BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2009), 158, 947–959

0007-1188/09
www.brjpharmacol.org

THEMED SECTION: MEDIATORS AND RECEPTORS IN THE RESOLUTION OF INFLAMMATION

REVIEW

Lipoxins: resolutionary road

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The resolution of inflammation is an active process controlled by endogenous mediators with selective actions on neutrophils and monocytes. The initial phase of the acute inflammatory response is characterized by the production of pro-inflammatory mediators followed by a second phase in which lipid mediators with pro-resolution activities may be generated. The identification of these mediators has provided evidence for the dynamic regulation of the resolution of inflammation. Among these endogenous local mediators of resolution, lipoxins (LXs), lipid mediators typically formed during cell–cell interaction, were the first to be recognized. More recently, families of endogenous chemical mediators, termed resolvins and protectins, were discovered. LXs and aspirin-triggered LXs are considered to act as 'braking signals' in inflammation, limiting the trafficking of leukocytes to the inflammatory site. LXs are actively involved in the resolution of inflammation stimulating non-phlogistic phagocytosis of apoptotic cells by macrophages. Furthermore, LXs have emerged as potential anti-fibrotic mediators that may influence pro-fibrotic cytokines and matrix-associated gene expression in response to growth factors. Here, we provide a review and an update of the biosynthesis, metabolism and bioactions of LXs and LX analogues, and the recent studies on their therapeutic potential as promoters of resolution and fibro-suppressants.
British Journal of Pharmacology (2009) **158,** 947–959; doi:10.1111/j.1476-5381.2009.00386.x; published online 28 September 2009

This article is part of a themed issue on Mediators and Receptors in the Resolution of Inflammation. To view this issue visit http://www3.interscience.wiley.com/journal/121548564/issueyear?year=2009

Keywords: lipoxin; anti-inflammatory; resolution of inflammation; anti-fibrotic; leukocytes; mesangial cells

Abbreviations: 15-HETE, 15-eicosatetraenoic acid; AA, arachidonic acid; AhR, aryl hydrocarbon receptor; AjA, ajulemic acid; ALXR, lipoxin A_4 receptor; ATL, aspirin-triggered lipoxin; 15-epi-LXA_4 (5*S*,6*R*,15*R*-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid); COX-2, cyclooxygenase-2; CTGF, connective tissue growth factor; CysLT, cysteinyl leukotriene receptor; EGF, epidermal growth factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; LO, lipoxygenase; LT, leukotriene; LX, lipoxin; LXA_4, lipoxin A_4 (5*S*, 6*R*,15*S*-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid); LXB_4, lipoxin B_4 (5*S*,14*R*,15*S*-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid); PDGF, platelet-derived growth factor; SOCS-2, suppressor of cytokine signalling 2; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α; VEGF, vascular endothelial growth factor

Introduction

Inflammation is a key process in effective host defence. It is a critical response to microbial invasion and tissue injury, and is characterized by site-specific accumulation and activation of leukocytes. The resolution of such inflammatory responses is necessary to re-establish homeostasis, limiting excessive tissue injury and minimizing the development of chronic inflammation, and depends on the biological actions of several anti-inflammatory and pro-resolving mediators, expressed by various cell types, as well as on apoptosis and clearance of inflammatory cells (Lawrence *et al.*, 2002; Serhan and Savill, 2005; Serhan, 2007; Serhan *et al.*, 2007). A failure of any step in this process may lead to chronic inflammation with possible further tissue destruction, fibrosis and eventually organ failure. The first evidence that the resolution of inflammation is an active rather than a passive process came

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Received 22 April 2009; accepted 27 May 2009

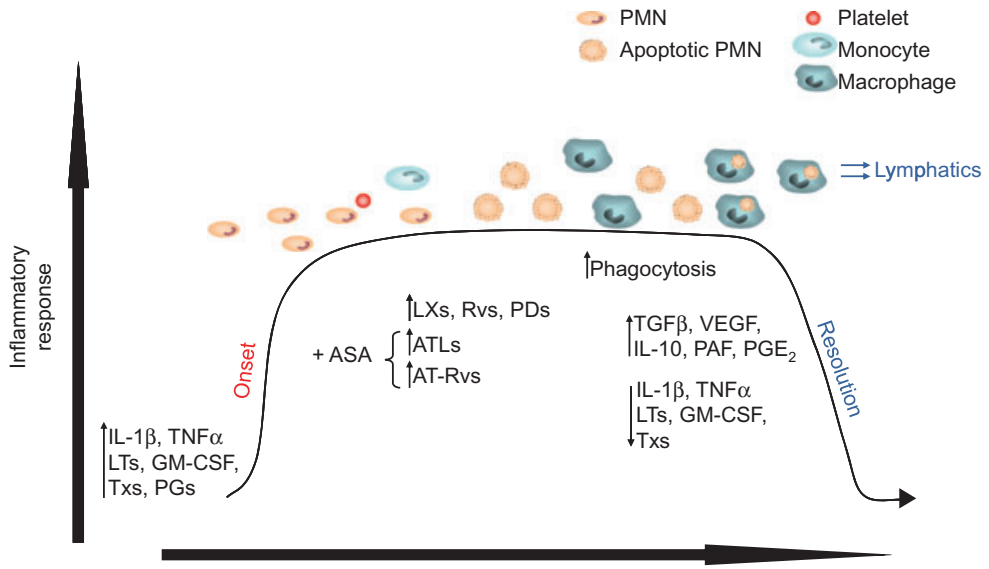


Figure 1 Representation of the temporal cellular and biochemical events in the onset and resolution of inflammation. The early phase of inflammation is characterized by the release of pro-inflammatory mediators and extravascular accumulation of neutrophils, followed by infiltration of monocytes that differentiate into macrophage. This phase is characterized by the formation of anti-inflammatory and pro-resolution mediators (LXs, resolvins). These mediators stop further neutrophil trafficking and facilitate the removal of apoptotic cells. The ingestion of apoptotic cells results in potent anti-inflammatory effects through the production of anti-inflammatory cytokines such as TGF-β1, IL-10 and PGE_2, and the decrease of release of pro-inflammatory mediators, including IL-8, TNF-α and TXA_2. This figure is adapted from Serhan *et al.* (2007). IL = interleukin; TNF-α = tumour necrosis factor-α; LTs = leukotrienes; Tx = thromboxane; GM-CSF = granulocyte–macrophage colony-stimulating factor; PGs = prostaglandins; ASA = aspirin; LXs = lipoxins; Rvs = resolvins; PDs = protectins; ATL = aspirin-triggered lipoxins; ATRv = aspirin-triggered resolvins; TGF-β = transforming growth factor β; VEGF = vascular endothelial growth factor; PAF = platelet-activating factor; PGE_2 = prostaglandin E_2.

