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The Arachidonate 12/15 Lipoxygenases

A Review of Tissue Expression and Biologic Function

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Introduction

The lipoxygenases are lipid-peroxidating enzymes implicated in the physiology of inflammatory diseases including psoriasis, atherosclerosis, arthritis, glomerular nephritis and airway inflammation *(1–4)*. These enzymes catalyze the stereospecific oxygenation of arachidonic acid resulting in the generation of hydroperoxy-eicosatetraenoic acid (HPETE) intermediates which are subsequently reduced to hydroxy-eicosatetraenoic acids (HETEs). The names of the mammalian lipoxygenases, the 5-, 12- and 12/15-lipoxygenases, are derived from the positional specificity of oxygenation in the arachidonic acid carbon backbone. The human airway/leukocyte 12/15-lipoxygenase and its mammalian homologs are distinguished from the 5- and platelet 12-lipoxygenases not only by the different positional specificity of oxygenation, but by their unique enyzmologic properties and tissue patterns of expression. Although the 12/15-lipoxygenases generate predominately either 12S-HETE or 15S-HETE depending on specific structural elements, these enzymes produce significant amounts of both metabolites and thus are referred to as the 12/15-lipoxygenases in this article. Recently, a second human 15-lipoxygenase was cloned, which exhibits more stringent positional specificity and is expressed in skin, lung and prostate tissues *(5)*. Although this second 15-lipoxygenase produces similar arachidonic acid metabolites as the 12/15-lipoxygenase, it likely has a distinct physiologic role.

Although this article will focus on the regulation of tissue expression and the physiologic roles of the 12/15-lipoxygenases, important biochemical and genetic studies continue to provide new information

and reagents that are yielding new insights into the physiologic roles of these enzymes. The cloning of the mammalian 12/15-lipoxygenases have enabled the correlation of structural data with specific enzymatic characteristics including substrate specificity and catalytic properties. Recently, these studies have focused on the structural elements that influence positional specificity of oxygenation and have determined specific amino acids that affect the ratio of 12S-HETE and 15S-HETE formed from arachidonic acid by the 12/15-lipoxygenases *(6)*. In addition, the three dimensional X-ray crystallographic structure of the related soybean lipoxygenase-1 was recently solved and will facilitate pending crystallographic studies of the mammalian lipoxygenases *(7)*. These crystallographic studies can provide structural details that further the understanding of substrate and positional specificity and perhaps aid in the development of specific inhibitors.

Regulation of Protein Expression

Expression of the human arachidonate 12/15-lipoxygenase and its homologous enzymes in rabbit, bovine, porcine, murine and rat cell systems is regulated by tissue specific mechanisms and soluble modulators of inflammation. This regulation of protein expression and enzymatic activity occurs through multiple mechanisms.

The tissue specific expression of 12/15-lipoxygenase is well described in airway epithelial cells, eosinophils, monocyte/macrophages and reticulocytes *(8–11)*. The lipoxygenases from these cells are identical based on their antibody cross reactivity, enzymatic activity profile and the primary sequences of cloned cDNAs *(12–14)*. Although 12/15-lipoxygenase activity exists in other cells including smooth muscle cells *(15,16)*, endothelial cells *(17,18)*, adrenal epithelium *(19)*, myometrial *(20)*, and keratinocytes *(21,22)*, it is unclear whether expression in these cells results from the original 12/15-lipoxygenase, the recently cloned 15-lipoxygenase or other yet uncharacterized 12/15-lipoxygenase activities.

Reticulocyte 12/15-lipoxygenase is highly expressed in rabbits during bleeding-induced reticulocytosis *(11)*. The early studies established the purification protocol, identified enzymatic properties of the protein including its substrate specificity and suicidal inactivation and provided a plausible physiologic role for this enzyme in reticulocyte maturation. These in vitro findings were later confirmed with in vivo measurements of 15-lipoxygenase enzymatic activity in rabbit reticulocytes and in humans with hemolytic disorders. *(23,24)*.

