Minireview

The diversity of the lipoxygenase family

Many sequence data but little information on biological significance[1]

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Abstract Lipoxygenases form a family of lipid peroxidising enzymes, which oxygenate free and esterified polyenoic fatty acids to the corresponding hydroperoxy derivatives. They are widely distributed in both the plant and animal kingdoms. During the last couple of years more and more lipoxygenase isoforms have been discovered but for most of them the biological significance remains unclear. This review attempts to classify the currently known mammalian lipoxygenase isoforms and critically reviews the concepts for their biological importance.

Key words: Atherogenesis; Inflammation; Lipid peroxidation; Cell development; Eicosanoid

1. Introduction

Lipoxygenases (LOXs) form a family of lipid peroxidising enzymes, which occur in both the plant and animal kingdoms [1]. LOXs have also been detected in lower marine organisms (sea urchins, starfish, surf clams and corals [2–5]), but they are obviously not expressed in bacteria or yeast. Most of our early knowledge on LOXs originates from studies of the soybean LOX-1 and other plant isoenzymes. However, because of space limitations the present review will focus on mammalian LOXs only.

For a long time it was believed that LOXs did not occur in animals but in 1974 the formation of (12*S*,5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxyeicosa-5,8,10,14-tetraenoic acid (12-HETE) was described, when human thrombocytes were incubated with exogenous arachidonic acid [6]. This discovery marked the starting point of animal LOX research and over the following years more and more LOX isoforms were discovered. In 1975 a LOX was detected in rabbit reticulocytes, which was capable of oxidising phospholipids and biomembranes [7]. This enzyme was purified to homogeneity and well characterised with respect to its protein chemical and enzymatic properties [8]. For the time being it is the only animal LOX for which the three-dimensional X-ray structure is available [9]. The structural identification of the slow reacting substance of anaphylaxis [10] and the finding that arachidonate 5-LOXs are involved in leukotriene biosynthesis marked a milestone in animal LOX research and prompted many scientists to intensify their activities in this field.

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[1] This paper is dedicated to Prof. Shozo Yamamoto to honor his achievements in lipoxygenase research.

Starting in 1974 the diversity of the mammalian LOX family has been growing constantly. Meanwhile 18 different LOX sequences have been published representing at least seven different isoforms analysed in seven mammalian species. Among the different species the diversity of the LOX family is best investigated in mice. Six different LOX isoforms encoded by six different genes have been described so far in mice and it may be predicted that in the near future the diversity of the LOX family is expected to grow further. There are unpublished data in our laboratories, and in other laboratories suggesting that the expression pattern of LOXs in mice and other mammals may be even more complex.

In sharp contrast to the multiplicity of sequence information there are few clear cut data as to the biological relevance of these enzymes. The role of 5-LOX in the biosynthesis of leukotrienes is generally accepted [11]. The reticulocyte-type 15-LOXs have been implicated in cell maturation and differentiation [12,13] and several lines of experimental evidence support this hypothesis. However, the final proof is still lacking. Unfortunately, for all other LOX isoforms our knowledge of their biological roles is very limited.

This review is intended to stress the discrepancy between the growing knowledge of the structural biology of mammalian LOXs on the one hand and the disappointing advancement in the field of the biological importance of these enzymes. In this respect the current situation in LOX research mirrors the situation of the human genome project. Plenty of structural data are already available but their functional relevance remains to be investigated in the future.

2. Stereochemistry of the LOX reaction

Although the detailed mechanism of the LOX reaction still remains a matter of discussion its radical nature is commonly agreed upon. Formally, the LOX reaction consists of three consecutive steps (Fig. 1): (i) stereo-selective hydrogen abstraction from a doubly allelic methylene group; (ii) radical rearrangement ([+2] and [−2] [14]) which is accompanied by a *Z*,*E*-diene conjugation; (iii) stereospecific (*S*- or *R*-) insertion of molecular dioxygen and reduction hydroperoxy radical intermediate to the corresponding anion. From the stereochemical point of view each of these steps can proceed in different ways.

