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Lipoxin-mediated signaling: ALX/FPR2 interaction and beyond

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ABSTRACT

In the aftermath of tissue injury or infection, an efficient resolution mechanism is crucial to allow tissue healing and preserve appropriate organ functioning. Pro-resolving bioactive lipids prevent uncontrolled inflammation and its consequences. Among these mediators, lipoxins were the first described and their pro-resolving actions have been mainly described in immune cells. They exert their actions mostly through formyl-peptide receptor 2 (ALX/FPR2 receptor), a G-protein-coupled receptor whose biological function is tremendously complex, primarily due to its capacity to mediate variable cellular responses. Moreover, lipoxins can also interact with alternative receptors like the cytoplasmic aryl hydrocarbon receptor, the cysteinyl-leukotrienes receptors or GPR32, triggering different intracellular signaling pathways. The available information about this complex response mediated by lipoxins is addressed in this review, going over the different mechanisms used by these molecules to stop the inflammatory reaction and avoid the development of dysregulated and chronic pathologies.

1. Introduction

Resolution of inflammation ensues from an acute response to halt the inflammatory reaction and prevent excessive tissue damage and chronic inflammation once the initial danger signal is suppressed [1,2]. An efficient resolution mechanism is crucial for tissue healing and preserving appropriate organ functioning. The resolution process was initially thought to be a passive process until Serhan et al. first discovered in 1984 a series of molecules that actively inhibited leukocyte recruitment [3]. This shifted the paradigm and proved that resolution is indeed an active process where specific mediators are deliberately produced to control the clearance of the inflammatory signals by multiple complementary mechanisms [4,5]. Since then, a wide range of molecules involved in this process has been identified, including proteins and peptides (annexin A1, galectin-1), nucleosides (adenosine), and bioactive lipids [6]. These molecules have been demonstrated to prevent uncontrolled inflammation and its consequences by modulating processes other than inflammatory signaling, such as promoting tissue remodeling and regeneration or improving the antioxidant response, playing a relevant role in cardiovascular and neural tissues (for review see [7–9]). Among these mediators, pro-resolving bioactive lipids represent the largest family of this group and are commonly named "Specialized Pro-resolving Mediators" (SPMs).

1.1. Specialized pro-resolving mediators

SPMs derive from essential omega-3 and omega-6 fatty acid oxidation and are produced mainly by the action of 5-, 12- and/or 15-lipoxygenases (ALOX) by transcellular biosynthesis (Fig. 1) [4]. Since ALOX are shared enzymes for the synthesis of both inflammatory (i.e.

Abbreviations: Aβ42, β-Amyloid (1−42); AhR, aryl hydrocarbon receptor; AKT, serine/threonine kinase; ALX, Lipoxin A receptor; AnxA1, annexin A1; ARNT, AhR nuclear translocator; ATL, aspirin-triggered lipoxin; COX, cyclooxygenase; CysLT, cysteine-leukotriene; ERK, extracellular signal-regulated kinase; EC_{50}, half maximal effective concentration; FPR1, formyl-peptide receptor 1; FPR2, formyl-peptide receptor 2; GPCR, G-protein coupled receptor; GPR32, G-protein-coupled receptor 32; IFN-γ, interferon γ; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-22, interleukin 22; ALOX, lipoxygenase; LTA4, leukotriene A4; LXs, lipoxins; LXA_4, lipoxin A_4, LXB_4, lipoxin B_4; Mars, maresins; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NSAID, non-steroidal anti-inflammatory drugs; PGDH, prostaglandin dehydrogenase; PKA, protein kinase A; SAA, serum amyloid A; SPMs, specialized pro-resolving mediators; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TGF-β, Transforming growth factor β; TNF-α, Tumor necrosis factor alpha; Rvs, resolvins.