In nondisease states, 12/15-lipoxygenase is constitutively expressed in surface airway epithelium and circulating and tissue based eosinophils *(8,25,26)*. In both cell types, enzyme expression is confined

to the cytoplasm exclusive of the nucleus or granules *(8,27)*. When airway epithelial cells are harvested and cultured, expression markedly diminishes over 4 d. In contrast, expression of eosinophil 12/15-lipoxygenase is maintained in vitro when the cells are cultured in the presence of GM-CSF (10 ng/mL).

Significant expression of 12/15-lipoxygenase in monocytes/macrophages appears to require exogenous stimuli or recruitment into inflamed tissue. For example, although enzyme activity is low or undetectable in quiescent peripheral blood monocytes, high levels of activity are found in macrophages recruited in immune complex mediated glomerulonephritis and the "foamy" macrophages associated with atherosclerotic lesions including a transplant coronary artery atherosclerosis *(3,28,29)*. The mediators inducing expression of 12/15-lipoxygenase in these specific situations deserve further study and likely involve inflammatory cytokines or bioactive lipids.

The association of 12/15-lipoxygenase expression and activity with inflammation suggested that inflammatory mediators might regulate 12/15-lipoxygenase activity. Indeed, several inflammatory mediators have been found to dramatically affect 12/15-lipoxygenase protein expression in cultured monocytes/macrophages and airway epithelial cells. Interleukin-4 (IL-4) and IL-13 induce 12/15-lipoxygenase mRNA, protein and enzymatic activity in cultured monocytes probably through a STAT6-dependent pathway *(10,30)*. This potent induction is specific to these cytokines and not other TH2 cytokines or the TH1 cytokines. In addition, angiotensin II induces monocyte expression of 12/15-lipoxygenase, providing a potential link between expression of the enzyme to the pathophysiology of hypertension and atherosclerosis *(31,32)*. Finally, epidermal growth factor and transforming growth factor induce 12/15-lipoxygenase activity in BT-20 breast carcinoma cells, presumably through posttranslational mechanisms *(33)*.

γ-Interferon, endotoxin and glucocorticoids block expression of human 12/15-lipoxygenase at physiologic concentrations in cultured monocytes. The inhibition of 12/15-lipoxygenase by glucocorticoids is likely a tissue specific effect that is evident in monocytes and not in airway epithelial cells (unpublished observation, D. Conrad). Although the role of these inhibitory effects in vivo needs to be determined, it likely involves mechanisms that antagonize the physiologic functions of the 12/15-lipoxygenases.

The tissue specific and inflammatory mediator dependent expression of 12/15-lipoxygenase appears to involve transcription, translation and posttranslational mechanisms that integrate effects from diverse signal transduction pathways. A 150-bp fragment from the proximal promoter of the rabbit gene directs reporter gene expression in a erythroid specific manner *(34)*. A functional silencing response ele-

ment and an associated protein binding activity that correlates with transcriptional inhibition was demonstrated in nonerythroid cells *(35)*.These studies support a role for transcription in regulating the tissue specific expression in rabbit erythrocytes. The 5'-flanking sequence of the human 12/15-lipoxygenase also contains AP2, GATA-1, IL-4, CACCC, and shear stress response elements, however the functional significance of these elements remains to be confirmed *(36)*.

In erythroid cells, posttranscriptional mechanisms also play an important role in regulating 12/15-lipoxygenase because its expression is limited to exnucleated reticulocytes. The 3' untranslated region of the rabbit 15-lipoxygenase cDNA contains pyrimidine-rich repeats that are postulated to regulate its expression in reticulocytes *(37,38)*. Recently, ribonucleoproteins K and E1 were found to bind these pyrimidine repeats and inhibit protein translation *(39,40)*. Although these repeats are evident in the human cDNA, the relevance of this regulatory mechanism in human or nonerythroid cells remains to be demonstrated in part because it has been difficult to identify mature, untranslated 12/15-lipoxygenase mRNA in these cell systems.

The activity of human 12/15-lipoxygenase is also directly regulated. Enzymatic activity terminates via an irreversible inactivation process that is dependent on the hydroperoxide intermediate *(11,41)*. Kinetic parameters indicate that the 12/15-lipoxygenase catalyzes approx 600 oxygenations prior to inactivation *(42)*. Although early studies correlated enzyme inactivation with oxidation of a methionine residue, when the specific methionine was identified and mutated, it was found to be nonessential for activity and its oxidation not required for inactivation *(43,44)*. Finally, although no proteins analogous to the 5-lipoxygenase activating protein (FLAP) have been identified, there is evidence of a Ca^{2+}-dependent translocation of 12/15-lipoxygenase to cellular membranes that may be important in regulating cellular enzymatic activity *(45,46)*.