2.1. Hydrogen abstraction

With arachidonic acid as substrate hydrogen can be removed from three different doubly allelic methylenes (C-7, C-10, C-13). Since each double allelic methylene binds a pro-*S* and a pro-*R* hydrogen, six different hydrogen atoms

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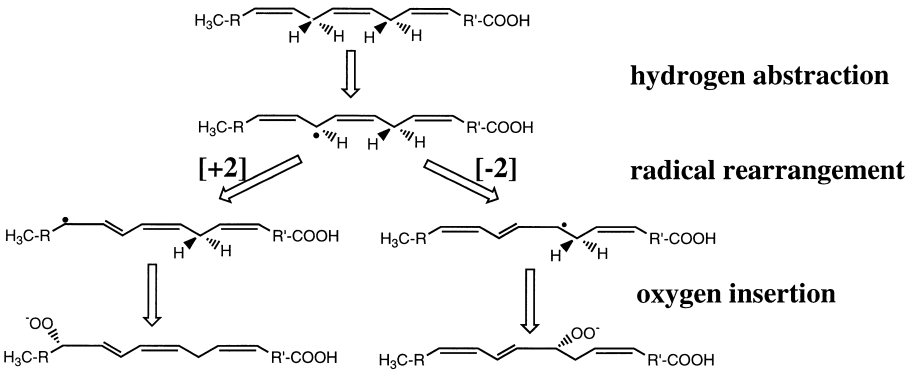

Fig. 1. Radical mechanism of the lipoxygenase reaction.

may be removed. However, most mammalian LOXs select just one hydrogen and which one depends on the orientation of the substrate fatty acid at the active site.

2.2. Radical rearrangements

The classical mechanism of the LOX reaction involves the formation of a pentadienyl radical. In this intermediate the density of the radical unpaired electron may be delocalised over the entire pentadienyl system which requires a planar structure of this part of the substrate molecule (Fig. 1). However, more recent structural data [15] suggest that the formation of a planar pentadienyl radical may be hindered sterically. Thus, the formation of a dioxygen-bridged allyl radical was proposed in which the radical electron may not be delocalised over the entire pentadienyl system but rather over a part of it. Recent spectroscopic studies on the interaction of the soybean LOX-1 with linoleic acid suggested the formation of such a dioxygen bridged allyl radical [16]. According to this hypothesis the direction of the radical rearrangement ([+2] or [−2]) depends on the conformation the fatty acid may adapt at the active site.

2.3. Oxygen insertion

At the present time it is believed that LOXs may have neither a specific dioxygen binding site nor a separate tunnel through which the second substrate may penetrate into the active site. Instead, it has been suggested that oxygen insertion proceeds diffusion-controlled and that the gas may pass through the fatty acid binding cavity. If this is true additional assumptions must be made in order to explain the high degree of chirality of most LOX products.

3. Diversity of the lipoxygenase family and lipoxygenase classification

According to the currently used nomenclature, LOXs are categorised with respect to their positional specificity of arachidonic acid oxygenation. Until recently it was believed that three major LOX isoforms may exist in mammals: (i) arachidonate 5-LOXs which introduce molecular dioxygen at carbon 5 of the arachidonic acid backbone, (ii) arachidonate 12-LOXs which catalysed the formation of (12*S*,5*Z*,8*Z*,10*E*,14*Z*)-12-hydroperoxyeicosa-5,8,10,14-tetraenoic acid (12*S*-HpETE)