with the discovery of pro-resolution biochemical signalling circuits (Serhan *et al.*, 2000; 2007; Bannenberg *et al.*, 2005). During the initial phase of inflammation, eicosanoids including prostaglandins and leukotrienes (LTs) play important role as local mediators in the development of an inflammatory condition, evoking potent chemotactic responses of leukocytes whose activation is coupled to the production of proinflammatory (Th1-derived cytokines) at sites of inflammation (Borgeat and Naccache, 1990). This is a biphasic process; the second stage is coupled to the biosynthesis of lipid mediators that actively limit inflammation and promote resolution. The new genus of pro-resolving mediators of molecules include lipoxins (LXs) and their aspirin-triggered carbon-15 epimers (ATL) (Levy *et al.*, 2001; Serhan, 2005), as well as the recently discovered resolvins and protectins which are derived from ω-3 fatty acids (Serhan *et al.*, 2000; 2008a,b). Resolvins and protectins were first identified in self-resolving murine exudates using the murine dorsal air pouch model of inflammation (Serhan *et al.*, 2000). In parallel studies, it was demonstrated that prostaglandin E2 and D2 stimulate the translation of neutrophil 15-lipoxygenase (LO) involved in LX biosynthesis, providing evidence for class switching within the eicosanoid pathways during the evolution of an inflammatory exudate (Levy *et al.*, 2001). Figure 1 shows the cellular and molecular mechanisms involved in the onset and resolution of inflammation.

In this review, we will give an overview and an update of the role of LXs as pro-resolution and anti-fibrotic agents with particular focus on the potential development of LX analogues as therapeutics.

Biosynthesis of LXs

The term LXs is an acronym for LO interaction products. These lipid mediators were first recognized to have dual anti-inflammatory and pro-resolution activities (Maderna and Godson, 2003; Kieran *et al.*, 2004; McMahon and Godson, 2004; Serhan, 2005). 5*S*,6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoicacid (LXA_4) and its positional isomer 5*S*,14*R*,15*S*-trihy-droxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid (LXB_4) are the principal species formed in mammals (Serhan *et al.*, 1986a,b). LXs are typically formed by transcellular metabolism through distinct biosynthetic pathways depending on the cellular context (Kieran *et al.*, 2004; McMahon and Godson, 2004; Chiang *et al.*, 2005; Serhan, 2005). There are two main LO-mediated pathways of LX biosynthesis in human cells and tissues. The first of these involves the sequential lipoxygenation of arachidonic acid by 15-LO in epithelial cells and monocytes, and 5-LO in neutrophils (Serhan *et al.*, 1984a,b). This pathway not only leads to LX biosynthesis, but also reduces LT formation, resulting in an inverse relationship between LT and LX byosynthesis in human leukocytes (Serhan, 1989). Indeed, it has recently been shown that in acute post-streptococcal glomerulonephritis up-regulation of 15-LO and subsequent LX biosynthesis supersede production of proinflammatory LTB_4 (Wu *et al.*, 2009). The second major route of LX formation involves platelet/leukocyte or platelet/leukocyte microaggregate interactions that promote LX formation by transcellular conversion of the 5-LO epoxide product, LTA_4 to LXA_4 and LXB_4 by the LX-synthetase activity of the 12-LO in platelets (Serhan

and Sheppard, 1990). Interestingly, platelets are not able to produce LXs on their own, but this pathway has been highlighted as a major route for LX formation within the vasculature where activated platelets become a major source of LXs after adhesion to neutrophils (Chiang *et al.*, 2005; Serhan, 2005).

In addition to the transcellular routes, another recognized source of LX biosynthesis involves a form of cellular 'priming' with the esterification of 15-HETE in inositol-containing phospholipids within the membranes of human neutrophils (Brezinski and Serhan, 1990). Discovery of this pathway suggests that during disease or host defence, precursors of LX biosynthesis might be stored within the membranes of the inflammatory cells and released after stimulation (Brezinski and Serhan, 1990).

The signalling networks involved in LX formation show even greater complexity given the potential regulation of biosynthetic enzymes by specific cytokines (Serhan *et al.*, 1996). For example, interleukin 4 (IL-4) and IL-13, putative negative regulators of inflammatory and immune responses, promote transcellular LX generation through enhanced expression of 15-LO in monocytes and epithelial cells (Nassar *et al.*, 1994; Munger *et al.*, 1999). Cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-3 up-regulate 5-LO transcripts (Ring *et al.*, 1996), while pro-inflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor (TNF-α) have been shown to induce cyclooxygenase-2 (COX-2), thus potentially contributing to the formation of ATLs *in vivo* (Parente and Perretti, 2003).

LXs are generated *in vivo* within an inflammatory milieu, and it has been suggested that an impaired LX biosynthesis may correlate with an inability to resolve the acute inflammatory reaction contributing to a more chronic inflammatory phenotype (Lee *et al.*, 1990; Brezinski *et al.*, 1992; Chiang *et al.*, 1999; Munger *et al.*, 1999; Bandeira-Melo *et al.*, 2000; Pouliot *et al.*, 2000; Bonnans *et al.*, 2002; Karp *et al.*, 2004). Recently, it has been described that exogenous resolvin E1 stimulated the production of endogenous LXA_4 during the resolution of allergic airway (Haworth *et al.*, 2008). There is a growing body of evidence that indicates an immunomodulatory role for LXs during infections. *Toxoplasma gondii*, a protozoan parasite, which encode their own 15-LO, has been shown to activate LXA_4 biosynthesis, resulting in increased evasion of the parasite from host defence (Aliberti *et al.*, 2002; Bannenberg *et al.*, 2004b).

ATLs

Aspirin triggers the generation of epimeric forms of LXs (Claria and Serhan, 1995). Cells that express COX-2 (i.e. vascular endothelial cells, epithelial cells, macrophages, neutrophils) are able to produce ATLs by the actions of aspirin that triggers the endogenous formation of carbon-15 epimeric LXs, namely ATL (Claria and Serhan, 1995). In particular, in a cytokine primed milieu, aspirin acetylation of COX-2 switches the catalytic activity of the enzyme to an *R*-LO with the formation of 15*R*-HETE that is rapidly converted by 5-LO to 15-epimeric-LXA_4 or 15-epimeric LXB_4 (Claria and Serhan, 1995). Interestingly, ATL formation has been detected *in vivo* in various murine models of inflammation such as peritonitis (Chiang *et al.*, 1998), dorsal air pouches (Perretti *et al.*, 2002) and in aspirin-intolerant asthmatics (Sanak *et al.*, 2000). Administration of low doses of aspirin to healthy subjects significantly increases plasma levels of ATL with a concomitant inhibition of thromboxane biosynthesis, suggesting that ATL may account for some of the beneficial effects of aspirin that are not strictly related to its anti-thrombotic actions (Chiang *et al.*, 2004). A further synthetic route for the production of 15-epi LXA_4 has been demonstrated in rat myocardium in response to statins and the PPAR-γ ligand pioglitazone (Birnbaum *et al.*, 2006; 2007), providing a novel mechanism for immune regulation by statins.