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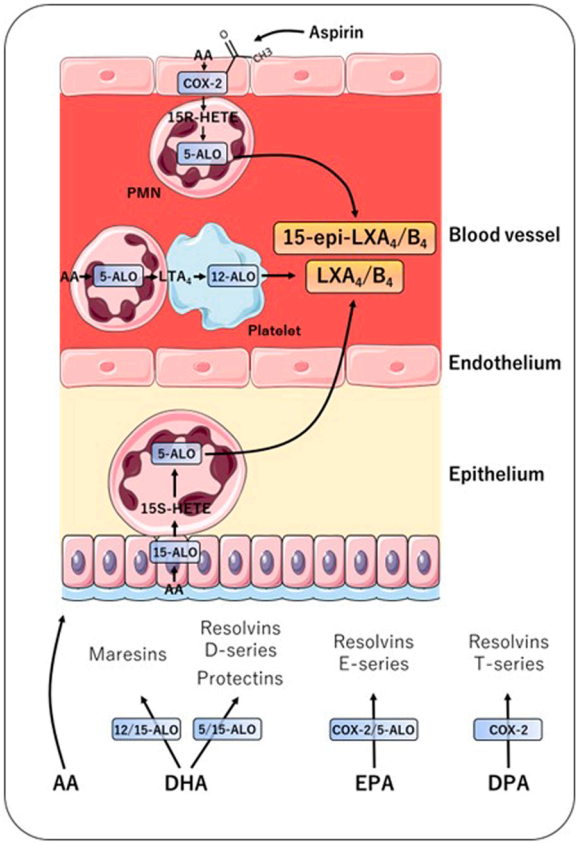

Fig. 1. Outline of the main routes for the biosynthesis of SPMs. SPMs can be synthesized from 4 different precursors: docosahexaenoic acid (DHA) can be converted into maresins through 12- and 15-ALO or into D-series resolvins or protectins through 5- and 15-ALO. Moreover, eicosapentaenoic acid (EPA) can be used by COX-2 and 5-ALO to yield E-series resolvins and docosapentaenoic acid (DPA) generates T-series resolvins through COX-2. For the synthesis of lipoxins, arachidonic acid (AA) is used in the three different biosynthetic pathways. In blood vessels, PMNs interact with endothelial cells to produce lipoxin, in a process known as transcellular biosynthesis. AA is taken up by the endothelium and transformed into 15-R HETE by COX-2. This process is enhanced by COX-2 acetylation, which can be mediated by aspirin. 15R-HETE then goes to the PMN cell, where it is converted into 15-epi-lipoxin A4/B4 by 5-ALO. PMNs can also convert AA into LTA4 through 5-ALO. After that, LTA4 is carried out to platelets to end up its transformation into LXA4/B4, which is mediated by 12-ALO. Finally, PMNs can also interact with epithelial cells, where AA is transformed into 15S-HETE. This intermediate goes into the PMN, where 5-ALO converts it into lipoxin A4/B4. Parts of this figure were drawn using pictures from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 unported license.

leukotrienes) and pro-resolving molecules, transcellular biosynthesis provides a mechanism to rapidly shift the production of pro-inflammatory lipid mediators to SPMs mainly based on the inflammatory context. Depending on the biosynthetic route, which is defined by the precursor molecule and the lipoxygenase isoform involved, SPMs are classified into four types: lipoxins (LXs) [10], resolvins (Rvs) [11], protectins (PDs) [12] and maresins (Mars) [13]. Each type of SPM exerts complementary pro-resolving effects and interacts with distinct receptors, thus modulating different cell types and signaling pathways [14,15]. Among all SPMs, lipoxins are the best-known pro-resolving compounds with a key role in numerous pathophysiological processes and will be the main focus of this review.

1.1.1. Lipoxins

LXs were the first SPM described and are the only known SPM synthesized from arachidonic acid (an omega-6 fatty acid) [16]. LXs can be found in four forms: LXA_4 and LXB_4, named native LXs, and their epimers 15-epi-LXA_4 and 15-epi-LXB_4, also called aspirin-triggered LXs (ATLs) [17,18]. While native LXs are produced by 5-, 12- and/or 15-LOX, ATLs are generated by acetylated cyclooxygenase-2 (COX-2), whose acetylation is primarily mediated by aspirin [19]. Some studies have suggested that other post-translational modifications of COX-2, such as statin-induced S-nitrosylation [20] or even cytochrome P450 hydroxylation, can also execute this initial step and produce ATLs, indicating that these enzymes could contribute to resolution in specific inflammatory environments [21].

As bioactive autacoids, LXs effects are intended to be local and transitory; therefore, they undergo rapid inactivation via C15 oxidation and C13-C14 reduction mainly by 15-prostaglandin dehydrogenase (15-PGDH) [22]. Since 15-PGDH action is stereospecific, ATLs are degraded at approximately 50% of the conversion rate of native LXs, hence exhibiting an increased half-life [23]. However, LXs can also be inactivated by cytochrome P450 ω-hydroxylases [24] and are pH- and light-sensitive [25]. For these reasons, synthetic LXs analogs have been designed by chemically modifying the original molecule to further boost their action and prevent rapid decomposition [26].

