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Review

Evolutionary aspects of lipoxygenases and genetic diversity of human leukotriene signaling

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ABSTRACT

Leukotrienes are pro-inflammatory lipid mediators, which are biosynthesized via the lipoxygenase pathway of the arachidonic acid cascade. Lipoxygenases form a family of lipid peroxidizing enzymes and human lipoxygenase isoforms have been implicated in the pathogenesis of inflammatory, hyperproliferative (cancer) and neurodegenerative diseases. Lipoxygenases are not restricted to humans but also occur in a large number of pro- and eucaryotic organisms. Lipoxygenase-like sequences have been identified in the three domains of life (bacteria, archaea, eucarya) but because of lacking functional data the occurrence of catalytically active lipoxygenases in archaea still remains an open question. Although the physiological and/or pathophysiological functions of various lipoxygenase isoforms have been studied throughout the last three decades there is no unifying concept for the biological importance of these enzymes. In this review we are summarizing the current knowledge on the distribution of lipoxygenases in living single and multicellular organisms with particular emphasis to higher vertebrates and will also focus on the genetic diversity of enzymes and receptors involved in human leukotriene signaling.

Contents

Abbreviations: AA, arachidonic acid; EPA, 5,8,11,14,17-eicosapentaenoic acid; DHA, 4,7,10,13,16,19-docosahexaenoic acid; LOX, lipoxygenase; COX, cyclooxygenase; PG, prostaglandins; Tx, thromboxane; cPLA2, cytosolic phospholipase 2; LTA4H, leukotriene A4 hydrolase; LTC4S, leukotriene C4 synthase; GGT, gamma-glutamyltranspeptidase; DPEP, dipeptidase; Mya, million years ago; Bya, billion years ago; LX, lipoxins; RS, resolvins.

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1. Introduction

Polyunsaturated fatty acids (PUFAs) are important constituents of membrane lipids, which impact membrane functionality [1]. In addition, they also constitute substrates for the biosynthesis of signaling molecules such as prostaglandins [2], leukotrienes [3] or endocannabinoids [4]. Linoleic acid (C18:Δ2, n-6) and arachidonic acid (C20:Δ4, n-6) are abundant polyenoic fatty acids in the ester lipids of mammalian membranes but alpha- (C18:Δ3, n-6) and gamma-linolenic acid (C18:Δ3, n-3), eicosapentaenoic acid (C20:Δ5, n-3) and docosahexaenoic acid (C22:Δ6, n-3) also occur in lower abundance. However, the cellular concentrations of free polyenoic fatty acids are rather small. In order to be converted to prostaglandins, leukotrienes and related substances polyenoic fatty acids must be released from the membrane ester lipids and subsequently be oxygenated via two major alternative metabolic routes (Fig. 1). The cyclooxygenase (COX) pathway of the arachidonic acid cascade leads to the biosynthesis of classical prostaglandins (PGE2, PGF2, PGD2), thromboxanes (TxA2) and prostacyclin (PGI2). In contrast, leukotrienes, (LT), lipoxins (LX), resolvins (RS) and others are biosynthesized via the lipoxygenase (LOX) pathway [5]. Leukotrienes are the most extensively studied LOX products [6] and their biosynthesis involves a concerted action of several enzymes such as cytosolic phospholipase A2 (cPLA2), 5-LOX (ALOX5), Leukotriene A4 hydrolase (LTA4H), leukotriene C4 synthase (LTC4S), gamma-glutamyltranspeptidase (gGTs) and dipeptidases (DPEPs).

There are several current review articles [5–10], which together provide a detailed overview on chemistry, enzymology, biological roles and medical relevance of LOX and leukotriene signaling. However, to the best of our knowledge evolutionary aspects and genetic variability of LOX and of leukotriene signaling have never been reviewed before. This paper is aimed at filling this gap. After a short introduction into the field we will summarize our current knowledge on classification, biosynthesis and physiological importance of LOX (chapter 2) and leukotriene signaling (chapter 3). Then we will address evolutionary aspects of leukotriene signaling (chapter 4) and this part of the paper is focused on distribution of LOX isoforms and other enzymes of leukotriene biosynthesis within the three domains of life on this planet. The growing number of sequenced genomes of living and extinct organisms has led to identification of an increasing number of potential LOX and/or LOX-like sequences and it would exceed the frame of this review to refer to all of them. Instead, we selected frequently employed model organisms, which represent different stages in the evolution of life on earth and searched their genomes for putative LOX sequences. Since for most of these sequences no functional data are currently available, we used our knowledge on structural biology of these enzymes to draw functional conclusions. Finally, we will summarize the current knowledge on genetic variability of human leukotriene signaling (chapter 5). For this purpose we evaluated the public databases summarizing naturally occurring mutants of human LOX and other enzymes of leukotriene signaling. Here again, the databases are rapidly growing and it is not possible to consider all naturally occurring variants for this review. In this sense the review is somewhat selective and we are not aiming at completeness. However, we would like to apologize to those distinguished colleagues whose work we have not found space to describe and to reference.

2. Leukotrienes: classification, biosynthesis and physiological importance

Leukotrienes (LTs) are pro-inflammatory LOX products regulating the extent of the inflammatory reaction [6,10,11]. When formed in pathological quantities these mediators induce pain, fever, and inflammation. LTs are biosynthesized from arachidonic acid (AA) via the consecutive action of different enzymes (Fig. 1). The reaction cascade is initiated by the liberation of AA from the cellular ester lipids by cytosolic phospholipase A2 (cPLA2). There are two principle types of leukotrienes, which exhibit different bioactivities. (i) Cysteinyl-free leukotrienes (LTA4, LTB4) are biosynthesized from arachidonic acid via consecutive dioxygenation (formation of LTA4) and subsequent enzymatic epoxide hydrolysis. For these reactions the 5-lipoxygenase (ALOX5) [12] and leukotriene A4 hydrolase (LTA4H) [13] are responsible. As allylic epoxide LTA4 is very unstable and undergoes rapid hydrolysis. Thus, it may not exhibit systemic bioactivity. LTB4 functions as potent chemoattractant for inflammatory cells and induces chemokinesis and