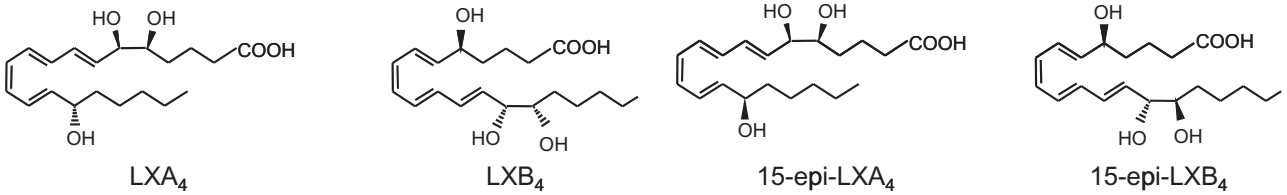
Metabolic inactivation of LXs

LXs are rapidly generated in response to stimuli, act locally and undergo rapid metabolic inactivation. Using monocytes or isolated enzymes, it has been possible to demonstrate that the major route of LXs degradation is via dehydrogenation at C-15 and possibly by ω-oxidation at C-20 (Serhan *et al.*, 1995; Clish *et al.*, 2000). A similar inactivation pathway was also shown for LXB_4 (Maddox *et al.*, 1998). ATLs are converted *in vitro* to their 15-oxo-metabolite with a slower rate compared to native LXs, indicating that the hydrogenation step is highly specific (Serhan *et al.*, 1995). Furthermore, ATLs, when generated *in vivo*, display longer biological half-life than native compounds and enhanced ability to evoke bioactions (Serhan *et al.*, 1995; Maddox *et al.*, 1997; Clish *et al.*, 1999).

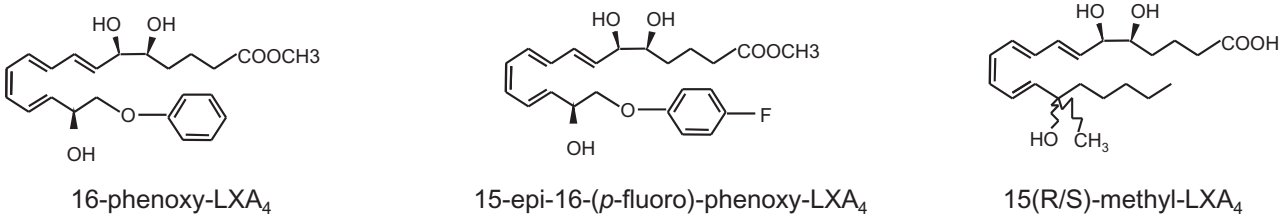
Synthetic LX analogues

The rapid inactivation and short half-life of LXs *in vivo* have prompted the development of novel analogues designed to resist metabolism, maintain their structural integrity and bioavailability and their potential beneficial bioactions. The initial design of metabolically stable LXA_4 analogues focused on identifying poor substrates for PGDH, which maintained potency in *in vitro* assays. The discovery that 15-epi-LXA_4 was equipotent in *in vitro* assays to LXA_4, but was a poorer substrate for PGDH, provided support for exploiting these observations in novel analogue design. However, although 15-epi-LXA_4 has enhanced metabolic stability over LXA_4 *in vivo*, its pharmacokinetics remain poor, which, in addition to low chemical stability, creates challenges for development of analogues with better therapeutic potential. Therefore, a series of LX and ATL analogues were designed with specific modifications of the native structures of LXA_4 and LXB_4, such as the addition of methyl groups on C-15 and C-5 of LXA_4 and LXB_4, respectively (Serhan *et al.*, 1995), and phenoxyl or para-fluoro-phenoxyl groups at C-16 of both LXA_4 and 15-epi ATL, protecting the molecules from the ω-oxidation and dehydrogenation *in vivo* (Serhan *et al.*, 1995; Maddox *et al.*, 1997; Clish *et al.*, 1999). Consequently, these analogues were widely used in a number of studies exploring the biological functions of LX and ATL in experimental models of disease (Scalia *et al.*, 1997; Takano *et al.*, 1997; Filep *et al.*, 1999; Hachicha *et al.*, 1999; Jozsef *et al.*, 2002; Ariel *et al.*, 2003). A second

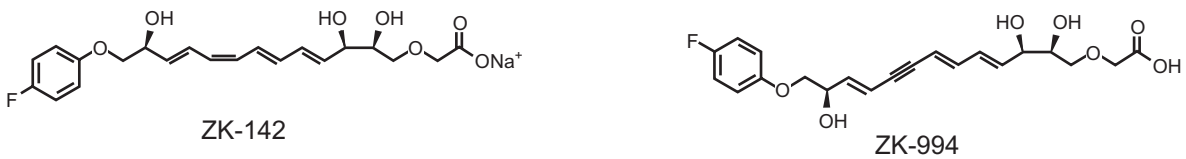
Endogenous lipoxins



First-generation LXA_4 analogues



Second-generation LXA_4 analogues: 3-oxa



Benzo LXA_4 analogues

Figure 2 Structure of native lipoxins (LXs), 15-epi-LXs and synthetic analogues. The figure shows the structure of the native LXs (LXA_4 and LXB_4), aspirin-triggered LXs [aspirin-triggered lipoxin (ATL); 15-epi-LXA_4 and 15-epi LXB_4]. In order to increase the half-life of LXA_4, and ATL, analogues resistant to enzymatic conversion by ω-oxidation and PGDH were designed (e.g. 16-*p*-fluorophenoxy-15-epi-LXA_4 methyl ester) (Takano *et al.*, 1998; Clish *et al.*, 1999; Gewirtz *et al.*, 1999; Karp *et al.*, 2004). Modification of the tetraene structure to a trienyne further enhanced chemical stability as depicted here in the structure of the 3-oxa LX analogue ZK-142 and its 11-dehydro analogue ZK-994, which are topically and orally active anti-inflammatory agents (Guilford *et al.*, 2004). More recently, a new class of lipoxin analogues featuring a benzo-fused ring system have been designed and proved to be as potent as native LXA_4 in a series of *in vitro* and *in vivo* studies (O'Sullivan *et al.*, 2007; Petasis *et al.*, 2008).

generation of LX stable analogues, 3-oxa-LXA_4 analogues, with enhanced chemical and metabolic stability, has shown potency and efficacy comparable to ATL in diverse animal models after topical, intravenous or oral delivery (Bannenberg *et al.*, 2004a; Guilford *et al.*, 2004). More recently, we have developed a stereoselective synthesis of chemically stable aromatic LXA_4 and LXB_4 analogues (O'Sullivan *et al.*, 2007). This synthetic route establishes the required stereochemistry by way of Sharpless epoxidation, Pd-mediated Heck coupling and diastereoselective reduction reactions (Figure 2). LXs, ATL and their stable analogues share potent protective actions in controlling inflammation, and provide new opportunities to explore the actions and therapeutic potential for LXs and ATL as it will be outlined later in this review.