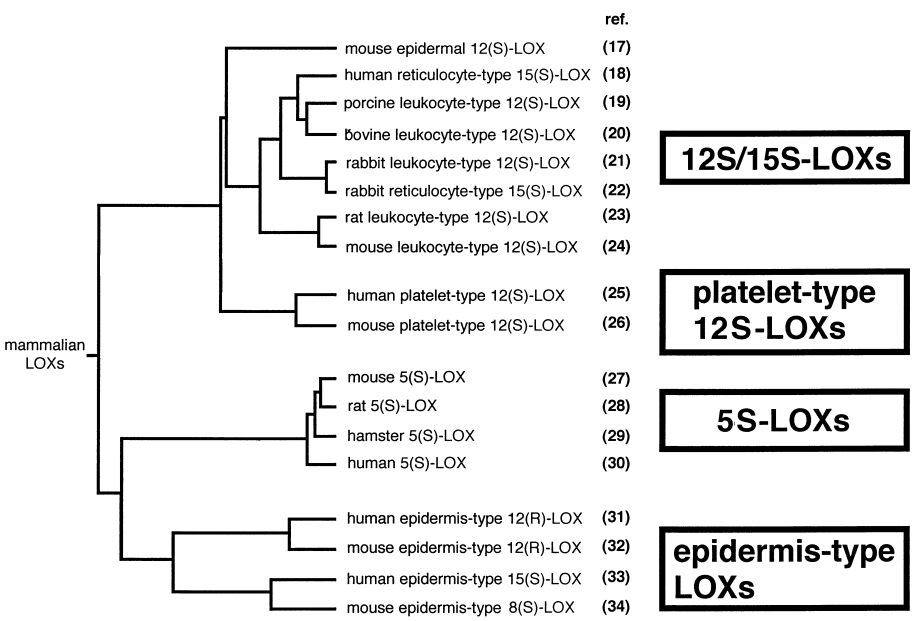

Fig. 2. Phylogenetic tree of mammalian LOXs.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
1		93.2	93.2	91.9	40.7	35.8	39.2	38.6	37.1	37.1	37.6	37.3	35.6	36.6	40.1	35.9	38.7	38.1	1	human 5(S)-LOX (J03571)
2	6.4		95.8	95.5	40.4	34.9	38.2	37.9	36.2	36.5	36.5	36.7	34.4	35.5	39.2	34.7	37.6	36.8	2	hamster 5(S)-LOX (U43333)
3	6.8	3.7		96.4	40.4	35.2	37.7	37.7	37.0	36.8	36.8	37.0	35.0	36.3	39.8	35.0	38.4	38.0	3	mouse 5(S)-LOX (L42198)
4	7.6	4.3	3.1		40.0	34.7	37.0	37.1	35.9	35.9	35.9	36.0	34.1	35.3	38.5	34.1	37.5	36.9	4	rat 5(S)-LOX (J03960)
5	56.2	56.1	56.5	56.7		32.5	35.6	35.6	34.8	34.8	34.8	34.8	33.6	34.6	77.5	33.8	48.7	47.3	5	mouse epidermis-type 8(S)-LOX (U93277)
6	60.4	61.6	61.0	61.4	62.3		59.4	59.5	65.7	58.9	65.6	59.2	61.9	66.3	33.4	61.8	28.9	28.2	6	mouse epidermal 12(S)-LOX (X99252)
7	57.7	58.7	59.1	59.6	61.6	40.3		84.6	64.3	56.6	65.2	56.7	60.8	65.4	35.6	60.9	35.7	34.8	7	human platelet-type 12(S)-LOX (M38792)
8	58.0	58.7	58.9	59.1	60.7	40.0	15.4		63.0	57.0	63.3	57.2	59.4	63.1	34.4	59.4	34.2	33.8	8	mouse platelet-type 12(S)-LOX (U04334)
9	58.8	59.5	58.8	59.4	61.0	33.8	35.0	36.1		71.9	88.7	72.1	78.4	86.0	36.3	78.3	32.9	32.0	9	bovine leukocyte-type 12(S)-LOX (M62516)
10	59.1	59.6	59.2	59.9	61.0	40.8	42.7	42.1	28.1		70.4	99.5	71.3	72.8	34.7	71.2	33.0	32.3	10	mouse leukocyte-type 12(S)-LOX (L34570)
11	58.5	59.3	59.2	59.8	61.0	34.0	34.1	35.8	11.3	29.6		70.6	79.2	86.0	35.1	79.3	32.0	31.5	11	porcine leukocyte-type 12(S)-LOX (M31417)
12	58.8	59.3	58.9	59.6	61.0	40.5	42.6	42.0	27.9	0.5	29.4		71.5	73.3	34.8	71.3	33.2	32.1	12	rat leukocyte-type 12(S)-LOX (L06040)
13	60.8	61.9	61.4	62.1	62.6	37.6	38.4	39.6	21.6	28.7	20.8	28.5		80.8	34.1	99.1	31.8	32.1	13	rabbit leukocyte-type 12(S)-LOX (Z97654)
14	59.2	60.1	59.3	60.0	60.9	33.6	34.5	36.3	13.6	26.7	13.6	26.3	18.7		34.9	81.0	32.2	28.7	14	human reticulocyte-type 15(S)-LOX (M23892)
15	56.9	57.3	57.2	58.0	21.9	62.6	61.1	60.6	59.3	60.9	60.3	60.9	61.7	60.5		34.4	49.2	48.7	15	human epidermis-type 15(S)-LOX (U78294)
16	60.5	61.6	61.4	62.1	62.4	37.8	38.2	39.6	21.7	28.8	20.7	28.7	0.9	18.6	61.4		32.0	32.3	16	rabbit reticulocyte-type 15(S)-LOX (M27214)
17	58.2	59.1	58.5	59.2	49.8	64.8	61.7	62.9	64.0	63.8	64.9	63.7	65.2	64.1	49.1	65.0		85.6	17	human epidermis-type 12(R)-LOX (AF038461)
18	59.0	59.8	59.3	59.9	51.1	65.0	62.4	63.4	64.6	64.4	65.2	64.6	64.7	64.7	49.4	64.6	14.4		18	mouse epidermis-type 12(R)-LOX (AF059251)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		

