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**Lipoxins: regulators of resolution**

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**Telephone 353-1-716-6731 Abstract**

Persistent inflammation underlies many of the most prevalent diseases in the developed world including atherosclerosis and diabetes. There is a growing appreciation that inflammation and its active resolution may be modulated by endogenously produced lipids [1]. Preeminent amongst these mediators are the lipoxins [LX]. The acronym lipoxins describes the provenance of these mediators: lipoxygenase interacting products. The LX are eicosanoids and display both anti-inflammatory and pro-resolving bioactions [2]. More recently other pro-resolving lipid mediators have been described including the resolvins and neuroprotectins [3]. In effective host defence LX biosynthesis is characterised by a switch from pro-inflammatory prostaglandin and leukotriene (LT) generation from arachidonic acid (AA) to LX production coincident with a return to tissue homeostasis. Here we will provide an overview of LX pharmacokinetics, bioactions and summarise the evidence to date that indicates that LX are potential therapeutic agents for disorders involving cardiovascular and renal inflammation, leading to tissue damage and organ fibrosis.

#### **LX: synthesis, metabolism and cellular targets**

LX are typically formed by transcellular metabolism of arachidonate involving sequential lipoxygenase [LO] activity within an inflammatory milieu. Epithelial-monocyte 15 LO activity produces 15(S)hydroperoxyeicosatetraenoic acid from AA which can then be converted by neutrophil 5-LO to generate LXA<sub>4</sub> [5S,6R,15S-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid] [2]. Production of LXA<sub>4</sub> by this pathway diverts metabolism of AA from biosynthesis of proinflammatory leukotrienes. LXA<sub>4</sub> can also be generated by the actions of platelet 12-LO to convert the 5-LO epoxide product LTA<sub>4</sub> to LXA<sub>4</sub> and its positional isomer LXB<sub>4</sub> [2]. Aspirin acetylation of COX-2 in endothelial and epithelial cells inhibits the formation of prostaglandins and thromboxanes whilst shifting its enzymatic activity towards the generation of 15R-HETE which is converted by leukocyte 5LO to generate 15-epi-LX, designated aspirin-triggered LX i.e. ATL (See figure 1) [2]. Other potential sources of LX synthesis are linked to storage of precursors in membranes of inflammatory cells that may be released at the site of injury [4].

LXA<sub>4</sub> binds with high affinity to at least one G-protein coupled receptor (GPCR) that has been cloned, characterised and designated ALX/FPR2 receptor [5]. This receptor is part of the formyl peptide receptor superfamily. A specific LX recognition site was initially established in human polymorphonuclear neutrophils (PMN), however further experiments have demonstrated that this receptor is expressed in cells of diverse lineages including myeloid, epithelial and mesenchymal cells [6]. In addition to binding LXA<sub>4</sub> with high affinity [subnanomolar K<sub>d</sub>] the ALX /FPR2 binds several other agonists including lipids and peptides with different affinities resulting in activation of distinct signalling pathways that depend on the cell type and system. A detailed review of the characterisation of this receptor has recently been published and recommends the nomenclature ALX/FPR2 in lieu of the previous ALXR and fPRL-1 designations [5]. Recent data highlight an additional 'pro-resolving' GPCR activated by both LXA<sub>4</sub> and Resolvin D1 i.e. GPR32 [7]. Although the exact signalling mechanisms involved in LX bioactions remain to be fully elucidated the cellular targets and effects in both in vitro and in vivo models continues to grow. The partial antagonism of a subclass of peptide receptors (CysLTs) is a potential mechanism through which LXs may contribute to the anti-inflammatory actions of LX in several tissues other than leukocytes [8,9]. Further studies show that LX and ATL inhibit proliferation induced by growth factors such as PDGF [9], EGF [10], CTGF [11] and VEGF [12,13] with a mechanism that involves cross talk between ALX/FPR2 and receptor tyrosine kinases. Another potential receptor for LX is the ligand activated transcription factor aryl hydrocarbon receptor (AhR), with both innate and acquired immune responses in dendritic cells being modulated through AhR and ALX/FPR2 activation [14]. It is noteworthy that the concentration of LXA<sub>4</sub> that elicit these responses is much higher than that associated with ALX/FPR2 mediated responses. LX are rapidly generated in response to stimulation, act in an autocrine or paracrine manner and undergo rapid metabolic inactivation. It has been shown that both LXA<sub>4</sub> and LXB<sub>4</sub> are degraded via dehydrogenation at C-15 [18] and possibly ω-oxidation at C-20. ATLs are converted to their 15-oxometabolite with a slower rate compared to native LX indicating the specificity of the hydrogenation step [2].