LXA_4 and ATL receptors

Several mechanisms have been proposed to underlie the bioactions of LXs as shown in Figure 3. These include activation of a high-affinity LX-specific G-protein coupled receptor, activation of subclasses of cysteinyl peptide receptors and/or cellular uptake of LX which in turn facilitates interactions with intracellular targets such as nuclear receptors (Fiore *et al.*, 1992; Simchowitz *et al.*, 1994; Schaldach *et al.*, 1999; Chiang *et al.*, 2000; 2004; McMahon *et al.*, 2001; Planaguma *et al.*, 2002).

A specific LX recognition site was first described in human neutrophils, and demonstrated to be responsible for the specific LXA_4-evoked actions on these cells (Fiore *et al.*, 1992).

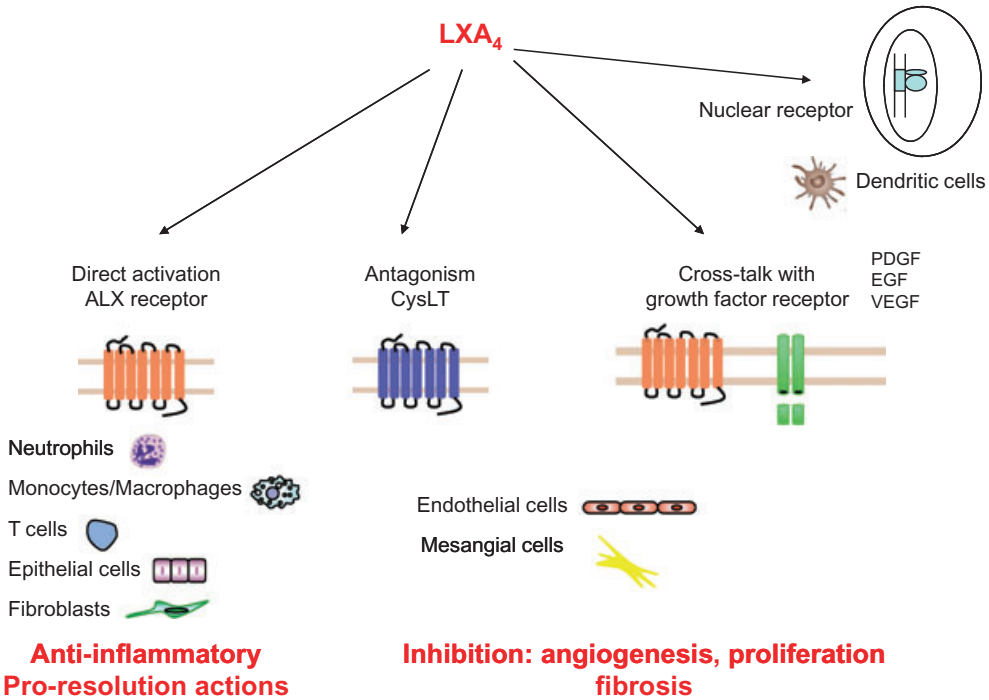


Figure 3 Lipoxin (LX) and receptors. The actions of LXs and aspirin-triggered lipoxins are mediated through several mechanisms. These include activation of high-affinity, LX-specific G-protein coupled receptor (ALXR), interaction of subclasses of cysteinyl peptide–LTs receptor. Direct activation of the lipoxin receptor results in anti-inflammatory and pro-resolution activities. Indirect inhibition, through other receptors such as CysLT and growth-factor receptors (such as vascular endothelial growth factor and platelet-derived growth factor receptors), reduces angiogenesis, and mesangial cell proliferation and fibrosis. Another potential receptor of LXA_4 is the nuclear receptor aryl hydrocarbon receptor, which triggers expression of suppressor of cytokine signalling 2 in LX-stimulated DC.

This G-protein coupled receptor was later designated as ALXR (FPRL-1) (Serhan, 1997; Chiang *et al.*, 2005; 2006). Although LXA_4 and LXB_4 share many of the biological activities, LXB_4 does not bind ALXR, and the LXB_4 receptor remains to be identified. Human ALXR belongs to a family of three members (FPR1, FPRL-1/ALXR and FPR3), and is expressed in several types of leukocytes such as neutrophils (Fiore *et al.*, 1994), monocytes (Maddox *et al.*, 1997), activated T cells (Ariel *et al.*, 2003), as well as resident cells such as intestinal epithelial cells (Kucharzik *et al.*, 2003), synovial fibroblasts (Sodin-Semrl *et al.*, 2000), bronchial epithelial cells (Bonnans *et al.*, 2003), astrocytes (Decker *et al.*, 2009) and renal mesangial cells (McMahon *et al.*, 2000). Transcription of ALXR had been shown to be up-regulated by various cytokines, suggesting regulation of receptor expression in an inflammatory milieu (Gronert *et al.*, 1998; Sodin-Semrl *et al.*, 2000). It has recently been shown that gene and cell surface expression of ALXR are significantly decreased in peripheral blood leukocytes of asthmatic subjects compared to healthy individuals (Planaguma *et al.*, 2008).

The GPCR-designated ALXR can bind pleiotropic ligands, that is, both lipid and peptides eliciting either pro-inflammatory or anti-inflammatory responses (Chiang *et al.*, 2000). Among the various ligands are MHC binding peptide (a potent necrotactic peptide derived from NADH dehydrogenase subunit 1 from mitochondria) (Chiang *et al.*, 2000), antimicrobial peptides (e.g. LL37 and temporin A) (De *et al.*, 2000; Chen *et al.*, 2004), truncated chemotactic peptides (e.g. CKbeta8-1) (Elagoz *et al.*, 2004), a urokinase-type plasminogen activator receptor fragment (Resnati *et al.*, 2002) and the HIV envelope peptides (Su *et al.*, 1999a; Le *et al.*, 2000). ALXR can also bind prion protein (Le *et al.*, 2001b), serum amyloid A (Su *et al.*, 1999b) and amyloid β_{42} (Le *et al.*, 2001a).

