play central roles in xenobiotic metabolism and lipid oxidation. CYP-dependent arachidonate oxidation occurs through three pathways, allylic oxidation, ω hydroxylation, and olefin epoxidation. These result in a series of oxygenated metabolites, including epoxides and fatty acid alcohols (for review, see 15).

Nonhepatic CYP arachidonate metabolites act as intracellular signaling molecules in vascular tissue. The major EC CYP isoforms are PGI synthase and TXS, which generate PGI_2 or TXA_2, respectively, from PGHS-derived PGH_2 (described earlier). Both enzymes are controlled through transcriptional regulation, although the pathways are not well characterized. For example, TXS is inducible in EC by xenoreactive antibodies, whereas IL-1β elevates PGI synthase in tandem with PGHS-2 (12, 18).

Additional EC-derived CYP products include the epoxides, 11,12-EET and 5,6-EET. 11,12-EET is avidly esterified into endothelial phospholipid pools and mediates vascular relaxation, possibly accounting for a component of EDHF activity (14, 86, 106). Preformed EETs in endothelial membranes can influence vascular function by altering membrane characteristics, ion transport, or lipid-dependent signaling pathways (79). For example, 5,6-EET mediates vasodilation by either increasing NO production through stimulating Ca^{2+} influx into EC or by directly activating smooth muscle K_{ca} channels (14, 41, 47, 79).

GENERATION OF FREE RADICAL SPECIES BY PGHS OR LOX

Lipid peroxidation enzymes generate free radical intermediates during catalysis. For example, both PGHS and LOX form enzyme-bound lipid alkyl ($L^{\cdot}$) and peroxyl ($LOO^{\cdot}$) radicals that are ultimately converted into hydroperoxides (LOOH) before release from the active site. At low O_2 tension, a small proportion of lipid radicals (up to 10%) escape the active site (H. Kühn and P. Ludwig, unpublished observations). These react with O_2 at diffusion-controlled rates to form free $LOO^{\cdot}$, which can then propagate secondary nonenzymatic lipid peroxidation. Because this is not controlled by LOX, a proportion of racemic products is formed. This reaction may be a significant source of LOOH in late atherosclerotic lesions, where stereospecificity of lipid peroxidation products is lost (57).

Although they do not directly bind or activate O_2, PGHS and LOX can generate superoxide anion ($O_2^{\cdot-}$) through secondary side-reactions involving oxidation of certain peroxidase substrates. In these reactions, substrates, including NAD(P)H and GSH are oxidized to radicals [*i.e.*, $NAD(P)^{\cdot}$ and $GS^{\cdot}$, respectively] that can ultimately react with O_2 either directly, or indirectly forming $O_2^{\cdot-}$ (58, 88, 94). To date, these reactions have only been observed using purified enzyme, and it is unknown whether they contribute to free radical levels in intact cells or tissue.

REGULATION OF PGHS, LOX, AND CYP BY REACTIVE OXYGEN AND NITROGEN SPECIES

Lipid oxidation enzymes are regulated in several ways through the action of reactive oxygen and nitrogen species. In general, enzyme turnover is activated by oxidation [*e.g.*, for LOX or PGHS by LOOH, hydrogen peroxide (H_2O_2), or peroxynitrite ($ONOO^-$)] and inhibited by reduction (*e.g.*, nordihydroguaiaretic acid and baicalein as LOX inhibitors, or removal of LOOH or H_2O_2 by glutathione peroxidase or catalase-dependent reduction) (48, 59, 61, 87, 89, 95).

NO inhibits LOX turnover through scavenging the enzyme-bound LOO·, but exerts no direct effect on PGHS turnover *in vitro* (26, 77). The lack of effect on PGHS turnover is intriguing, because NO can interact with this enzyme in multiple ways, including scavenging of the catalytic tyrosyl radical and acting as a reducing peroxidase substrate (40, 78).

In contrast to its lack of effect on purified PGHS, NO has multiple and often contradictory effects on PGHS expression and activity in intact cells. In several systems (including purified recombinant cyclooxygenase-2, intact platelets, EC, RAW 264.7 cells, an *ex vivo* model of renal inflammation, and following *in vivo* administration of ·NO donors to rats), ·NO highly stimulates prostaglandin production (30, 65, 90–92). However, other investigators have found ·NO either to be inhibitory toward PGHS, or to have no effect on either PGHS activity (platelets) or LPS-induced expression in RAW 264.7 cells (26, 73, 99). In some cell types, however (rat microglial cells and peritoneal macrophages), ·NO suppresses LPS-induced cyclooxygenase-2 expression, resulting in apparent enzyme inhibition (42, 71).

CONCLUSIONS

Oxidized lipid mediators generated by PGHS, LOX, or CYP are of central importance in the normal physiology of the endothelium, with their aberrant generation playing a major role in the pathogenesis of inflammatory vascular disease. In addition, these enzymes generate a small amount of lipid radicals that may propagate nonenzymatic lipid peroxidation, a hallmark of atherosclerotic lesions. Although much is known regarding function and control of these pathways in EC (especially PGHS and LOX), others, especially the CYP enzymes, are less studied. Studying the biological roles and signaling pathways of CYP in EC is becoming a major focus of research in vascular biology and will undoubtedly lead to a fuller understanding of their roles in both normal homeostasis and vascular pathophysiology.

ACKNOWLEDGMENTS

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ABBREVIATIONS

CYP, cytochrome P450; 15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2; EC, endothelial cell(s); EDHF, endothelium-derived hyperpolarizing factor; EET, epoxyeicosatetraenoic acid; eNOS, endothelial nitric oxide synthase; HETE, hydroxyeicosatetraenoic acid; HUVEC, human umbilical vein endothelial cells; IL, interleukin; L·, lipid alkyl radical; LOO·, lipid peroxyl radical; LOOH, lipid hydroperoxide; LOX, lipoxygenase; LPS, lipopolysaccharide; NO, nitric oxide; $O_2^{\cdot -}$, superoxide anion; PGD_2, PGE_2, PGG_2, and PGH_2, prostaglandin D_2, E_2, G_2, and H_2, respectively; PGHS, prostaglandin H synthase; PGI_2, prostacyclin; PGI synthase, prostacyclin synthase; PPAR, peroxisome proliferator-activated receptor; TXA_2, thromboxane A_2; TXS, thromboxane synthase; VEGF, vascular endothelial growth factor.

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