LX have been shown to act as anti-inflammatory agents in numerous models of disease. Initial observations focused on inhibition of PMN trafficking reflecting inhibition of both PMN and endothelial cell activation. However over the past decade or so it has become apparent that LX exert potent proinflammatory actions on numerous cell types to inhibit pro-inflammatory cytokine production, metalloproteinase activity, epithelial integrity and neuropathic pain in various models of disease [reviewed in 3]. Indeed in several human diseases the balance between LX and LTs is skewed [3]. Whereas LX inhibit PMN function they activate monocytes/macrophages in a reparative, pro-resolution context as highlighted below [6]. A key step in this field of resolution therapeutics has been the development of analogues that are less susceptible to metabolic inactivation, maintain structural integrity and beneficial actions of LX and ATL. Recent advances have enabled highly efficient stereoselective biosynthesis of several novel analogues that mimic the bioactions of endogenously generated LX and ATL. These include benzo [15-17] and pyridine-LX

analogues[18] .

### **LX : endothelial dysfunction and atherosclerosis**

Studies from both animal models and humans have implicated a significant inflammatory component to the pathogenesis of atherosclerosis [19]. Advanced complicated atheromatous plaques that set the stage for overt clinical events in atherosclerosis are preceded by less complex lesions. Atherosclerosis is triggered by the retention of apolipoprotein B-containing lipoproteins in the subendothelial wall which triggers a chronic inflammatory response. The earliest lesions are defined by an increase in intimal macrophages and grossly visible fatty streaks, that may progress to advanced atheromata or disappear. The factors that enable some lesions to progress while others regress remain unclear however, more complicated lesions develop all the hallmarks of defective resolution of inflammation, including impaired apoptosis and egress of inflammatory cells [20,21]. Endothelial dysfunction is the common link between cardiovascular disease risk factors and the earliest event in the cascade of incidents that results in atherosclerosis. When endothelial cells (ECs) undergo inflammatory activation, an increase in the expression of adhesion molecules such as selectins, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) promotes the adhesion and recruitment of inflammatory cells such as monocytes, neutrophils, lymphocytes and macrophages which leads to increased local production of cytokines, growth factors and matrix metalloproteinases (MMPs).

LX have a number of direct actions on endothelial cells that are protective and, consistent with their role in resolution, may modulate endothelial dysfunction. LX stimulates prostacyclin [2] and nitric oxide (generation by endothelial cells [22] . A key aspect of the anti-inflammatory properties of aspirin have been attributed to ATL induction of heme oxygenase-1 (HO-1) and NO generation[22,23]. Restoring the balance in endothelial dysfunction may help limit adverse effects in vascular tone, reducing local oxidative stress and limiting vessel wall inflammation by reducing adhesion molecule and chemokine expression. Furthermore , recent evidence suggest that 15-epiLXA<sub>4</sub> plays a key role in mediating atorvastatin and pioglitazone reduction in vessel wall inflammation [24] limiting infarct size [25]. Statins regulate the production of S-nitrosylated COX-2 which produces 15R-HETE, a precursor of 15-epi-LXA<sub>4</sub>. When COX-2 is both acetylated and S-nitrosylated the enzyme is inactive, thus altering the balance between proresolution LX and proinflammatory leukotrienes ( LTs) and providing potential adverse interactions among statins, thiazolidiones and high dose aspirin [26]. Furthermore in a clinical trial comparing low-dose aspirin with higher doses, ATL levels were significantly higher in the low dose group and inversely proportional to thromboxane-A<sub>2</sub> levels, a marker of platelet activation [27]. Therefore, monitoring ATL levels clinically may represent a method for maximising therapeutic efficacy of aspirin therapy and minimising adverse effects.