Another ligand of particular interest is annexin 1, a glucocorticoid-inducible protein (Perretti *et al.*, 2002) that mediates many of the anti-inflammatory actions of glucocorticoids in models of acute and chronic inflammation (reviewed in Perretti and Flower, 2004; Lim and Pervaiz, 2007; Perretti and D'Acquisto, 2009). Interestingly, glucocorticoids induce up-regulation of the expression of ALXR by leukocytes and in *in vivo* model of dermatitis (Sawmynaden and Perretti, 2006; Hashimoto *et al.*, 2007). Recently, a novel peptide agonist of ALXR with potent anti-inflammatory and cardioprotective effects was identified using a computational platform (Hecht *et al.*, 2009). These data highlight the therapeutic potential of ligands designed as agonists of the ALXR in applications such as acute and chronic inflammation.

The binding of lipids and small peptides to the receptor occurs with different affinities and/or at discrete interaction sites, facilitating activation of distinct signalling pathways that depends on the cell type and system (Bae *et al.*, 2003). *N*-glycosylation of ALXR is proposed to be important for ligand specificity and may play a role in switching receptor functions at local host defence sites, suggesting receptor versatility (Chiang *et al.*, 2000).

Mouse and rat ALXR homologues have been cloned from a spleen cDNA library (Takano *et al.*, 1997) and from peripheral blood leukocytes, respectively (Chiang *et al.*, 2003). The

overall homology between the human, murine and rat receptors is relatively high in particular in their second intracellular loop (100%) and between the sixth transmembrane domain (97%), suggesting important roles for these regions in ligand recognition and functional G protein coupling.

The partial antagonism of a subclass of peptide-LT receptors (CysLTs) is a potential mechanism through which LXs may contribute to the anti-inflammatory bioactions of LXs in several tissues and cell types other than leukocytes (Badr *et al.*, 1989; McMahon *et al.*, 2000; Gronert *et al.*, 2001; Chiang *et al.*, 2006). In mesangial cells, LXs (nanomolar) are potent inhibitors of proliferative responses to LTD_4 by modulating LTD_4-induced transactivation of the platelet-derived growth factor (PDGF) receptor and subsequent phosphotidylinositol 3-kinase activation and mitogenic responses (McMahon *et al.*, 2000). The counter-regulatory responses identified for LX were insensitive to a CysLT1-specific receptor antagonist, but blocked by a non-selective antagonist (McMahon *et al.*, 2002). These data are intriguing given the proposal that the interaction between CysLT1 and CysLT2 receptors regulates inflammatory responses such that activation of the CysLT2 receptor can exert a net inhibitory response on CysLT1 receptor responses (Jiang *et al.*, 2007). By analogy, it might be proposed that LXA_4 activation of the CysLT2 receptor regulates the pro-inflammatory response of the CysLT1; however, this has not been definitively demonstrated.

Further studies show that LXs inhibit proliferation induced by growth factors such as PDGF, epidermal growth factor (EGF) and connective tissue growth factor (CTGF) with a mechanism that involves cross-talk between AXLR and receptor tyrosine kinases (McMahon *et al.*, 2000; 2002; Wu *et al.*, 2006). This inactivation seems to be mediated through the coupling of the ALXR to the activation of the protein tyrosine phosphatase, SHP-2, and it is proposed that the association of the PDGF receptor β within lipid raft microdomains renders it susceptible to LXA_4-mediated dephosphorylation by possible reactivation of oxidatively inactivated SHP-2 (Mitchell *et al.*, 2007). The ALXR ligand annexin-1 also regulates protein phosphorylation of EGF and PDGF receptors (Mitchell *et al.*, 2007).

It is noteworthy that LX-mediated dephosphorylation of intracellular proteins seems to be a recurrent feature of LXA_4 signalling. In addition to dephosphorylation of receptor tyrosine kinases, LX-stimulated phagocytosis of apoptotic leukocytes as described below is dependent on dephosphorylation of myosin IIA (Reville *et al.*, 2006). Recent evidence highlights the importance of LXA_4 as regulators of eosinophil responses to GM-CSF through inhibition of protein tyrosine phosphorylation (Starosta *et al.*, 2008). Additionally, LXA_4 and ATL have been shown to regulate vascular endothelial growth factor (VEGF) receptor-2 phosphorylation in endothelial cells (Fierro *et al.*, 2002; Cezar-de-Mello *et al.*, 2006; 2008; Baker *et al.*, 2009).

Another potential receptor for LXA_4 is the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor. In a murine hepatoma cell line, LXA_4 has been shown to bind and activate AhR (Schaldach *et al.*, 1999). In dendritic cells, LXA_4, signalling through AhR and ALXR modulate innate and acquired immune responses (Machado *et al.*, 2006). It has recently been demonstrated that both LXA_4 and ATL acting via the AhR inhibit innate immune responses of dendritic cells by up-regulating suppressor of cytokine signalling 2 (SOCS-2), which in turn promotes ubiquitinylation and degradation of TNF receptor-associated factor-6, a component of TNF-α, TLR signalling pathways (Machado *et al.*, 2008). It should be noted that responses to the AhR require concentrations of LXA_4 in the micromolar range, whereas cellular responses generated through ALXR (or CysLT) are typically maximal in the nanomolar range, and the Kd of the ALXR is subnanomolar (Fiore *et al.*, 1994).

Anti-inflammatory, pro-resolution and anti-fibrotic effects of LXs

LXs and ATLs have been shown to modulate specific actions in cells involved in the immune–inflammatory response (Figure 4) (for extensive reviews, see: McMahon *et al.*, 2001; Kieran *et al.*, 2004; Maderna and Godson, 2005; Serhan, 2005; Serhan *et al.*, 2007; 2008b). The role for LXs as anti-inflammatory molecules is well defined, with bioactions involving the inhibition of neutrophil and eosinophil recruitment and activation (Lee *et al.*, 1989; Colgan *et al.*, 1993; Soyombo *et al.*, 1994; Papayianni *et al.*, 1995; 1996; Filep *et al.*, 1999). In addition, LXs and ATLs are proposed to directly stimulate gene expression (i.e. NAB1) that is involved in endogenous anti-inflammation and resolution (Qiu *et al.*, 2001) and to regulate NF-kB activation (Decker *et al.*, 2009).