LXs and their analogs elicit their actions mainly by binding to ALX receptor, also known as formyl peptide receptor 2 (ALX/FPR2) or formyl peptide receptor-like 1 (FPRL1), whose structure has been recently described [27,28]. ALX/FPR2 is a G protein-coupled receptor (GPCR) that is expressed in the surface of numerous cell types like immune cells (i.e., neutrophils [29], monocytes/macrophages [30]) and other specialized cells like enterocytes [31] and fibroblasts [32,33]. Although it was thought that the majority of LXs actions were mediated by their specific interaction with ALX/FPR2, in the last years it has become evident that LXs can also activate other receptors, like aryl hydrocarbon (AhR), cysteine-leukotriene (CysLT) and G-protein-coupled receptor 32 (GPR32) triggering alternative molecular signaling pathways. Due to the limited information available related to the involvement of these receptors in the resolution of the inflammatory response, this topic is currently attracting the interest of numerous research groups. Indeed, a better understanding of the molecular mechanisms and signaling pathways modulated by native SPMs as endogenous mediators remains of paramount importance to design more effective approaches to fight inflammation from within.

2. Lipoxin receptors

2.1. ALX/FPR2

The lipoxin receptor known as ALX/FPR2 belongs to the largest and most functionally diverse family of G-protein-coupled receptors and its biological function is complex, mainly due to its capacity to mediate variable cellular responses [34]. Firstly, it is considered a “promiscuous” receptor because it can bind different ligands, triggering opposite responses [35]. Thus, whereas molecules like serum amyloid A (SAA) or amyloid beta 42 (Aβ42) bind to ALX/FPR2 as pro-inflammatory signals, annexin A1 (AnxA1), resolvin D1 and LXs and their analogs elicit anti-inflammatory and pro-resolving responses [34]. Moreover, FPR2 activates both pro- and anti-inflammatory signal transduction pathways also in a cell-background-specific manner, such that the same ligand may promote seemingly opposing functional outcomes in different cell types [9,36–38]. One example of this is the proatherogenic activity of ALX/FPR2 observed in animal models deficient in the LDL receptor and in human carotid atherosclerotic lesions. The presence of FPR2 increases atherogenesis but, at the same time, promotes plaque stability [39]. The underlying mechanisms of these diversities in the control of inflammation remain to be fully elucidated and may depend on the ALX/FPR2 conformation. In fact, this receptor can trigger cell responses as a monomeric unit, or it can also undergo dimerization (making homodimers or heterodimers with FPR1) leading to alternative intracellular signaling (Fig. 2). Interestingly, the binding of LXs to the ALX/FPR2

