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The role of lipoxygenases in pathophysiology; new insights and future perspectives

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ABSTRACT

Lipoxygenases (LOXs) are dioxygenases that catalyze the formation of corresponding hydroperoxides from polyunsaturated fatty acids such as linoleic acid and arachidonic acid. LOX enzymes are expressed in immune, epithelial, and tumor cells that display a variety of physiological functions, including inflammation, skin disorder, and tumorigenesis. In the humans and mice, six LOX isoforms have been known. 15-LOX, a prototypical enzyme originally found in reticulocytes shares the similarity of amino acid sequence as well as the biochemical property to plant LOX enzymes. 15-LOX-2, which is expressed in epithelial cells and leukocytes, has different substrate specificity in the humans and mice, therefore, the role of them in mammals has not been established. 12-LOX is an isoform expressed in epithelial cells and myeloid cells including platelets. Many mutations in this isoform are found in epithelial cancers, suggesting a potential link between 12-LOX and tumorigenesis. 12R-LOX can be found in the epithelial cells of the skin. Defects in this gene result in ichthyosis, a cutaneous disorder characterized by pathophysiologically dried skin due to abnormal loss of water from its epithelial cell layer. Similarly, eLOX-3, which is also expressed in the skin epithelial cells acting downstream 12R-LOX, is another causative factor for ichthyosis. 5-LOX is a distinct isoform playing an important role in asthma and inflammation. This isoform causes the constriction of bronchioles in response to cysteinyl leukotrienes such as LTC_4, thus leading to asthma. It also induces neutrophilic inflammation by its recruitment in response to LTB_4. Importantly, 5-LOX activity is strictly regulated by 5-LOX activating protein (FLAP) though the distribution of 5-LOX in the nucleus. Currently, pharmacological drugs targeting FLAP are actively developing. This review summarized these functions of LOX enzymes under pathophysiological conditions in mammals.

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1. Introduction

Lipoxygenases (LOXs) catalyze the oxygenation of polyunsaturated fatty acids such as arachidonic acid and linoleic acid [1,2]. The oxygenated lipids initiate subsequent biological reactions, activate cellular signaling mechanisms through specific cell surface receptors, or are further metabolized into potent lipid mediators. LOX can be found not only in mammals, but also in plants. Historically, biochemical characterizations have been performed mainly on soybean LOX isoforms. While the overall structure of mammalian LOX enzymes seems to be similar, each isoform has unique properties, such as substrate specificity (Table 1, reviewed in [3]). In most cases, the structure depends on the shape of the substrate cavity and the coordination of histidine residues or alternatives to a non-heme iron atom at the catalytic center [4,5]. Importantly, LOX enzymes require a lag period for the activation of enzymes from an inactive ferrous form to an active ferric form by either molecular oxygen or lipid hydroperoxides. Enzymatic activity is also regulated by the N-terminal β-barrel region of polypeptides, where this region has a similar amino acid sequence to the C2-like domain; thus, Ca^{2+}-mediated activation via interaction with the plasma membrane has been proposed. Earlier studies have shown that LOX enzymatic activity can be inhibited by phenolic antioxidants such as nordihydroguaiaretic acid and caffeic acid, suggesting a beneficial role of dietary polyphenol intake [6]. Alternatively, synthesized drugs for LOX are relatively limited thus far. The 5-LOX inhibitor zileuton has been accepted and used successfully for the control of asthma. Currently, inhibitors for 5-LOX activating protein are actively developed by many pharmaceutical companies [7]. These inhibitors essentially modulate the transportation of 5-LOX from the nucleus to the cytoplasm, leading to suppressive 5-hydroperoxyeicosatetraenoic acid (5-HPETE) production. This mode of action of 5-LOX inhibitor is unique, and there are no similar regulatory mechanisms and drugs for other LOX isoforms.

From a genetic point of view, the alignment of LOX isoform nucleotides encoded by arachidonate lipoxygenase (*ALOX* in humans and *Alox* in mice) genes has revealed that *ALOX5* and other *ALOX* genes have separate origins. The other *ALOX* genes seem to have originated from fewer genes, as human *ALOX* genes are found in a cluster in chromosome 17p13.1 and murine *Alox* genes are found in chromosome 11 as active enzymes [8]. The expression levels of *ALOX* genes are partially controlled by cytokines, such as *ALOX15*, whose expression increases in response to Th2 cytokines. *ALOX* enzymatic activity is also regulated by tissue distribution and cell type. *ALOX12B*, *ALOXE3*, and *ALOX15B* are expressed mainly in the skin and other epithelial cells, whereas *ALOX15*, *ALOX12*, and *ALOX5* are expressed in hematopoietic/immune cells. They are involved in atherosclerosis, neuronal disorder, immune modulation, skin diseases, and maintenance of the epithelium. The roles of human enzymes (Table 2) seem to be slightly different from what is expected from phenotypes of knockout mice (Table 3), which shows that these oxygenated lipids are uniquely and finely regulated in humans and mice.

2. 15-Lipoxygenase (15-LOX)

15-LOX is a prototypical enzyme catalyzing oxygenation of polyunsaturated fatty acids. Among various mammalian species, rabbit reticulocyte LOX has been characterized from earlier studies and often used as standard for biochemical assays. When the

Table 1
Properties of LOX enzymes.

Proteins	15-LOX	15-LOX-2	12-LOX	12R-LOX	eLOX-3	5-LOX	FLAP
Human							
Gene	*ALOX15*	*ALOX15B*	*ALOX12*	*ALOX12B*	*ALOXE3*	*ALOX5*	*ALOX5AP*
Products[a]	15S-HPETE	15S-HPETE	12S-HPETE	12R-HPETE	Epoxyalcohols	5S-HPETE	NA
Expression	Leukocytes	Epithelium, leukocytes	Myeloids, skin, epithelium	Skin, epithelium	Skin, epithelium	Leukocytes	Leukocytes
Mouse							
Gene	*Alox15*	*Alox15b*	*Alox12*	*Alox12b*	*Aloxe3*	*Alox5*	*Alox5ap*
Products[a]	12S-, 15S-HPETE	8R-HPETE, epoxyalcohols	15S-, 12S-HPETE	12R-HPETE	Epoxyalcohols	5S-HPETE	NA
Expression	Leukocytes	Skin, epithelium, leukocytes	Platelet, skin, epithelium	Skin, epithelium	Skin, epithelium	Leukocytes, epithelium	Leukocytes

NA, not available. [a]Arachidonic acid as a substrate except eLOX-3 where 12R-HPETE as a substrate.