The actions of LXs and ATL are not limited to counter-regulating the evolution of inflammation, but also to promote resolution at different levels. LXs stimulate monocyte chemotaxis and adherence, without causing degranulation or release of reactive oxygen species (Maddox *et al.*, 1997), suggesting that the actions of LXs are related to the recruitment of monocytes to sites of injury. These monocyte activities may be host protective in view of the important role of these cells in wound healing and resolution at inflammatory sites. Indeed, LXs and ATLs stimulate the *in vitro* clearance of apoptotic cells by human monocyte-derived macrophages in a non-phlogistic manner (Godson *et al.*, 2000; Mitchell *et al.*, 2002; Reville *et al.*, 2006). LXs stimulate phagocytosis of exogenously administered excess apoptotic PMN in a murine model of thioglycollate-induced peritonitis *in vivo*, suggesting that LXs rapidly promote the clearance of apoptotic leukocytes within an inflammatory milieu (Mitchell *et al.*, 2002). Consistent with a role for LX promoting the resolution of inflammation are the observations that LX-stimulated phagocytosis is associated with increased transforming growth factor-β1 (TGF-β1) release from macrophages, and a decrease of IL-8 and monocyte chemoattractant protein-1 (MCP-1) release (Godson *et al.*, 2000). The effect of LXs on phagocytosis of apoptotic cells by macrophages is mediated by protein kinase C and PI-3-kinase (Godson *et al.*, 2000; Mitchell *et al.*, 2002). A modulatory role for cAMP is suggested by the observation that LX-induced phagocytosis is inhibited by a cell permeant cAMP analogue, and mimicked by a protein kinase A inhibitor (Godson *et al.*, 2000). Furthermore, LXs prime macrophages for chemotaxis and phagocytosis, through

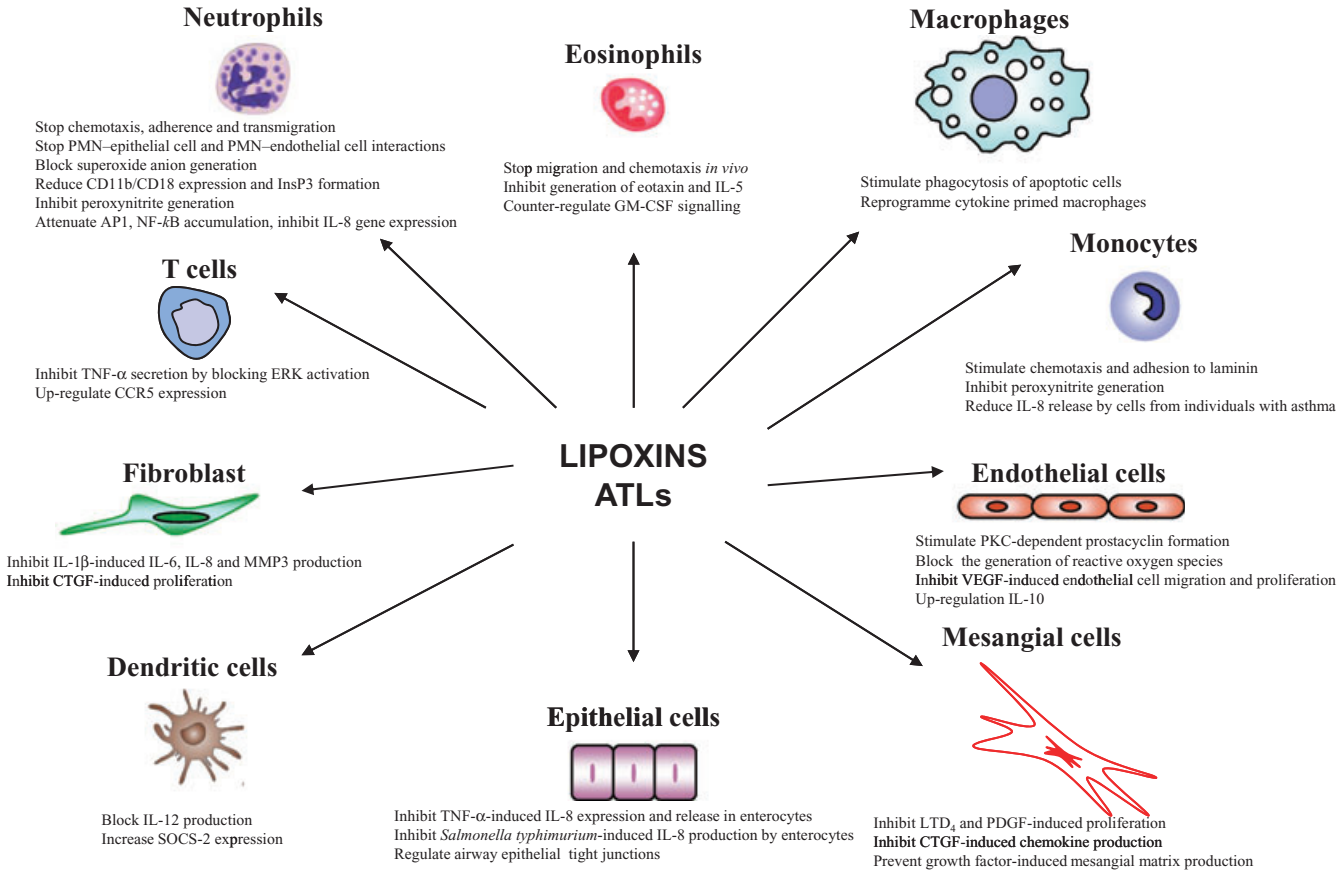


Figure 4 Target cells for lipoxin A_4 and aspirin-triggered lipoxin bioactions.

myosin IIa assembly, re-organization of the cytoskeleton, promoting the cell polarization and formation of actin filaments and pseudopodia (Maderna *et al.*, 2002; Reville *et al.*, 2006). Assembly of non-muscle myosin is coupled to serine dephosphorylation, a process stimulated by LXA_4 through a process that may involve phosphatase activation as described in mesangial cells (Mitchell *et al.*, 2007).

Other ligands of ALXR, and in particular endogenous annexin-1 and its peptidomimetic Ac2-26, promote phagocytosis of apoptotic cells through a mechanism involving ALXR and changes in F-actin re-organization (Maderna *et al.*, 2005). Interestingly, we have shown that cells undergoing apoptosis release annexin-1 that can then stimulate phagocytosis through ALXR (Scannell *et al.*, 2007), demonstrating that the ALXR is activated by soluble 'eat me' signals released from apoptotic cells. Figure 5 illustrates the possible mechanisms of LXs in the phagocytosis of apoptotic cells and resolution of inflammation.

In addition to promoting resolution by non-phlogistic phagocytosis of apoptotic cells, LX can act to reprogramme cytokine-primed macrophages from a classic pro-inflammatory (M1) phenotype to an alternatively activated phenotype demonstrating enhanced phagocytic capacity for apoptotic cells (Mitchell *et al.*, 2002). This feature may suggest novel therapeutic strategies in chronic inflammation characterized by massive macrophage infiltration.