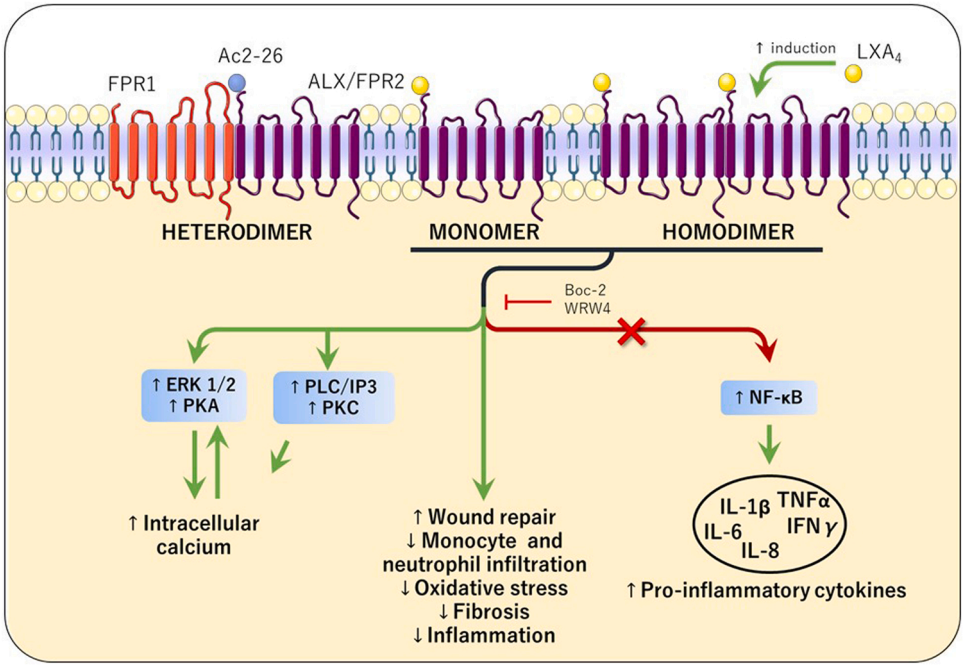

Fig. 2. Main anti-inflammatory and pro-resolving effects induced by LXA_4 through ALX/FPR2 receptor. FPR2 can exist in a monomeric stage but it can also dimerize, triggering different intracellular signaling. LXs promote FPR2 homodimerization, driving a pro-resolving signaling mainly mediated by the inhibition of NF-kB-related pro-inflammatory response, the modulation of intracellular calcium influx through PLC and PKA and the induction of several beneficial effects. These effects can be inhibited by Boc-2 or WRW4, antagonists of FPR2. FPR2/ALX can also form heterodimers with FPR1, which has been observed to be involved in pro-inflammatory responses, modulated by mediators such as the peptide Ac2–26. Parts of this figure were drawn using pictures from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 unported license.

receptor promotes its homodimerization driving to anti-inflammatory response while other mediators like the Ac2–26 peptide (the N-terminal domain of annexin A1, which recapitulates the full activity of the protein), induce heterodimerization with FPR1, resulting in the opposite response [40,41]. Interestingly, it has been described that FPR1 activation in intestinal epithelial cells by Ac2–26 promotes wound repair of the intestinal mucosa [42].

Among all the known endogenous ligands for ALX/FPR2, LXs show one of the highest binding affinities (Kd ~ 0.8 nM) [43]. Furthermore, ALX/FPR2 expression is increased by the activation of its promoter by LXA_4 in a positive feedback manner [44], and by glucocorticoids [45]. Different inhibitors have been used over the years to discern the functions of this receptor. The peptide t-Boc–FLFLF (Boc-2) has been broadly used for this purpose. However, Boc-2 has been shown to be non-specific for ALX/FPR2 as it more efficiently inhibits FPR1 [46]. In this sense, WRWWWW (WRW4) was discovered to block ALX/FPR2 in a more specific manner [47], and its use has increased over time, becoming the most commonly used antagonist in recent years [48,49]. Additionally, *Fpr2/3* knockout (the ortholog of the human ALX/FPR2 receptor) and RNA silencing models have been developed. Thus, it has been described that in a mouse model of ischemia/reperfusion LXs biosynthesis is compromised in *Fpr2/3* null mice (the murine homologues that recapitulate human *FPR2*) [50]. However, authors observed LX synthesis was increased Fpr2/3 + /+ mice during reperfusion phase, which was likely derived from transcellular biosynthesis occurring in platelet/neutrophil aggregates helping to reduce the inflammatory environment from the ischemic insult. Furthermore, other groups have shown that these mice failed to respond to aspirin-induced 15-epi-LXA_4 upregulation and exogenous LXA_4 administration [51]. Most of these studies completely abolished LXs effects, hence the importance of ALX/FPR2 in their signaling is highlighted. Accordingly, it is known that the interaction of LXs with ALX/FPR2 modulates many critical intracellular functions including cell migration, proliferation, differentiation, apoptosis, intracellular communication, and cell survival, with particular importance in immune cell activity [52]. It is important to emphasize that all the described ALX/FPR2-mediated LXs effects are pro-resolving, although the specific molecular signaling can be different depending on the cellular context.