Considerable evidence supports the early involvement of the monocyte derived macrophage, the most prominent cellular component of the innate immune system during the development of atherosclerosis. The recruitment of these cells to an activated endothelium leads to maturation of monocytes into macrophages, which lead to local production of many mediators that increase vessel wall inflammation. This activation is associated with the up-regulation of pattern recognition receptors for innate immunity such as the scavenger receptors SR-A and CD36, and the toll-like receptors [28] which internalize a broad range of molecules including the oxidized low density lipoproteins (oxLDL). The consequence is the formation of intracellular cholesterol pools and the development of macrophages into lipid loaded foam cells with associated increased inflammation. Oxidised LDL has also been shown to encourage enhanced production of the inflammatory eicosanoid LTB<sub>4</sub> to an even greater extent than LDL, thus encouraging further vascular inflammation. Hyperlipidaemia elicits a profound enrichment of a proinflammatory subset of monocytes in mouse models of atherosclerosis. These cells are characterised by high levels of Ly6C and may correspond to a human monocyte subset marked by the presence of P-selectin glycoprotein ligand (PSGL)[29]. These data suggest that there is persistent recruitment of inflammatory monocytes that differentiate into proinflammatory macrophages ( M1) in established lesions.

LX are potent stimulators for peripheral blood monocytes and trigger rapid and concentration dependent uptake of apoptotic neutrophils by macrophages [30]. Hence, LX are potent chemo-attractants for monocytes, however, seem not to activate macrophages in the classical way (M1) but rather through the alternative activation pathway to result in a non-phlogistic modified 'reparative' phenotype [30,31]. LX recruited monocytes show features of alternative activation including reduced secretion of the pro-inflammatory cytokines IL-8 and MCP-1 , TGF- $\beta$  release [32] and increased scavenging of resident apoptotic cells.[Interestingly, select peptide ALX/FPR2 agonists also stimulate macrophage phagocytosis of apoptotic PMN [32,33]]. The recruitment of macrophages and their potential programming to a 'reparative' phenotype provides a second mechanism in the resolution of inflammation, because clearance of accumulated apoptotic cells from a locus of inflammation is important for re-establishment of tissue homeostasis [1].Importantly, several novel stable synthetic benzo [15,16,17] and pyridine LX analogues have been

demonstrated to mimic these bioactions of LX and to modify LPS-stimulated cytokine release [18].

Clinical human epidemiological have supported an anti-atherogenic role for 12/15 LO pathways [34,35] and although animal models have yielded some conflicting results there is experimental evidence to show that expression of 12/15-LO and several of its products, specifically LXA<sub>4</sub>, RvD1 (resolvin D1) and PD1 (protectin D1), are potent local acting proresolving mediators that regulate multiple proinflammatory cytokines produced by macrophages. In a mouse model with 12/15 LO  $\alpha$ -/- adding back these specific proresolving lipid mediators down-regulates gene expression of MCP-1, CCL5, TNF- $\alpha$  and IL-6, amongst others believed to play critical roles in controlling local inflammation and the development of atherosclerosis [20]. This was shown by improving endothelial dysfunction, by down regulating adhesion molecules and chemokines that shifts the local balance of inflammatory mediators, producing a proresolution milieu and limiting atherosclerosis development. In summary these findings suggest multiple potential therapeutic mechanisms for LX in modulating the pathogenesis of atherosclerosis ( see figure 2).

### **LX : glomerulonephritis and tubulointerstitial inflammation**

Acute glomerulonephritis represents an important cause of acute kidney injury (AKI) that unresolved may result in chronic kidney disease. The current mainstay therapy for this disease is immunosuppression and long term maintenance treatment is often required with risk of serious adverse effects. LX and ATL offer therapeutic potential, by switching the cellular response from inflammation in favor of resolution, with dissipation of local gradients of proinflammatory mediators. In the concanavalin A-ferritin model of immune complex glomerulonephritis (GN), treatment of rat neutrophils ex vivo with LXA<sub>4</sub> reduces their subsequent trafficking into inflamed glomeruli [ Modulation by LX of key inflammatory mediators such as NF- $\kappa$ B, IL-6 and proliferative pathways such as Akt and Jak-STAT indicate that LX may provide an effective therapy limiting tissue damage arising from inflammation but also modulate the process of renal fibrosis that may follow GN [36,37]. Recent experimental evidence has shown increase in LXA<sub>4</sub> during the resolution phase of acute post-Streptococcal glomerulonephritis [38]. The increased expression was shown not only in leukocytes but also in the glomeruli indicating both a systemic and local proresolution effect. At a cellular level LXA<sub>4</sub> has been shown to modulate the proliferation of mesangial cells induced by cytokines and growth factors that have been implicated not only in GN but also in other disorders such as diabetic nephropathy and in the development of renal fibrosis. LXA<sub>4</sub> has been shown to inhibit mesangial cell proliferation in response to LTD<sub>4</sub> [12,13] and to counteract PDGF-induced fibrosis related gene expression in mesangial cells and renal epithelia [39] suggesting that LXA<sub>4</sub> might act as a potential anti-fibrotic agent preventing growth factor induced matrix production and the progression of renal disease. This is further enhanced by other experimental evidence that shows LXA<sub>4</sub> modulates TNF $\alpha$  induced proliferation, cytokine release as well as CTGF mediated release of fractalkine, MCP-1 and RANTES [40].

