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Specialized Proresolving Mediators for Therapeutic Interventions Targeting Metabolic and Inflammatory Disorders

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Abstract

Uncontrolled inflammation is considered the pathophysiological basis of many prevalent metabolic disorders, such as nonalcoholic fatty liver disease, diabetes, obesity, and neurodegenerative diseases. The inflammatory response is a self-limiting process that produces a superfamily of chemical mediators, called specialized proresolving mediators (SPMs). SPMs include the ω-3-derived family of molecules, such as resolvins, protectins, and maresins, as well as arachidonic acid-derived (ω-6) lipoxins that stimulate and promote resolution of inflammation, clearance of microbes, and alleviation of pain and promote tissue regeneration via novel mechanisms. SPMs function by binding and activating G protein-coupled receptors, such as FPR2/ALX, GPR32, and ERV1, and nuclear orphan receptors, such as RORα. Recently, several studies reported that SPMs have the potential to attenuate lipid metabolism disorders. However, the understanding of pharmacological aspects of SPMs, including tissue-specific biosynthesis, and specific SPM receptors and signaling pathways, is currently limited. Here, we summarize recent advances in the role of SPMs in resolution of inflammatory diseases with metabolic disorders, such as nonalcoholic fatty liver disease and obesity, obtained from preclinical animal studies. In addition, the known SPM receptors and their intracellular signaling are reviewed as targets of resolution of inflammation, and the currently available information on the therapeutic effects of major SPMs for metabolic disorders is summarized.

Key Words: Specialized pro-resolving mediators, Resolvins, Maresins, NAFLDs, Adipose tissue

INTRODUCTION

Excessive inflammation is associated with various chronic diseases, including nonalcoholic steatohepatitis (NASH), diabetic obesity, and cardiovascular and neurodegenerative diseases. Under homeostatic conditions, acute inflammation is self-limiting and resolves by itself. An acute inflammatory response is divided into two phases: the pro-inflammatory initiation phase and the anti-inflammatory resolution phase. In the resolution phase, the cessation of immune cell infiltration occurs in response to chemotactic signals, apoptosis of polymorphonuclear cells, and active clearance of apoptotic cells and debris by macrophages. Charles Serhan was the first researcher to describe lipid mediators for self-resolution of inflammation, called specialized proresolving mediators (SPMs) (Serhan, 2017). His research group identified SPMs via liquid chromatography–tandem mass spectrometry-based analysis of self-limited exudates formed in *in vivo* animal models and human cells (Serhan *et al*., 2000). Serhan and colleagues demonstrated that SPMs led to activation of efferocytosis to remove apoptotic neutrophils and inflammatory molecules (Dalli and Serhan, 2012). Furthermore, SPMs could induce a polarity switch of macrophages from pro-inflammatory M1 to anti-inflammatory M2 to resolve acute inflammation and secrete tissue repair and wound healing molecules (Buckley *et al*., 2014). Presently, it is well known that SPMs modulate pro-inflammatory responses, host defense, pain, tissue remodeling, and organ dysfunction via immunological mechanisms.

During the resolution phase of acute inflammation, SPMs are biosynthesized from essential polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) (Fig. 1).

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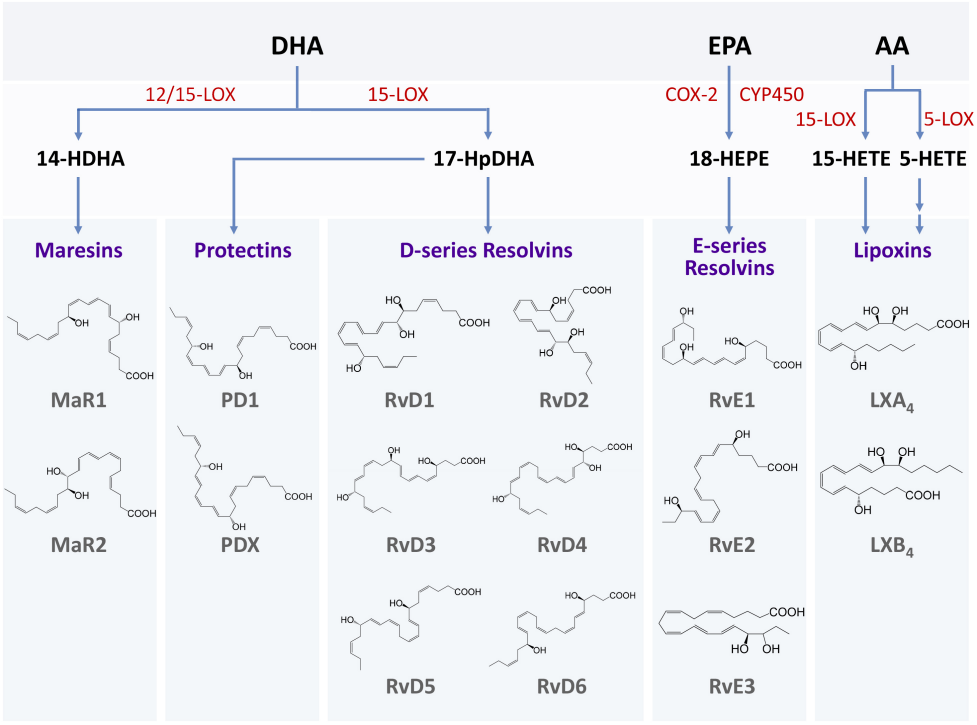