Fig. 3. Mutiple amino acid sequence comparison between mammalian LOXs.

and (iii) arachidonate 15-LOXs which oxygenate the substrate fatty acid at C-15. The arachidonic acid based nomenclature is straightforward and commonly accepted by the scientific community. However, the growing diversity of the LOX family requires a modification of this nomenclature since the old one groups together LOX isoforms, which are phylogenetically not closely related and clearly differ from each other with respect to their enzymatic properties (e.g. human reticulocyte-type 15*S*-LOX vs human epidermis-type 15*S*-LOX). On the other hand, according to the old nomenclature the rabbit leukocyte-type 12-LOX and the rabbit reticulocyte-type 15-LOX are categorised into different groups (12-LOX vs 15-LOX) despite the fact that they are 99% identical at the amino acid level. Similarly, the mouse leukocyte-type 12-LOX is more closely related to the human reticulocyte-type 15-LOX than to the mouse platelet-type 12-LOX and thus, the first two enzymes should be grouped together instead of the latter two.

Looking at the phylogenetic tree of mammalian LOXs (Fig. 2) it becomes evident that these enzymes may be sub-divided into four groups [17–34]. All leukocyte-type 12-LOXs and the reticulocyte-type 15-LOXs may be grouped together. This classification also makes sense from the enzymological point of view since these LOX isoforms are very similar to each other with respect to their enzymatic properties (substrate specificity, reactivity with complex lipid-protein assemblies [35]). Chimeric LOXs constructed from these isoforms are enzymatically active [36] and the positional specificity of arachidonic acid oxygenation is altered if critical amino acids are interchanged [36,37]. In contrast, attempts to construct chimera between platelet-type 12-LOXs and reticulocyte-type 15-LOXs did not lead to active LOX species (unpublished data). Currently it is not clear whether the mouse epidermal 12(*S*)-LOX should be included in this group. Although the sequence data support such a classification, the enzyme may differ from other members of this family with respect to its enzymatic properties. However, more detailed functional characterisation of this enzyme is needed to decide its final assignment.

The more recently discovered epidermis-type LOXs [31–34] may be grouped together although their positional specificity of arachidonic acid oxygenation is rather heterogeneous. Since the positional specificity of LOXs may reflect the spatial orientation of the substrate fatty acid at the active site, the structural features within the substrate binding pockets of these isoenzymes must be different. On the other hand, the human epidermis-type 15(*S*)-LOX shares a high degree (78%) of overall amino acid similarity (Fig. 3) with the mouse epidermis-type 8-LOX and in the region of the putative substrate binding cleft the similarity is even higher. However, when the reaction characteristics of both isoforms are compared one may conclude that the steps of the LOX reaction have a different stereochemistry (C-13 vs C-10 hydrogen removal, [+2]- vs [−2]-radical rearrangement). Unfortunately, for the time being, there are no direct structural data available for any of the epidermis-type LOXs and structural models on the basis of the X-ray data of the rabbit reticulocyte 15-LOX may not be useful because of the low degree of amino acid homology.

4. Biological role of mammalian lipoxygenases

For most LOX isoforms their biological roles are far from being clear. According to the concept of the arachidonic acid cascade LOXs are involved in the biosynthesis of lipid hormones such as leukotrienes, lipoxins and/or hydroxy fatty acids. However, certain LOX subtypes (reticulocyte-type 15(*S*)-LOXs, leukocyte-type 12(*S*)-LOXs) may play a biological role outside the arachidonic acid cascade.

