FEATURES OF MAMMALIAN LIPOXYGENASES

Bernd-I. Thiele, Mario Berger, Holger Thiele, Antje Huth and Iris Reimann

Institute of Biochemistry, University Clinics Charité, Humboldt-University
Berlin, Hessische Str. 3-4, D-10115 Berlin, Germany

INTRODUCTION

Lipoxygenases (LOXs) are enzymes which oxygenate polyenoic fatty acids containing 1,4-pentadiene structures to their corresponding hydroperoxy derivatives (Yamamoto, 1992). They are distributed over the whole animal and plant kingdoms.

According to the currently used nomenclature LOXs are classified with respect to their positional specificity of arachidonic acid oxygenation into 5-, 8-, 12- and 15-LOXs. 5-LOXs which introduce molecular oxygen at C-5 in arachidonic acid are involved in the biosynthesis of leukotrienes which are important mediators of anaphylactic and inflammatory processes (Samuelsson et al., 1987; Lewis et al., 1990). In contrast, the biological functions of 8-, 12- and 15-LOXs are less well investigated (Kühn, 1996). There is evidence for the implication of 15-LOX in red cell maturation (Rapoport, 1990) and atherogenesis (Kühn and Chan, 1997), and of 12- and 8-LOX in tumor metastasis (Honn et al. 1994) and skin carcinogenesis (Fürstenberger et al. 1991).

The expression of LOXs is regulated at the transcriptional (O’Prey and Harrison, 1995) and at the translational level (Thiele et al., 1982). In particular, the role of regulatory proteins which interact with the 3’-untranslated region of 15-LOX mRNA has been studied in detail in recent years (Ostareck-Lederer et al., 1994; Ostareck et al., 1997).

This article focuses exclusively on mammalian LOXs with emphasis on our results on the structure and regulation of expression of rabbit leukocyte-type 12- and 15-LOX.
RESULTS AND DISCUSSION

Classification of Mammalian Lipoxgenases

Since the first publication of a sequence of a mammalian LOX, a partial sequence of the rabbit reticulocyte 15-LOX (Thiele et al. 1987), the list of cloned LOXs is steadily growing. This list encompasses currently at least 16 enzymes of seven different mammalian species. LOXs are classified traditionally according to their positional selectivity in the oxygenation of arachidonic acid. In table 1, which summarizes numerical values of sequence homologies between mammalian LOXs at the amino acid level, they are arranged according to their positional specificity into 5-, 8-, 12- and 15-LOXs. The oxygenation of polyenoic fatty acids occurs in a stereospecific way. All mammalian LOXs isolated so far have proven to be (S)-lipoxygenases. LOXs with (R) specificity are known from lower animal phyla like the 12(R)-LOX from the coral *P. homomalla* (Brash et al. 1997).

<table>
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<th>Table 1. Sequence similarities of mammalian lipoxygenases</th>
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For the alignment the "MegAlign" programme of the Macintosh "DNA Star" package was used.
For each sequence the EMBL database accession number is shown.

Sequence alignments as performed in table 1 demonstrate that a classification with respect to positional specificity has become ambiguous. This is evident particularly in the group of the 12-LOXs. They are historically classified according to the tissues from which they primarily have been isolated into leukocyte-type, platelet-type and epidermal 12-LOXs. Homologies between the members of this group are however in the range of only about 60%. The other extreme is the rabbit leukocyte-type 12-LOX which has been cloned by us (see below). It is much more similar to the reticulocyte-type 15-LOX of the same species (99% homology) than to 12-LOXs of other tissue types. The newly discovered human 15-LOX2 is more related to the mouse epidermal 8-LOX than to the human reticulocyte-type 15-LOX1. These examples may demonstrate that a more comprehensive classification scheme based on sequence homology may be introduced. Such a new system should be oriented in gene structures rather than in enzymatic properties.