The most relevant and widely described pro-resolving effect of LXs is mediated by NF-κB inhibition, resulting in a lesser release of pro-inflammatory cytokines. This effect has been demonstrated in several cell types and it is mainly mediated by ALX/FPR2, contributing to resolving inflammation in different contexts. Thus, LXs or their analogs have been shown to inhibit NF-κB activation in dental pulp fibroblasts [53], hepatic stellate cells [54] and macrophages [55] or microglial cells [56,57] among other cell types. In macrophages, this inhibition induces a cytokine imbalance, driving macrophage polarization toward an M2-like pro-resolving phenotype [58]. Something similar occurred in microglial cells, where LXA_4 exerted its neuroprotective effects inducing the polarization of these immune cells to a "M2-phenotype" in a rat model of cerebral ischemia-reperfusion injury through the Notch signaling pathway [59]. Indeed, many groups have also investigated the effects of this reduction of pro-inflammatory cytokines expression and secretion induced by LXs-ALX/FPR2 signaling in different cell types, showing beneficial effects that support the LXs pro-resolving action. In this sense, it has been described that both IL-6 and IL-1β were down-regulated by LXA_4 in a rat model of subarachnoid hemorrhage, improving neurological functions [60] and that LXA_4 can also modulate TNF-α release and microglia activation through FPR2 receptors reducing neuropathic pain in a murine model of spinal cord hemisection [61]. Furthermore, LXA_4 and some LXs analogs can reverse the progression of diabetic kidney disease in murine models and the inflammatory and profibrogenic onset in cultured human renal epithelial cells [62,63]. Similar effects were observed in a rat model of diabetic nephropathy, where LXA_4 reduced the expression of TNF-α, IL-6, IL-8 and IFN-γ, and ameliorated the fibrosis in the kidney through the TGF-β/Smad pathway and ALX/FPR2 [64]. In addition, in mice infected with *Aspergillus fumigatus*, LXA_4 inhibited the expression of IL-1β, IL-6 and TNF-α along

with a reduction in oxidative stress [65].

Other anti-inflammatory effects attributed to LXs are the modulation of the survival and migratory capacity of immune cells. Therefore, the influence of these SPMs on cell fate is highly dependent on the cell type, but also on the timing of the inflammatory reaction. In fact, many groups have shown that LXs can modulate the survival/death balance differentially to promote resolution. For example, it is known that once the damaging agent has been removed, LXs act as pro-apoptotic inducers in neutrophils [66], but as anti-apoptotic mediators in macrophages [67], allowing the clearance of the affected area. Moreover, LXs also play an important role in reducing the infiltration of additional immune cells and ALX/FPR2 also mediates this LX-dependent response, limiting neutrophil [60,68–70] and monocyte infiltration [71,72]. Indeed, reduction of cell recruitment was impaired in ALX/FPR2$^{-/-}$ mice [73]. Interestingly, LXA_4 can also inhibit the migration of non-immune cells like HeLa, through ALX/FPR2 and NF-κB [74]. However, it has been demonstrated that, in undifferentiated cells, ALX/FPR2-mediated LXA_4 signaling has a pro-migratory effect, which is accompanied by an increase in proliferation and an improved wound repair, as shown in human periodontal ligament stem cells [75] and stem cells of the apical papilla [76]. This dual role is still under study and can be mainly relevant in the oncological context. The cell migratory capacity is also directly related to the modulation of intracellular ion currents (mainly calcium), which can be, in turn, regulated by ALX/FPR2. Thus, an increase in intracellular calcium concentration ($[Ca^{2+}]_i$) mediated by LXs has been described in human immune cells like peripheral blood monocytes [36] and neutrophils [77], contributing to regulating their chemotactic migration (for a review, see ref 31). Furthermore, this effect has been also described in non-immune cells such as cardiac cells [78] or rat conjunctival globet cells [79] where it appears to be mediated by different kinases depending on the cellular system, like ERK1/2 in human conjunctival globet cells [80] or PKA in human airway epithelial cells [81,82]. However, although LXA_4-dependent Ca^{2+} mobilization has been described in many cell types, there are cells respond to LXA_4 (reduction of inflammatory markers) that do not include this increase in intracellular Ca^{2+} in their mechanism of response. An example of these is the human astrocytoma cell line 1321N1 [83]. Interestingly, in addition to calcium, LXs appear to be also able to modulate other ion fluxes. For example, in a murine model of cystic fibrosis, LXA_4 has been shown to inhibit airway epithelial Na^+ absorption and increase whole-cell Cl^- currents, increasing the airway surface liquid height and improving lung functionality [82,84].

