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Review

Lipoxins and aspirin-triggered lipoxins in resolution of inflammation

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ABSTRACT

The resolution of the inflammatory response is highly regulated by the timely biosynthesis of a number of endogenous lipid mediators. Among these, lipoxins (LX) and their 15-epimers, aspirin triggered lipoxins (ATL) derived by the lipoxygenase (LO) route of arachidonic acid metabolism. In particular, they are formed and released by cells expressing 5-, 12- and 15-LO such as leukocytes, platelets, vascular endothelium and epithelium, alone or during transcellular interactions. ATL biosynthesis requires cyclooxygenase-2 acetylation by aspirin. LX and ATL exert potent bioactions on leukocytes, vascular and epithelial cells to stop inflammation and promote resolution.

They have shown to be beneficial in a broad spectrum of preclinical models of disease as well as in some clinical trials. Counter-regulatory signaling by LXA_4 and 15-epi-LXA_4 follows the activation of a G protein-coupled receptor, termed ALX/FPR2, which is emerging as a key anti-inflammatory receptor.

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1. The inflammatory response and its resolution

Acute inflammation is a physiological innate host response to injury aimed at removing pathological *noxae* and restoring homeostasis (reviewed by Majno and Joris (2004)). Resolution is the ideal outcome of an acute inflammatory response (Nathan and Ding, 2010; Serhan, 2004; Serhan and Savill, 2005), as its perpetuation leads to pathology. Timely recruitment of leukocyte subtypes is the key feature of acute inflammation, being polymorphonuclear neutrophils (PMN) the first to accumulate in inflamed tissues to attack the damaging agents (microbial, thermal, mechanical, etc.) followed by monocytes, which differentiate into macrophages (MΦ) within the tissue and start the resolution phase. This is mainly characterized by the MΦ removal of apoptotic PMN via nonphlogistic phagocytosis (efferocytosis). Macrophages also stimulate wound healing and tissue repair (Leibovich and Ross, 1975; Lucas et al., 2010).

Resolution has been traditionally regarded as the passive consequence of the dissipation of pro-inflammatory signals. Pioneeristic studies from Serhan and coworkers (Levy et al., 2001; Serhan et al., 2000, 1984a, 1984b) have established that resolution is a highly ordered active process, tightly regulated by a number of lipid mediators, enzymatically derived from essential polyunsaturated fatty acids (PUFA). These mediators or *"resolution agonists"* are collectively termed *specialized pro-resolving lipid mediators* (SPM) (Serhan et al., 2008) or *immunoresolvents* (Dalli et al., 2013a, 2013b; Winkler et al., 2013) reviewed by Serhan and Chiang (2013).

The lipoxins (LX), an acronym for *"lipoxygenase interaction products"*, are the first discovered class of immunoresolvents (Serhan et al., 1984b). Later on, LX epimers, termed aspirin-triggered LX (ATL) were reported (Claria and Serhan, 1995). A large body of experimental, preclinical and clinical data have now established the anti-inflammatory and pro-resolution properties of LX and related receptors.

In this review, we will summarize our current knowledge of LX and ATL, focusing on their clinical relevance and receptor signaling.