AKI following tubular insult is a common cause of renal dysfunction and mortality, arising as a consequence of sepsis, ischaemia or radiocontrast. Therapy for such renal injury is limited, primarily supportive and does not alter the course of the acute renal injury or the increased risk of CKD that follows as a consequence. LX are potential therapeutics in AKI, as they can influence a variety of relevant pathophysiologic functions such as vascular tone, endothelial and epithelial cell injury and cytokine release, and leukocyte recruitment and clearance ( see figure 3) . Altered haemodynamic responses during AKI occur as a consequence of many causes and there is evidence that this endothelial and vasomotor dysfunction may persist [41,42]. We have outlined earlier how LX may improve such endothelial dysfunction, reducing oxidative stress, improving bioavailability of mediators such as NO, HO-1 which play an important role in AKI [43]. With regard to vascular tone LXA<sub>4</sub> opposes the vasoconstrictor properties of LTD<sub>4</sub> and attenuates LTD<sub>4</sub> triggered decrease in renal blood flow and glomerular filtration rate ( GFR) and may correlate inversely with the degree of activation of the renin-angiotensin system and immune mediated effects of angiotensin II [2,3].

The stable lipoxin analogue, 15-epi-16-(FPhO)-LXA<sub>4</sub>-Me, is protective in experimental murine renal reperfusion injury in vivo [44]. Administration of the ATL, prior to ischemia, resulted in significant functional and morphologic protection and attenuated chemokine and cytokine responses. Using a transcriptomic approach to explore the events that underlie this protective effect, we found that treatment with the ATL, prior to injury, modified the expression of many differentially expressed pathogenic mediators, including cytokines, growth factors, adhesion molecules, and proteases [45]. Lipoxin modulated transcriptomic response included many genes expressed by renal parenchymal cells and was not merely reflective of a reduced renal mRNA load by blunted leukocyte recruitment. Of particular interest is the LX induction of SOCS 1 and 2 ( suppressor of cytokines) proteins and KIM-1 expression in this setting. SOCS proteins have been identified as inducible feedback inhibitors of cytokine receptors and have been shown to be of crucial importance for the limitation of inflammatory responses, modulating dendritic cell and macrophage function

[46] and represent an important target for promoting resolution of inflammation. KIM-1 has recently come to prominence as a more reliable biomarker than serum creatinine in both human and animal models of AKI [47]. KIM-1 may not only represent an AKI prognostic marker but also an important target for therapeutic intervention as this glycoprotein also confers on epithelial cells the ability to recognize and phagocytose dead cells that are present in the post-ischaemic kidney and contribute to the obstruction of the tubule lumen that characterizes AKI [48]. The importance of clearing apoptotic debris in promoting resolution of inflammation has been outlined earlier and further exploration of potential LX induction of KIM-1 may have important implications for development of therapeutic s for AKI.

## Conclusions:

There is a growing appreciation of the importance of persistent inflammation in the pathogenesis of many prevalent diseases . The successful resolution of inflammation and return to tissue homeostasis is an important therapeutic goal in diseases such as atherosclerosis and glomerulonephritis, where treatment benefit is often offset by adverse effects. LX are a class of lipid mediator that play key roles in controlling and programming of the acute innate inflammatory response and its resolution. The potential therapeutic applications of LX and their stable analogues as outlined here are significant. Furthermore, given the fact that two of the most widely prescribed drugs worldwide, aspirin and statins, have as a significant part of their mechanism of action the ability to generate endogenous mediators of resolution, it is likely that modulators of inflammatory resolution are likely to have a promising future in drug development.