Effects of 12/15-Lipoxygenase Expression

The substrate specificity of the 12/15-lipoxygenase profoundly influences its physiologic function. Unlike the 5- and platelet 12-lipoxygenase, the 12/15-lipoxygenase catalyzes oxygenation of several polyenoic free fatty acids and similar substrates esterified in complex lipids *(11,47,48)*. This broad substrate specificity allows the 12/15-lipoxygenase to produce an array of bioactive lipids, including the HPETEs and HETEs, from arachidonic acid and the hydroperoxy-octatetraenoic acids (HPODEs) and the hydroxy-octatetraenoic acids (HODEs) from linoleic acid. The 12/15-lipoxygenases also generate higher order oxygenation products including 5S,15S-diHETE, 8S,15S-diHETE, 5-oxo-15-

hydroxy-HETE, and the lipoxins. The effects of these bioactive lipids are determined by the cellular context of 12/15-lipoxygenase expression and the coexpression of enzymes capable of further metabolizing these lipid products. In general, the mono-HETEs, mono-HPETEs, and lipoxins have inhibitory effects on inflammation, whereas several of the di-HETEs have potent proinflammatory effects. The effects of these metabolites on hematologic and nonhematologic cells are summarized in Tables 1 and 2.

Cellular Effects of Lipoxygenase Metbolites

The initial studies of the role of 12/15-lipoxygenase focused on its interactions with the 5-lipoxygenase pathway. Both 15-HPETE and 15-HETE suppress 5-HETE and leukotriene B_4 (LTB_4) production and conversely, 5-HETE inhibits 15-HETE production from rabbit polymorphonuclear leukocytes *(49,50)*. 15S-HETE inhibits T-lymphocyte mitogenesis and human eosinophil leukotriene C_4 (LTC_4) secretion, blocks neutrophil migration across activated endothelium and inhibits superoxide anion production and degranulation from activated neutrophils *(51–54)*. 15-HPETE, but not 15-HETE downregulates Fc gamma receptors on human T cells and monocytes *(55)*. Both, 14,15-diHETE and lipoxin A inhibit natural killer cell activity *(56,57)*. Finally, 15-HPETE downregulates important proinflammatory processes including endotoxin-induced TNF production in monocytes and the TNF induced expression of ICAM-1, E-selectin and VCAM-1 via protein kinase C dependent pathways *(58,59)*. Although these anti-inflammatory effects suggest that 12/15-lipoxygenase plays an important role in counterregulating the effects of pro-inflammatory mediators, they remain to be confirmed with in vivo studies using specific inhibitors or genetically altered mice lacking the 12/15-lipoxygenase.

Several dioxygenation products of 12/15-lipoxygenase are associated with significant proinflammatory effects. The best studied, 8S,15S-diHETE, is a neutrophilic chemotactic factor. Its chemotactic activity was demonstrated both in vitro and in an in vivo chemotactic assay in dogs *(60,61)*. In addition, the 12/15-lipoxygenase metabolites, 5,15-diHETE and 5-oxo-15-HETE are potent eosinophil chemotactic factors that may provide a positive feedback loop leading to eosinophil recruitment in allergic inflammation *(62,63)*.

A very important group of eicosanoids generated by the 12/15-lipoxygenases are the lipoxins which are trihydroxy metabolites of arachidonic acid produced from 5- and either a 12- or 15-lipoxygenase. The cellular effects of the lipoxins are mediated partly by G-protein coupled receptors *(64,65)*. Monocytes/macrophages expressing both 5- and 15-lipoxygenase generate physiologically significant amounts of lipoxin A_4 and B_4. Alternatively, the lipoxins are formed by a transcellular

Table 1
Cellular Effects of 12/15-Lipoxygenases and Their Metabolites in Hematologic Cells