The pro-resolving action triggered by LXs-ALX/FPR2 interaction is particularly significant in those diseases with a chronic inflammatory background. Most studies have focused predominantly on the beneficial role of LXs in multiple pathological models such as asthma, endometriosis, periodontitis and even neurological and cardiovascular disorders. Asthma is one of the most studied diseases regarding LXs and ALX/FPR2 [85–87]. Indeed, the levels of ALX/FPR2 and LXs were shown to be downregulated in the peripheral blood of patients with severe asthma compared with healthy volunteers [88] and in asthmatic children [89]. In mice models of acute lung injury (ALI), 15-epi-LXA_4 inhibited platelet aggregation [90] and reduced pulmonary edema [91], ameliorating lung injury. Both groups used ALX/FPR2 inhibitors to confirm that the effects were mediated by ALX/FPR2. Accordingly, in radiation-induced lung injury, LXA_4 ameliorated lung damage, fibrosis and inflammation through ALX/FPR2 [92]. Interestingly, a recent study suggested that ALX/FPR2-mediated LXA_4 promotion of resolution in acute distress respiratory syndrome could be regulated by IFN-β [93].

All the described effects reinforce the idea that LXA_4 signaling through ALX/FPR2 is extremely beneficial. However, inhibiting the inflammatory response in the early phases or promoting a premature resolution could be counterproductive. A balanced acute response is needed to address the challenge caused by the inflammatory process.

2.2. AhR receptor

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor of the basic Helix-Loop-Helix (bHLH)-PAS (Per-Arnt-Sim) superfamily. AhR was initially recognized as the mediator of the toxicity of some environmental contaminants such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), dibenzofurans, and related halogenated biphenyls [94,95]. Upon ligand binding, AhR translocates into the nucleus and dimerizes with the AhR nuclear translocator (ARNT); the heterodimer then binds to dioxin-response elements (DREs) located in the promoter region of receptor-regulated genes, such as *Cyp1a1*, *Cyp1a2, Cyp1b1, Cyp2s1*, A*hr*, *Nqo1* and *Gstta1*. Most of these genes are involved in xenobiotic metabolism, leading to a wide variety of toxic responses which are associated with persistent and unmodulated activation of the AhR pathway [96,97]. Strong evidence supports that modulated activation of the AhR pathway has important functions in normal physiology. Furthermore, different studies have shown the existence of endogenous AhR ligands that have been related to vascular and cardiac homeostasis [98], the function of the immune system [99], and the development of tumors [100]. In this line, Schaldach et al. [101] reported that LXA_4, is a potential ligand for AhR. In this seminal paper, they demonstrated that LXA_4 was able to induce a concentration-dependent response in a DRE-driven CAT reporter construct, to transform AhR into an active DRE-binding form, and to activate the transcription of the associated gene *Cyp1a1*. Furthermore, AhR competitive binding experiments allowed them to prove that 100 nM LXA_4 produced a half-maximal (EC_{50}) displacement of TCDD binding. It was well known that the cytochrome P450 family of enzymes metabolize arachidonic acid [102] and since CYP1A1 expression is regulated by the activated AhR, they proposed that the metabolism of LXA_4 might be autoregulated by this system. Chronic ozone exposure has also been postulated to induce LXA_4 production, which activates AhR and controls lung inflammation by reducing IL-22 expression [103]. More recently, LXA_4 has been proposed to promote the resolution of the inflammatory response by activating autophagy via the AhR/mTOR/AKT pathway [104]. Therefore, at present, although there is an experimental basis to sustain that LXA_4 can activate AhR, there is very little information on the physiological role of AhR activation in the anti-inflammatory effects mediated by this SPM.

2.3. CysLT1

Cysteinyl-leukotrienes (CysLTs) are a family of inflammatory lipid mediators generated by a variety of cells, such as basophils, eosinophils, mast cells, and macrophages [105]. CysLTs are synthetized from arachidonic acid, which produces leukotriene-A4 (LTA4) through 5-LOX. LTA4 interacts with glutathione leading to CysLTs formation, which acts on different receptor subtypes: CysLT1, 2 and 3 [106]. At the pathophysiological level, the CysLT1 receptor has been mainly related to respiratory problems [107]; by promoting bronchoconstriction and altering vascular permeability and mucus production.