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## Overview of biosynthesis of LXA<sub>4</sub> and Aspirin-triggered 15-epi LXA<sub>4</sub> [1,2]

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**Figure 2 Potential therapeutic effects of LX in atherosclerosis:** LXA<sub>4</sub> and ATL may modulate multiple targets in atherosclerosis including endothelial dysfunction, monocyte recruitment and differentiation; additionally, LX may also mediate the effects of established therapies including aspirin, statins and thiazolidiones

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**Figure 3 Potential therapeutic impact of LX in renal diseases:** The bioactions of LX and ATL on both stromal and infiltrating cells in kidney disease suggest that they have distinct anti-inflammatory, pro-resolution and anti-fibrotic activities that may be exploited for therapeutic gain and may be subverted in chronic, unresolved renal inflammation. As highlighted in the cartoon above the actions of LX and ATL include modulation of vascular tone and endothelial dysfunction, macrophage

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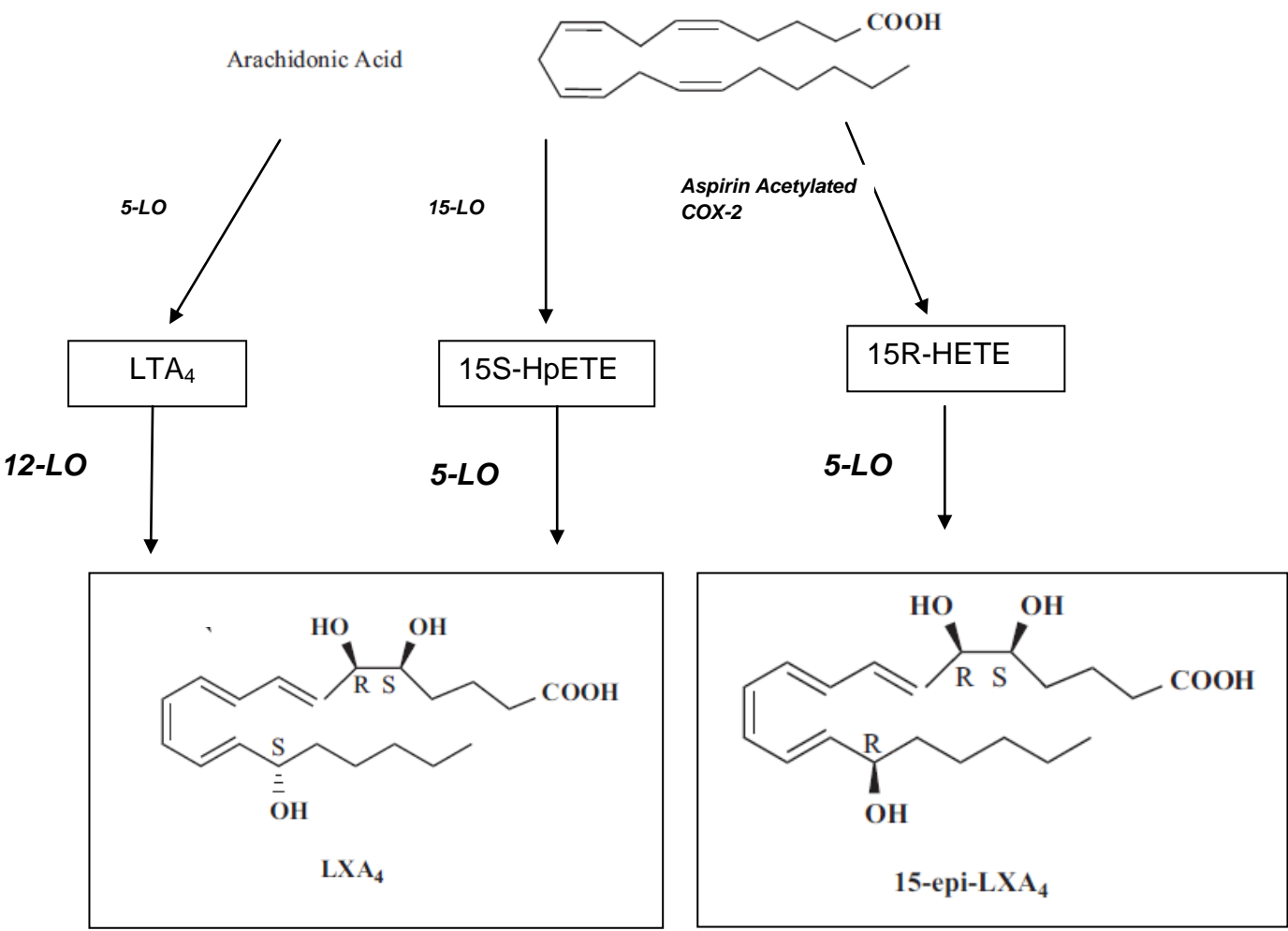
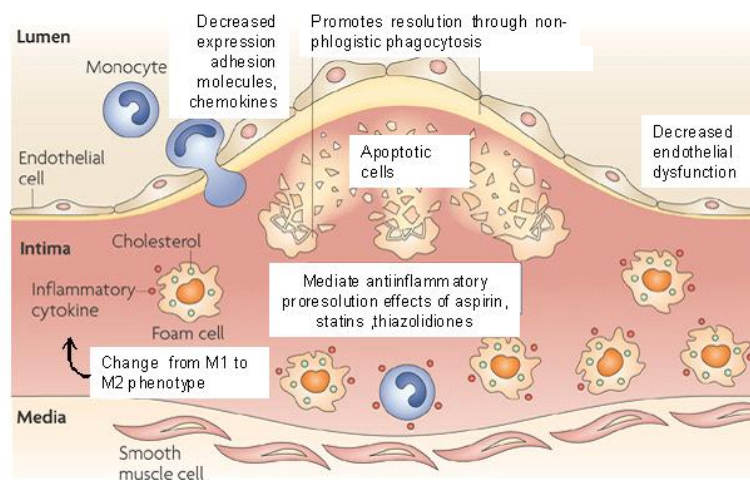