Cells	Species	Effect	Metabolite	Reference
Lymphocytes	Mice	Mitogenesis	15-HETE	*123*
	Human	↓Mitogenesis	15-HPETE	*51,124, 125*
	Human	↓Fc Gamma R	15-HPETE	*55*
Neutrophils	Human	↑Chemotaxis	8,15-diHETE	*60,61*
	Human	↓Chemotaxis	Lipoxins	*73*
	Human	↓5LO Metabolites	15-H ETE	*126*
	Human	↓Transmigration	15-HETE	*53,75*
	Rat, Human	↑Chemotaxis	5,12-diHETE	*127*
	Human	↑Superoxide anions, degranulation	Lipoxins	*69*
	Rabbit	↓LTB_4	15-HETE	*49,126*
	Human	↑Superoxide anions, degranulation	15-HETE	*54*
Monocytes	Human	LDL oxidation	Enzymatic action	*2,112,113*
	Human	↓TNF Secretion, cell adhesion molecule expression	15-HPETE	*58,59*
Natural killer cells	Human	↑Activity	14,15-diHETE, Lipoxins	*56,57*
Eosinophils	Human	↑Chemotaxis	5,15-diHETE, 5-oxo15-HETE	*62,63*
Platelets	Human	↓Platelet LO activity	15-HETE	*128,129*
Reticulocytes	Human, rabbit	Reticulocyte maturation	Enzymatic action	*11,24*

Table 2
Cellular Effects of 12/15-Lipoxygenases and Their Metabolites in Nonhematologic Cells

Cells	Species	Effect	Metabolite	Reference
Adrenal	Bovine	↑Steroidogenesis	15-HETE	*130*
Airway epithelial	Human/dog	Mucus secretion, Cl-transport	15-HETE	*107,108*
Cardiomyocytes	Rats	↑β Adrenergic tone	15-HETE	*78*
Vascular smooth muscle	Rabbit/guinea pig/dog	Contraction	15-HETE	*131,132*
Bronchial smooth muscle	Human	Contraction	5- and 15-HETE	*106*
Bronchus	Human (in vivo)	↓ LTC_4-induced contraction	Lipoxins	*72*
Pituitary	Rat	↑ Prolactin secretion	15-HPETE,15-HETE	*88*
Pancreatic islet	Rat	↓Insulin	12-HPETE	*86,87,133*
Renal	Rat	↓Renin secretion	12-HPETE, 12-HETE	*119*
Spermatozoa		Acrosome reaction	15-HPETE/15-HETE	*89*

process when a 5-lipoxygenase expressing cell (i.e., neutrophil or macrophage) closely interacts with cells expressing a 12- or 15-lipoxygenase (platelet or airway epithelial cell). This transcellular route is believed to play an important role in generating lipoxins from respiratory epithelium and vascular endothelium *(66–68)*.

Although lipoxins induce neutrophil degranulation, superoxide anion generation and protein kinase C activation, these novel compounds also have potent anti-inflammatory properties that in most cases, counteract the effects of the 5-lipoxygenase metabolites *(68–70)*. Although the vasoactive properties of the lipoxins are species and tissue specific, in human pulmonary arteries, they induce endothelium dependent vasodilatation *(71)*. In vivo studies show that lipoxin A_4 inhibits LTC_4 induced contraction *(72)*. Lipoxins modify inflammatory reactions by inhibiting natural killer cell activity and antagonizing neutrophil chemotaxis and transmigration of neutrophils through epithelium and endothelium *(57,73–75)*.

Membrane Oxidation Effects

12/15-Lipoxygenases act directly on cellular membranes to produce oxygenated complex lipids that have been implicated in several well described signal transduction pathways. Expression of the 12/15-lipoxygenase "primes" the cells for lipoxygenase mediated signal transduction events by oxygenating arachidonic acid in the SN2 position of phosphatidylinositol. Subsequent action of phospholipases releases oxygenated lipid second messengers including 12S-HETE, 15S-HETE, oxygenated diacylglyceride and lipoxin precursors *(10,76)*.