Both CysLTs and LXs are lipid mediators that control inflammation, playing opposite roles. Related to their crosstalk, some authors have suggested that LXs can bind to CysLT1 receptor [108,109]. Interestingly, it has also been demonstrated that LXs can compete with CysLTs, acting as high-affinity antagonists on the CysLT1 receptor, thus contributing to solving inflammation [110]. Furthermore, reduced plasmatic LXs levels have been related to a worse prognosis, mainly in patients with respiratory diseases. Thus, patients with acute respiratory distress syndrome (ARDS) showed lower plasma levels of LXA_4 and other pro-resolving mediators, which were associated with an increased duration of ventilatory support and a longer stay at the intensive care unit [111]. Complementary, a relevant tendency for augmented circulatory CysLTs levels and increased CysLTs/LXA_4 ratio were found in non-survivors. Other studies have revealed that subjects with severe asthma showed decreased LXA_4 blood levels compared with individuals with moderate

asthma [112]. These changes were accompanied by increased levels of CysLTs in these samples from severe patients. Altogether, these data indicate that a significant imbalance in LXs/CysLTs production could be behind the worsening in pulmonary disease-affected patients.

Interestingly, another line of research has focused on comparing the anti-inflammatory effect of LXs analogs with the effects of the CysLTs receptor antagonist Montelukast. In this regard, Levy et al. used allergen-driven rodent models of inflammation to demonstrate that different LXs analogs reduced leukocyte lung trafficking to a higher degree than comparable doses of the CysLT1 receptor antagonist [113].

Altogether, these evidences uncover the relevance of the crosslink of LXs and CysLTs in their pathophysiological effects. It is mandatory to determine whether the balance of both lipid mediators can effectively modulate the resulting inflammatory response deepening into the molecular signaling driven for both lipids through CysLT1 receptor.

2.4. GPR32

GPR32 is a G-coupled receptor first identified by Krishnamoorthy et al. [114]. It is mostly expressed in immune cells including monocytes, leukocytes [114] and T lymphocytes [115] and in other cell types like immune and endothelial cells in the skin [116]. Although their ligands were initially thought to be primarily D- and E-series resolvins, LXA_4 has also been described to interact with this receptor and to transduce a pro-resolving signaling cascade [114].

Importantly, a murine homolog to human GPR32 has not been identified so far. This suggests that the pro-resolving actions observed by LXA_4 in experimental murine models are primarily attributed to ALX/FPR2 [114,117]. For these reasons, little is known about lipoxin-mediated effects via GPR32. Experimental models in human cell types hint that GPR32 signaling may contribute to LXs effects and resolution in humans. In this sense, Prevete et al. [118] found that FPR1 deletion or inhibition in gastric cancer cells induced a pro-angiogenic phenotype. This absence of FPR1 activity reduced 5- and 15-ALOX levels and decreased SPMs biosynthesis. Interestingly, GPR32 deletion in these cells also upregulated pro-angiogenic pathways similarly to FPR1 deletion, indicating that this receptor may be key to certain repair processes [118]. Furthermore, they observed that FPR1 deletion significantly decreased the secretion of several SPMs, including LXB_4 and RvD1, indicating that impaired resolution may explain the pro-inflammatory phenotype observed in *FPR1*$^{-/-}$ gastric cancer cells. However, whether LXs synthesis may also be reduced upon GPR32 deletion remains unknown and would be of high interest to elucidate this GPR32/LXs interplay.

In summary, GPR32 represents an interesting target for LXs action along with its other receptors, altogether making a cluster of resolution receptors [114] that synergize to promote resolution upon ligand interaction [18]. Elucidating the role of LXs in this context would help to discern the specific signaling and responses associated with each receptor and thus provide further information on the therapeutic potential of LXs for different pathologies [7].

3. Concluding remarks

We provide here an overview of the lipoxin pro-resolving actions specifically mediated by the different receptors with which they interact, clarifying the complexities of intracellular signaling mainly downstream FPR2 activation. We also review recent advances in other lipoxin-interacting receptors, including their potential role in the protective function of this SPM (Fig. 3). Although the knowledge about the signaling driven by FPR2 has improved in the last years, much remains to be done to improve our understanding of the implications of the other receptors in the final effect of this SPM. The answer to all these questions will undoubtedly help us to realize the complexity of the pro-resolving