Figure 1: Overview of biosynthesis of LXA<sub>4</sub> and Aspirin-triggered 15-epi LXA<sub>4</sub> [1,2]

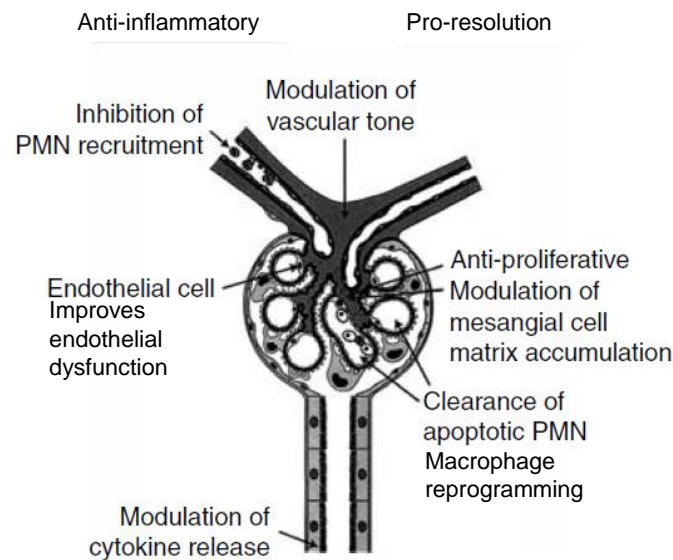


**Figure. 2 Potential therapeutic effects of LX in atherosclerosis**



**Figure 2 Potential therapeutic effects of LX in atherosclerosis:** LXA<sub>4</sub> and ATL may modulate multiple targets in atherosclerosis including endothelial dysfunction, monocyte recruitment and differentiation; additionally. LX may also mediate the effects of established therapies including aspirin, statins and thiazolidiones

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**Figure 3 Potential therapeutic impact of LX in renal diseases:** The bioactions of LX and ATL on both resident and infiltrating cells in kidney disease suggest that they have distinct anti-inflammatory, pro-resolution and anti-fibrotic activities that may be exploited for therapeutic gain. As highlighted in the cartoon above the actions of LX and ATL include modulation of vascular tone and endothelial dysfunction, macrophage reprogramming from proinflammatory to proresolution phenotypes with associated modification of the cytokine milieu. Further effects of relevance include nonphagocytosis of apoptotic cells, modulation of mesangial cell proliferation and maintenance of epithelial integrity.