5-LOXs are involved in the biosynthesis of leukotrienes, which constitute mediators of anaphylactic and inflammatory disorders [11]. Leukotriene antagonists and leukotriene synthesis inhibitors are currently being tested in clinical trials for their anti-asthmatic and/or anti-inflammatory potencies and preliminary results are very promising. Under certain conditions the 5-LOX is also expressed in cells which may not be related to anaphylactic and/or inflammatory reactions [38]. Thus, there may be additional roles for this enzyme outside the arachidonic acid cascade. Moreover, the intranuclear localisation of the 5-LOX in resting human alveolar macrophages [39] may suggest that the 5-LOX and/or 5-LOX products might be important for the regulation of gene expression.

The reticulocyte-type 15-LOX has been implicated in cell development and differentiation. During the maturation of rabbit reticulocytes this enzyme initiates the cytosolic breakdown of the remaining mitochondria during reticulocyte/erythrocyte transition [12]. Human peripheral monocytes do not express this type of 15-LOX [40] but in macrophages, which develop from peripheral monocytes, enzyme expression can be detected [41]. These data suggest a biological role of the enzyme either in monocyte/macrophage transitions and/or in macrophage function. Recently, it was reported that an

arachidonic acid 15-LOXs might be involved in organelle degradation during differentiation of the eye lens cell [13]. During the past couple of years an implication of 12/15-LOXs in atherogenesis has been discussed [42,43]. The enzyme is expressed in foamy macrophages [44] and is capable of oxidising low density lipoprotein in vitro to an atherogenic form [45]. Specific 12/15-LOX products can be detected in young atherosclerotic lesions [46] indicating the enzymes functionality. However, there is currently a debate in the literature about whether the LOX may act pro- and/or anti-atherogenically [47,48].

The possible role of 12/15-LOXs in cell differentiation and atherogenesis is related to its capability of oxygenating polyenoic fatty acids esterified to complex lipid/protein assemblies (biomembranes, lipoproteins). On the other hand, it may well be that these LOXs may also exhibit biological activities via the formation of bioactive lipids. In fact, the major products of 12/15-LOX pathway namely (12*S*,5*Z*,8*Z*,10*E*,14*Z*)-12-hydro(pero)xyeicosa-5,8,10,14-tetraenoic acid [12*S*-H(p)ETE), (15*S*,5*Z*,8*Z*,11*Z*,13*E*)-15-hydro(pero)xyeicosa-5,8,11,13-tetraenoic acid [15*S*-H(p)ETE] and (13*S*,9*Z*,11*E*)-13-hydro(pero)xyoctadeca-9,11-dienoic acid [13-H(p)ODE], are bioactive in cellular and supracellular assay systems [49]. However, it remains to be investigated whether these effects may be of physiological relevance in vivo.

For the other LOX isoforms, particularly for the platelet-type 12-LOXs and for the epidermis-type LOXs little is known about their biological role. 12-LOXs of either type have been implicated in the biosynthesis of hepoxilins and lipoxins. Hepoxilins may be involved in the regulation of ion transport across biomembranes and thus, 12-LOXs may play a role. Lipoxins which can be synthesised unicellularly in leukocytes via a concerted action of 5- and 12/15-LOXs or transcellularly by the leukocyte 5-LOX and the platelet 12-LOX appear to be involved in the regulation of immunological and haemodynamic processes. Here again, it remains to be shown whether any of these effects may be of biological importance in vivo.

5. Perspective

The discrepancy between the rapidly increasing knowledge of the structural biology of LOXs and the disappointing advances in research of the biological role of these enzymes may reflect a general trend in biomedical research. As a consequence of the human genome project tools and techniques for structural molecular biological research have been rapidly developed during the past several years. These days it may not be a major problem any longer to identify new LOX sequences using PCR techniques with degenerated primer combinations and commercially available DNA libraries. Primers can be easily designed by sequence comparison of database entries using programs which can be downloaded from the Internet. In contrast, in order to investigate the biological role of any enzyme more complex studies are required. Specific LOX inhibitors and/or transgenic animals (LOX knock outs or LOX overexpressing animals) are important tools for these kinds of investigations. Unfortunately only a few more or less specific LOX inhibitors are available, and two strains of LOX knock out mice have been established to date. Although both inhibitor studies and experiments with transgenic animals have gaps (e.g. lacking overall specificity, redundancy of LOX family) a combination of such experiments may be successful. Hopefully, more and more strains of LOX knock out mice and more specific LOX inhibitors may become available in the near future. With these tools in our hands we might be able to close the gap between structural and functional LOXs research.

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