As discussed earlier, LXs are potent inhibitors of mesangial cell proliferation in response to LTD_4 and growth factors with a mechanism that involves cross-talk between AXL and receptor tyrosine kinases (McMahon *et al.*, 2000; 2002; Mitchell *et al.*, 2004). In addition, LXA_4 can counteract PDGF-induced, fibrosis-related gene expression in mesangial cells, suggesting that LXA_4 might act as a potential anti-fibrotic agent, preventing growth factor-induced mesangial matrix production and the progression of renal disease (Rodgers *et al.*, 2005). PDGF-treated renal mesangial cells were shown to secrete factors that promote the onset of tubulointerstitial damage, as observed by epithelial-to-mesenchymal transformation in proximal tubular epithelial cells, an effect attenuated by pre-treatment with LXA_4 (Rodgers *et al.*, 2005). Further to these data, Wu *et al.* demonstrated that TNF-α-induced proliferation and cytokine release, as well as CTGF-mediated release of fractalkine, MCP-1 and RANTES, were modulated by LXA_4 in rat mesangial cells (Wu *et al.*, 2005; 2006). In addition to evidence that LX can maintain the integrity of renal epithelia are data demonstrating that LXA_4 stimulates the expression of ZO-1, claudin and occludin, and the maintenance of transepithelial resistance in cultured bronchial epithelial cells (Grumbach *et al.*, 2009).

The synthetic LX analogue 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4 inhibits VEGF-induced endothelial cell proliferation and migration via inhibition of actin polymerization and assembly of focal adhesions (Fierro *et al.*, 2002; Cezar-de-Mello *et al.*, 2006). In addition, in endothelial cells, the 15-epi-16-(para-fluoro)-phenoxy-LXA_4 induces the gene and protein expression of heme oxygenase-1 (HO-1), a key modu-

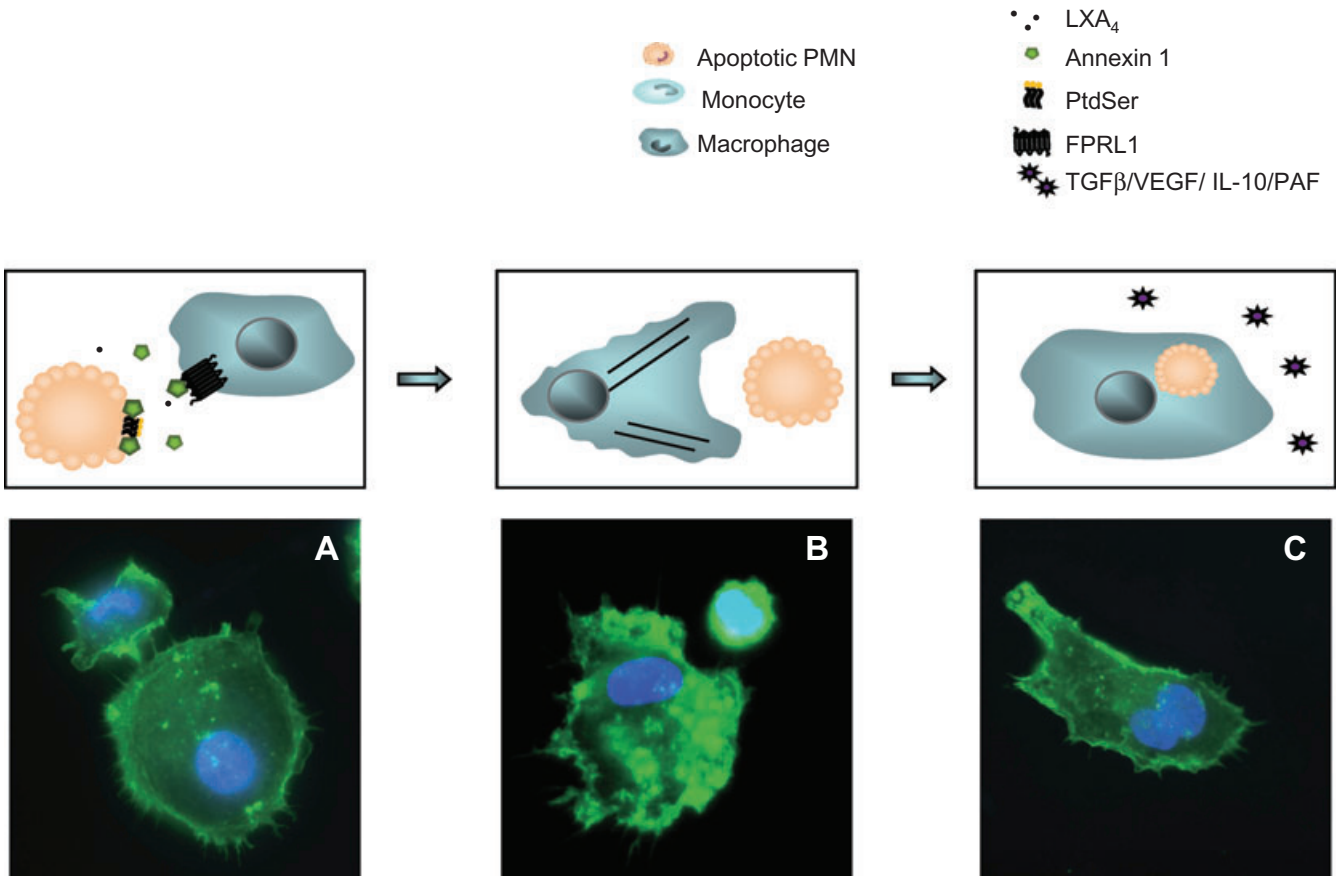


Figure 5 Phagocytosis of apoptotic cells by macrophages is augmented by ligands of the lipoxin (LX) receptor. LXs and other lipoxin A_4 receptor (ALXR) ligands (i.e. aspirin-triggered lipoxins and annexin-1) engage ALXR on the macrophages, leading to intracellular signalling events, including activation of the small GTPases RhoA, Rac and Cdc42; myosin assembly; and actin rearrangement, priming the macrophages for the phagocytosis of apoptotic cells. Following ingestion, the production of anti-inflammatory cytokines is increased, whereas the release of pro-inflammatory mediators is decreased as depicted in schematic. Images depict human monocyte-derived macrophages and apoptotic neutrophil (A); after stimulation with LXA_4 (1 nM), rearrangement of actin cytoskeleton is observed (B) and phagocytosis ensues (note two DAPI-stained nuclei in C).These conclusions are based on Maderna *et al.* (2002) and Reville *et al.* (2006).

lator of both innate and adaptative immunity (Nascimento-Silva *et al.*, 2005). The pathophysiological importance of this finding is reflected by the fact that HO-1 synthesis triggered by ATL is required for the inhibition of TNF-α-induced adhesion molecule expression on endothelial cells which may impair leukocyte influx during the resolution phase of inflammation. Mice lacking 15-LO type I have an impaired HO-1 response. Topical application of LXA_4 in these mice restores HO-1 expression and protects them from inflammatory challenge (Biteman *et al.*, 2007).