The cellular effects of 12S- or 15S-HETE are mediated through several well established signal transduction pathways. 15-HETE inhibits endotoxin-induced procoagulant activity and induces β-adrenergic hypersensitivity in rat cardiomyocytes via a protein kinase C dependent process *(77,78)*. 12S-HETE mediates important protein kinase C dependent processes involved with tumor cell adhesion to matrix, spreading and invasion *(79–82)*. 15S-HETE stimulates vascular smooth muscle cell mitogen-activated protein (MAP) kinase activity whereas in Syrian hamster embryo cells, 13-HPODE stimulates MAP kinase phosphorylation *(83,84)*. In addition, 15S-HETE blocks phospholipase C dependent production of inositol triphosphate and calcium release by LTB_4 and platelet activating factor *(54)*. The monoHETEs may also influence signal transduction pathways through interactions with nuclear hormone receptors, including the peroxisome proliferator-activated receptor-γ *(85,85a)*. The specific signal transduction pathways used by the mono-HETEs to stimulate the secretion of insulin, prolactin and steroids as weli as those involved with the acrosome induction and parturition need further clarification *(86–90)*.

Tissue Physiology Implications

Direct 12/15-lipoxygenase enzymatic activity on esterified polyenoic fatty acids produces lipid peroxides in cellular membranes and circulating lipoprotein complexes. These membrane changes implicate the enzyme in important physiologic processes, including reticulocyte mitochondrial degradation, the oxidative modification of low density lipoprotein (LDL) and airway host defenses *(11,28,91,92)*.

Reticulocyte Maturation

Investigations of reticulocyte maturation led to the characterization of the first 12/15-lipoxygenase *(11)*. In this study, rabbit reticulocyte 12/15-lipoxygenase was isolated, purified and found to preferentially oxygenate mitochondrial membranes and inhibit respiratory enzymes. Recently, ubiquinone was implicated in these mitochondrial changes *(93)*. The human reticulocyte 12/15-lipoxygenase is expressed in patients with hemolytic disorders and it causes mitochondrial enzyme inactivation as well *(24)*. In vitro, 15-HETE appears to support erythroblast mitogenesis and erythrocyte maturation *(94)*. Recent supporting studies have demonstrated that expression of 15-lipoxygenase facilitates organelle degradation by destabilizing membranes and allowing access to proteases *(94a)*. Although these studies support a role for 12/15-lipoxygenase in reticulocyte maturation, there was no evidence of anemia or red blood cell abnormalities when nontoxic inhibitors of 12/15-lipoxygenase were used in a rabbit model of atherosclerosis or in mice that lack the enzyme secondary to targeted mutations *(95,96)*.

Airway Inflammation

Airway inflammation is prominent in many pulmonary diseases including asthma, chronic bronchitis, and cystic fibrosis. The airway epithelium is ideally positioned to modulate the host inflammatory response to environmental stimuli. Early pulmonary based investigations suggested an important role for the lipoxygenases in mediating airway inflammation and hyperresponsiveness by demonstrating that inhalation of leukotriene B_4 causes airway inflammation and hyperresponsiveness *(97)*. When canine airway epithelial cells are incubated with arachidonic acid, LTB_4, 12S-HETE and 15-HETE are produced whereas human airway epithelial cells produce large amounts of 15-HETE, 12-HETE, diHETEs, and no 5-lipoxygenase metabolites *(98,99)*.

The specific induction of human 12/15-lipoxygenase by IL-4 suggests a role for this enzyme in the pathophysiology of allergic, T-H2 mediated inflammation *(10,100)*. Studies have demonstrated increased

12/15-lipoxygenase activity in the airways of asthmatic lungs and in the bronchoalveolar ravage from atopic patients after challenge with antigen *(101,102)*. Although this increased activity may result from increased enzymatic expression in airway epithelial cells, more recent studies suggest that it is due to recruitment of eosinophils into the airway *(27,103,104)*.

Although the 5-lipoxygenase pathway is implicated in airway inflammation, there is evidence that the 12/15-lipoxygenase modulates airway inflammation as well. In vitro data suggests the arachidonic acid metabolites of human 12/15-lipoxygenase can modify local inflammatory responses *(4)*. The ability of this enzyme to generate membrane lipid peroxides further supports a role for it in pulmonary host defenses *(92)*. In dogs,8S,15S diHETE is a neutrophilic chemotactic factor equipotent to LTB_4, whereas 5-,15 diHETE and 5-oxo-15-hydroxy diHETE are potent eosinophilic chemotactic factors *(61–63)*. Eosinophil 12/15-lipoxygenase has LTA_4 hydrolase activity that leads to leukotriene formation, is not inhibited by zileuton and therefore may be an additional target for therapeutic intervention *(105)*. In addition, 15-HETE also influences other processes associated with airways inflammation that contribute to airway disease including smooth muscle contraction *(106)*, mucus secretion *(107)*, and chloride secretion *(108)*.