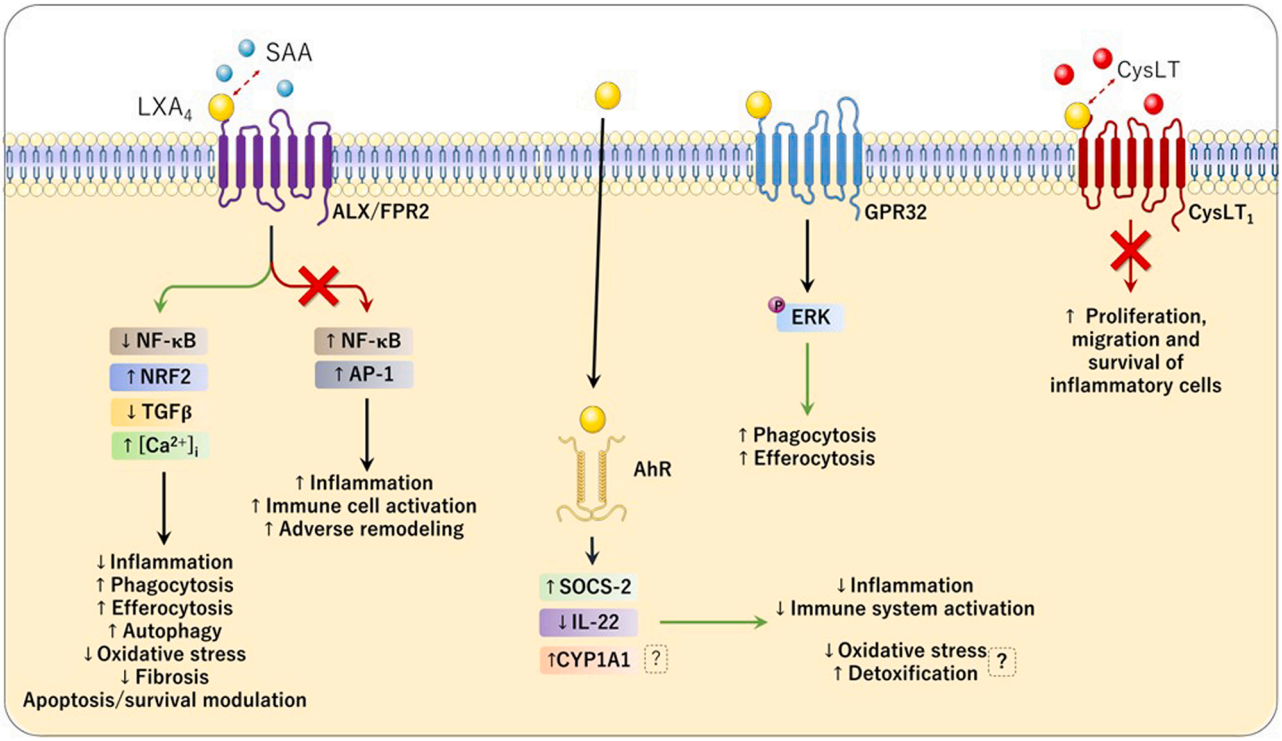

Fig. 3. Main signaling pathways activated by LXA_4 interaction with ALX/FPR2, GPR32, AhR and CysLT1 receptors. Pro-resolving effects of LXA_4 are mainly mediated by its interaction with ALX/FPR2 receptor, which mediates anti-inflammatory, antioxidant, anti-fibrotic and pro/anti-apoptotic responses. Upon internalization, LXA_4 can also interact with AhR receptor, thus modulating detoxification and immune system activation. This SPM can also interact with transmembrane receptor GPR32, which has been shown to promote both efferocytosis and phagocytosis. Finally, by binding to CysLT1 receptor, LXs can also block pro-inflammatory signaling mediated by CysLT. Parts of this figure were drawn using pictures from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 unported license.

actions of the LXs. Since the use of corticosteroids and NSAIDs to stop inflammation is limited by their extensive side effects, LXs among other SPMs are gaining importance as endogenous mediators with reduced side effects. Additionally, the availability of specific and robust analytical methods to quantify endogenous levels of SPMs remains an issue to address the function of these molecules in the control of the inflammation. Nonetheless, subsequent recent studies have reported the presence of specific pro-resolving lipid mediators in different experimental settings, using mass-spectrometry approaches [119–123]. Therefore, a better knowledge of their resolving actions can entail an excellent therapeutic option in future approaches to inflammatory pathologies like neurological or cardiovascular disorders and even cancer.

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CRediT authorship contribution statement

Sergio Sánchez-García, Rafael Íñigo-Jaén: Conceptualization, methodology, writing - original draft. **María Fernández-Velasco, Carmen Delgado Canencia**: Methodology, writing – original draft. **Patricia Prieto**: Conceptualization, writing – review & editing, visualization, supervision. **Lisardo Boscá**: Conceptualization, writing - review & editing, supervision, funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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