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Mini review

Role of epidermis-type lipoxygenases for skin barrier function and adipocyte differentiation

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Abstract

12R-lipoxygenase (12R-LOX) and epidermis-type LOX-3 (eLOX-3) are novel members of the multigene family of mammalian LOX. A considerable gap exists between the identification of these enzymes and their biologic function. Here, we present evidence that 12R-LOX and eLOX-3, acting in sequence, and eLOX-3 in combination with another, not yet identified LOX are critically involved in terminal differentiation of keratinocytes and adipocytes, respectively. Mutational inactivation of 12R-LOX and/or eLOX-3 has been found to be associated with development of an inherited ichthyosiform skin disorder in humans and genetic ablation of 12R-LOX causes a severe impairment of the epidermal lipid barrier in mice leading to post-natal death of the animals. In preadipocytes, a LOX-dependent PPARγ activating ligand is released into the cell supernatant early upon induction of differentiation and available evidence indicates that this ligand is an eLOX-3-derived product. In accordance with this data is the observation that forced expression of eLOX-3 enhances adipocyte differentiation.

Keywords: Lipoxygenase; Keratinocytes; Terminal differentiation; Ichthyosis; Epidermal barrier; Adipogenesis; Peroxisome proliferator activated receptor

Contents

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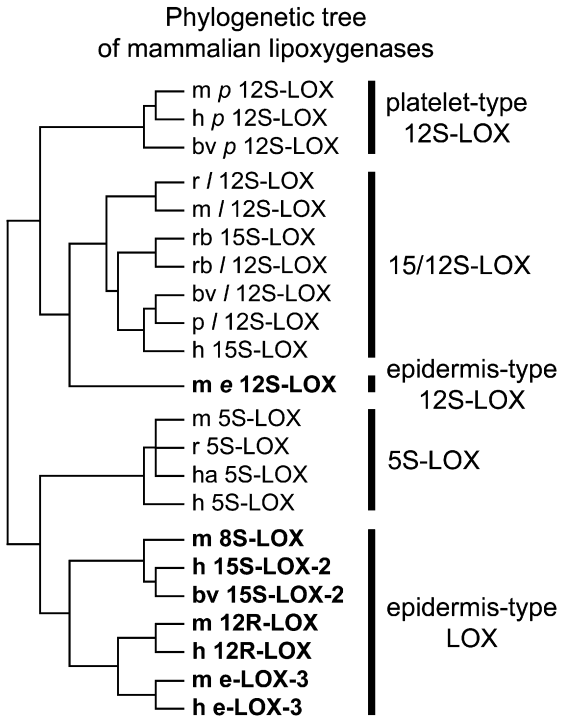

Fig. 1. Phylogenetic tree of mammalian lipoxygenases. Epidermis-type LOX are depicted in bold. 12R-LOX and eLOX-3 represent a novel structural class of mammalian LOX.

1. The mammalian lipoxygenase family

Lipoxygenases (LOXs) represent a wide family of non-heme, non-sulfur iron containing dioxygenases that catalyze the regio- and stereoselective dioxygenation of polyunsaturated fatty acids containing one or more (Z,Z)-1,4-pentadiene moieties. Mammalian LOXs are categorized as 5-, 8-, 12-, and 15-LOX according to the regio- and stereoselectivity of oxygen insertion into arachidonic acid. Additional complexity is given by the existence of isozymes with identical regioselectivity such as the leukocyte-type (l), platelet-type (p), and epidermis-type (e) 12-LOX and the 15-LOX-1 and 15-LOX-2. Primary arachidonic acid-derived products of the LOX isoforms are the corresponding S enantiomeric hydroperoxyeicosatetraenoic acids (HPETE) with the exception of 12R-LOX representing the only mammalian LOX isoform that directs molecular oxygen into the 12R position of arachidonic acid [1]. This 12R-LOX acts in sequence with the epidermis-type LOX-3 (eLOX-3), which is a hydroperoxide isomerase rather than a conventional LOX, to generate hydroxyepoxyeicosatrienoic acids [2–5].

The overall phylogenetic relationship of 22 distinct mammalian LOX sequences displaying subfamilies and relative distances between individual members is depicted in Fig. 1. The phylogenetic tree forms four distinct clusters: the group of p12-LOX, the group of the 12/15-LOX including human 15-LOX-1 and its mouse homolog l12-LOX, the cluster of 5-LOX, and the rather heterogeneous group of epidermis-type LOX comprising human and bovine 15-LOX-2 and its mouse ortholog 8-LOX, 12R-LOX and e-LOX-3. The members of the latter group are preferentially, but not exclusively, expressed in epidermis [6,7]. The e12-LOX is not definitely included in one of these groups and may represent a separate branch point in the LOX family. There is only a functional e12-LOX in mice, the orthologous gene in humans encodes a transcribed pseudogene [8,9].

12R-LOX and eLOX-3 attract particular attention because of their unusual large size that is attributed to an insertion of an extra segment of 31 and 41 amino acid residues, respectively [2,3,6]. This extra subdomain located on the surface of the catalytic domain near the entrance to the substrate binding pocket is unique among all LOX and is critically involved in enzymatic activity of the two isoforms. Moreover, functions in protein–protein-interaction and/or cellular distribution may be attributed to these specific subdomains.