The powerful anti-inflammatory, pro-resolution and more recently appreciated potential anti-fibrotic properties of LXs contribute to the overall anti-inflammatory mechanisms of LXs that can modulate the activation and migration of inflammatory cells.

LXs, ATLs and LX analogues in experimental model of diseases

There is reliable evidence that demonstrates that LXs or their stable analogue mimetics can reduce inflammation and symptoms in several experimental models of inflammatory disorders. As discussed earlier, the metabolism of LXs suggests that these molecules are highly susceptible to rapid inactivation; therefore, the availability of stable analogues has been a useful tool to extend the beneficial anti-inflammatory role of LXs to possible therapeutic applications.

One of the first analogues to be synthesized was 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4, an ATL analogue, widely used in systemic or topical therapy for a number of inflammatory conditions (Takano *et al.*, 1998; Clish *et al.*, 1999; Gewirtz *et al.*, 1999; Karp *et al.*, 2004). A role for LXA_4 in reducing cutaneous inflammation has been shown in a variety of skin inflammation models, including psoriasis, atopic dermatitis and allergic contact dermatitis (Takano *et al.*, 1997; Schottelius *et al.*, 2002; Guilford *et al.*, 2004). Topical application of LX analogues to mouse ear skin prevented vascular leakage and neutrophil infiltration in LTB_4/PGE_2-stimulated ear skin inflammation (Takano *et al.*, 1997; Schottelius *et al.*, 2002; Bannenberg *et al.*, 2004a).

The anti-inflammatory spectrum of activity of LXs is well documented in *in vivo* models of glomerulonephritis and acute renal failure (Badr *et al.*, 1989; Papayianni *et al.*, 1995;

Ohse *et al.*, 2004), as well as in *in vitro* models (McMahon *et al.*, 2000; 2002; Mitchell *et al.*, 2004; Rodgers *et al.*, 2005). In a murine model of ischaemic renal injury (IRI) disease, administration of 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4, before onset of experimental ischaemia, resulted in a significant functional and morphological protection with a markedly reduced neutrophil infiltration to the IRI kidney, while maintaining glomerular function and morphology, and attenuating chemokine and cytokine responses including up-regulation of SOCS-2 (Leonard *et al.*, 2002). Using a transcriptomic approach to investigate the mechanism underlying the protective action of LXA_4, specific cohorts of genes whose expression was altered in renal IRI and modulated by 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4 were identified (Kieran *et al.*, 2003). Some of these genes included chemoattractants, cytokines, chemokines and chemokine receptors, growth factors and their receptors, adhesion molecules and molecules implicated in maintaining epithelial barrier function such as claudins (Kieran *et al.*, 2003). These data are especially noteworthy given the evidence that LXA_4 regulates transepithelial resistance in bronchial epithelia by a mechanism that includes up-regulation of claudin expression. It has been proposed that defective LX biosynthesis in cystic fibrosis (Karp *et al.*, 2004) and asthma (Levy, 2005) could contribute to compromised epithelial barrier function (Grumbach *et al.*, 2009). *In vivo* models of peritonitis have frequently been used to highlight anti-PMN trafficking effects of LX analogues (O'Sullivan *et al.*, 2007). Interestingly, a recent report demonstrated the effect of ajulemic acid (AjA), a synthetic cannabinoid, on enhanced LXA_4 production, an effect attributed to the observed reduction in peritoneal infiltration in a mouse model where AjA treatment before zymosan-induced peritonitis was associated with LO-dependent LX generation (Zurier *et al.*, 2009).

A second generation of LX/ATL analogues was designed to subvert metabolism by β-oxidation through insertion of a 3-oxa group and to have improved chemical stability (Guilford *et al.*, 2004). The changes resulted in significantly enhanced stability and plasma half-life, maintaining similar biological activity with a better pharmacokinetic profile over the 15-epi analogue (Fiorucci *et al.*, 2004; Guilford *et al.*, 2004; Levy *et al.*, 2007). The potent anti-inflammatory and protective actions of LXs in intestinal inflammation make them an attractive candidate as a potential therapy for various inflammatory conditions of the digestive system, including Crohn's disease and ulcerative colitis. Indeed, ATL is protective in intestinal inflammation in a mouse model of dextran sodium sulphate-induced colitis (Gewirtz *et al.*, 2002), and the β-oxidation resistant 3-oxa-ATL (ZK-192) has been shown to potently attenuate trinitrobenzene sulphonic acid (TNBS)-induced colitis, a Crohn's disease model (Fiorucci *et al.*, 2004). When orally administered, ZK-192 reduced TNBS colitis both in preventive and therapeutic regimens, attenuating weight loss, macroscopic and histological colon injury, mucosal neutrophil infiltration, colon wall thickening, as well as decreasing mucosal mRNA levels for several inflammatory mediators (Fiorucci *et al.*, 2004).

In asthma, the ZK-994 LX/ATL analogue (5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluoro-phenoxy)-3-oxa-5,6,15-trihydroxy-7,9,13-hexadecatrien-11-ynoic acid was effective in reducing airway inflammation and airway bronchoconstriction (Levy *et al.*, 2007).

Recently, we have described the activity of new LX analogues that show the substitution of the reactive hexatriene system with an aromatic ring. Beside a capacity to stimulate *in vitro* phagocytosis of apoptotic cells by macrophages, these LX analogues show potent anti-inflammatory activity *in vivo* (O'Sullivan *et al.*, 2007). We used an *in vivo* model of mouse peritonitis, and examined neutrophil trafficking to the peritoneal cavity in response to zymosan A challenge. When administered intravenously, (1R)-3a inhibited the acute inflammatory cell recruitment into mouse peritoneum.

Summary

The successful resolution of inflammation is an integral component of effective host defence. The various steps of resolution are regulated by endogenous mediators and by clearance of apoptotic cells by phagocytes. In this context, LXs are a class of lipid mediators that serve as local endogenous anti-inflammatory and pro-resolution signals. The potential therapeutic applications of LXs and their stable synthetic analogues are significant; it will be of interest to learn whether these or related agonists of resolution can be exploited in a therapeutic context to ensure the effective restoration of tissue homeostasis and prevention of fibrosis subsequent to an inflammatory response.

Acknowledgements

Work in the authors' laboratory is supported by the Science Foundation Ireland, EU FP6 Eicosanox Programme LSHM-CT-2004-005033 and The Government of Ireland Programme for Research in Third Level Institutions.

Note added in proof

During the final revision of this manuscript a new nomenclature for the FPR family of receptors was recommended by the International Union of Basic and Clinical Pharmacology LXXIII. On the basis of this classification, LXA4 is defined as an endogenous ligand for FPR2/ALX, instead of the previously used nomenclature of FPRL1/ALXR as used in this review (Ye *et al.*, 2009).

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