2. LX and ATL: structure and biosynthesis

The leading compounds of the LX series, identified in incubations of human leukocytes with arachidonic acid (AA) or 15*S*-hydroperoxy-5,8,11,13-eicosatetraenoic acid (HpETE), are termed LXA_4##(5*S*,6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid) and LXB_4 (5*S*,14*R*,15*S*-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid) (Serhan et al., 1984a). These eicosanoids display the UV absorption spectrum typical of tetraenes, with preeminent bands at λ_{max}^{MeOH} 287, 300, 315 nm, a weaker band at 270 nm and a molar extinction coefficient of 50,000 M^{-1} per cm. Typical mass spectrometry signatures are: diagnostic ions at *m/z* ***333*** [351-H_2O], ***315*** [351-2H_2O], ***307*** [351-CO_2], ***289*** [351-H_2O–CO_2], ***271*** [351-2H_2O–CO_2], ***251*** [351-CHO$(CH_2)_4CH_3$], ***235*** [351-CHO$(CH_2)_3COO^-$], ***233*** [351-H_2O–CHO$(CH_2)_4CH_3$], ***219*** [351-CHO$(CH_2)_3COO^-$–O], ***207*** [351-CO_2–CHO$(CH_2)_4CH_3$], ***189*** [351-H_2O–CO_2–CHO$(CH_2)_4CH_3$], ***135*** [351-CHO$(CH_2)_3$–COOH–CHO$(CH_2)_4CH_3$], ***115*** [CHO$(CH_2)_3COO^-$] for LXA_4, and *m/z* ***333*** [351-H_2O], ***315***[351-2H_2O], ***307*** [351-CO_2], ***289*** [351-H_2O–CO_2], ***271*** [351-2H_2O–CO_2], ***251*** [351-CHO$(CH_2)_4CH_3$], ***233*** [351-H_2O–CHO$(CH_2)_4CH_3$], ***221*** [351-CHOCHOH$(CH_2)_4CH_3$], ***207*** [351-CO_2–CHO$(CH_2)_4CH_3$], ***189*** [351-H_2O–CO_2–CHO$(CH_2)_4CH_3$], ***163*** [351-CO_2–CH_2COHCHOH$(CH_2)_4CH_3$], ***129*** [$CH_3CO(CH_2)_3COO^-$] and ***115*** [CHO$(CH_2)_3COO^-$] for LXB_4.

The sequential oxygenation of arachidonic acid by 5- and 15-lipoxygenase (LO) is the first reported route of LX biosynthesis (Serhan et al., 1986). In this case, AA is attached by 5-LO to produce leukotriene (LT)A_4, which is converted to a 5*S*, 6*S*, 15*S*-epoxytetraene intermediate, subsequently transformed into LXA_4 and B_4. Alternatively, AA can be first utilized by 15-LO, yielding 15-HpETE and 15*S*-hydroxy eicosatetreanoic acid (HETE), which are transformed by 5-LO into the 5*S*, 6*S*, 15*S*-epoxytetraene, which gives both LXA_4 and B_4. These pathways occur in PMN, eosinophils (Serhan et al., 1987) and alveolar MΦ (Levy et al., 1993), or during cell/cell (tissue) interactions, for instance PMN/eosinophils (Serhan et al., 1987) or PMN/lung tissue (Edenius et al., 1990).

This route may be prevalent in the airways. Indeed, a concomitant reduction in LXA_4 formation and expression of 5-LO and 15-LO isoforms was detected in bronchoalveolar lavage cells and endobronchial biopsies from asthmatic patients (Planaguma et al., 2008). More direct evidence for the role of 15-LO in LX biosynthesis was obtained by transfecting the human 15-LO gene into the rat kidney (Munger et al., 1999).

An alternative route of LX biosynthesis involves 5- and 12-LO. The LX synthase activity of 12-LO was initially hypothesized on the basis of the observation that platelet (PLT)/PMN mixed incubations originate detectable amounts of LX (Edenius et al., 1988; Fiore and Serhan, 1990). The metabolic pathway was elucidated in experiments with human megakaryocytes or 12-LO-transfected cells (Sheppard et al., 1992), PLT exposed to LTA_4 (Romano and Serhan, 1992) and human PLT recombinant 12-LO incubated with LTA_4 in a cell-free system (Romano et al., 1993). This reaction proceeds via the 12-LO-catalyzed conversion of LTA_4 into a delocalized cation, which is attacked by water at carbon-6 to give LXA_4, and at carbon-14 to yield LXB_4 (Sheppard et al., 1992). The LX synthase capability of 12-LO may have pathophysiological significance, since 12-LO affinity