The lipoxins are also important potential modulators of airway inflammation that antagonize effects mediated by the 5-lipoxygenase pathway. Studies of bronchoalveolar lavage from asthmatic patients have demonstrated increased levels of these potent lipids *(109)*. Human alveolar macrophages, nasal polyp tissue and bronchial epithelium can convert LTA_4 into lipoxins *(110,111)*.

Atherosclerosis

In vitro, both purified 12/15-lipoxygenase and cells expressing the enzyme oxidize low density lipoprotein into its atherogenic form *(112,113)*. In a rabbit model of atherosclerosis, expression of the 12/15-lipoxygenase in "foamy" macrophages was detected with immunohistochemical and *in situ* hybridization studies *(2)*. In this model, 12/15-Lipoxygenase expression is prominent in early cellular lesions and colocalizes with epitopes of oxidized LDL. Parallel studies using human tissue have confirmed these findings *(28)*. Subsequent studies have identified the enzymatic "fingerprint" of 12/15-lipoxygenase in lipids extracted from early, cellular atheromas by demonstrating the predominance of the 15S-HETE isomer over the 15R isomer *(91,114)*. Overexpressing the human enzyme in endothelium results in increased atheroma formation *(115)*. These studies have stimulated the search for specific nontoxic inhibitors of 12/15-lipoxygenase and the development of murine lines that lack expression of the homologous 12/15-lipoxy-

genase. An inhibitor of the purified rabbit enzyme blocks early atheroma formation in a cholesterol-fed rabbit model of atherosclerosis *(95)*. Mice lacking 12-lipoxygenase because of targeted mutations have been developed and their peritoneal macrophages do not oxidize LDL to the same extent as heterozygote controls *(96)*. Although these studies support a pathogenic role for 12/15-lipoxygenase in atherosclerosis, a recent investigation in which the human enzyme was overexpressed in rabbit macrophages using the lysozyme promoter demonstrated a protective effect against the development of atherosclerosis and highlights the need for further study of this enzyme in atherosclerosis *(116)*.

Renal Physiology

12/15-Lipoxygenases are expressed in rabbit, human, and murine renal tissue *(11,117,118)*. Expression is associated with significant physiologic processes including regulation of vascular tone and immune complex-mediated inflammation. For example, 12S-HETE, 12S-HPETE, 15S-HETE, and 15S-HPETE are potent inhibitors of renin release in rat cortical slices whereas 5S-HETE has no effect *(119)*. In immune complex-mediated glomerular nephritis, these metabolites are produced and counteract the effects of leukotrienes including the reduction in glomerular filtration rates, exacerbation of proteinuria and neutrophil-mediated tissue destruction *(120,121)*. Finally, lipoxins are generated in the murine model of glomerular nephritis and have been implicated in regulating vascular tone *(67,122)*.

Summary

12/15-Lipoxygenase is a highly regulated lipid-peroxidating enzyme whose expression and arachidonic acid metabolites are implicated in several important inflammatory conditions including airway and glomerular inflammation as well as atherosclerosis. Tissue expression of the original 12/15-lipoxygenase is well characterized in reticulocytes, eosinophils, airway epithelial cells, and monocytes/macrophages and is likely in other cell systems and tissues under specific conditions. The physiologic role of this family of enzymes is dependent on the context in which it is expressed. In general, the arachidonic acid metabolites antagonize inflammatory responses and counteract the proinflammatory effects of the 5-lipoxygenase pathway. However, certain diHETEs are associated with pro-inflammatory effects, specifically neutrophilic and eosiniphilic chemotaxis. The direct action of these enzymes on complex lipids and cellular membranes also links them to such significant process as reticulocyte maturation, LDL oxidation in atherosclerosis and pulmonary host defenses. The availability of new specific inhibitors and murine lines that lack expression of the homologous 12-lipoxygenase

will allow confirmation of many of these effects with in vivo models of inflammation.

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