Fig. 1. SPMs and their biosynthesis. Biosynthesis of SPMs starts from the long-chain PUFAs such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA). Enzymes, including lipoxygenase (LOX) and cyclooxygenase (COX), convert PUFAs towards various SPM families. Maresins (MaR1 and MaR2), protectins (PD1 and PDX), and D-series resolvins (RvD1-RvD6) are derived from DHA. 14-Hydroxy docosahexaenoic acid (14-HDHA) is the intermediate of maresins produced by 12/15-LOX, and 17-hydroperoxy docosahexaenoic acid (17-HpDHA) is the intermediate of other SPM families derived from DHA. E-series resolvins (RvE1, RvE2, and RvE3) are synthesized from EPA. 18-Hydroxyeicosapentaenoic acid (18-HEPE) is the major intermediate which is produced by COX-2 or CYP450. Lipoxins (LXA_4 and LXB_4), the first SPMs identified, are biosynthesized from AA in two different routes by either 15-LOX or 5-LOX in different cells or tissues.

Resolvins are metabolites biosynthesized from ω-3 PUFAs, including DHA and EPA, via diverse lipoxygenases (LOXs), resulting in the production of D- and E-series resolvins (Serhan, 2017). D-series resolvins (RvD1–RvD6) are mainly derived from an epoxide of DHA via a reaction involving 15-LOX and 17S-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid (17-HDHA) (Chiang and Serhan, 2017). Furthermore, the biosynthesis of protectins (PDs) and maresins (MaRs) occurs from lipoxygenase-mediated epoxide intermediates of DHA. However, lipoxins (LXs) including LXA4 and LXB4 are synthesized from ω-6 arachidonic acid via conversion of 15-hydroperoxyeicosatetraenoic acid (Park *et al*., 2020). The biosynthesis of these SPMs is mainly initiated during the late phase of the acute inflammatory response, wherein polymorphonuclear neutrophils undergo apoptosis and macrophages perform efferocytosis (Buckley *et al*., 2014). Moreover, these lipid mediators can influence immune cell responses as well as tissue homeostasis.

The inflammatory response plays an essential role in modulating lipid metabolism-related diseases, such as obesity and nonalcoholic fatty liver disease (NAFLD). Acute and chronic inflammation involving recruitment of neutrophils and macrophages is associated with dysregulated metabolism following dampening of functions of homeostatic parenchymal cells (Lumeng and Saltiel, 2011). Obesity and NAFLD are often associated with nonresolving inflammation in adipose and liver tissues, which is a key pathological event that leads to insulin resistance and metabolic dysregulation (Spite *et al*., 2014). The persistent inflammation can lead to metabolic disorders. In addition, disrupted metabolic homeostasis drives the onset of inflammation. Thus, it is reasonable to hypothesize that SPMs could modulate lipid metabolism-related diseases via resolution of the feedback loop of inflammatory stimulations and metabolic dysfunctions. In this regard, dysregulation of SPM biosynthesis in adipose tissue, the liver, and other tissues is involved in the pathogenesis of lipid metabolic diseases (Spite *et al*., 2014). In this review, we summarize the following: 1) the role of SPMs in resolution of inflammatory diseases with metabolic disorders, such as NAFLD and obesity; 2) SPM receptors and their intracellular signaling as targets of resolution of inflammation; and 3) the therapeutic effects of major SPM species for the treatment of metabolic disorders with chronic inflammation.

RESOLUTION OF LIVER INFLAMMATION: IMPLICATIONS OF SPMS IN THE PROGRESSION OF NAFLD

NAFLD is an umbrella term for a range of hepatic diseases ranging from simple lipid accumulation (steatosis) to complicated inflammations (steatohepatitis). With impaired adipose

Table 1. Effects of SMPs in mouse liver, adipose, vessel, and neuron

Tissues	SPMS	Receptors	Effects in adipose and liver tissue	Ref
Liver	RvD1	Not studied	Suppresses TLR4-mediated inflammatory signalling in liver	Li *et al*., 2020
	RvD1	Not studied	Inhibits proinflammatory NF-κB activitiy	Kuang *et al*., 2016
	RvE1	Not studied	Inhibits proinflammatory NF-κB activitiy	Kuang *et al*., 2016
	RvE1	ChemR23/ERV1	Induces adiponectin in adipose tissue	González-Périz *et al*., 2009
	PD1	Not studied	Decreases TNF release of macrophages and DNA damage of hepatocytes	González-Périz *et al*., 2006
	MaR1	Not studied	AMPK-mediated inhibition of liver steatosis	Laiglesia *et al*., 2018b
	MaR1	Not studied	Suppresses lipotoxicity and ER stress	Rius *et al*., 2017
	MaR1	Not studied	Reduces ER stress via AMPK-SERCA2b pathway	Jung *et al*., 2018
	MaR1	Not studied	Regulates hepatocyte metabolism by modulating FGF21	Martinez-Fernandez *et al*., 2019
	MaR1	RORα	Induces M2 polarity of liver macrophages	Han *et al*., 2019
	MaR1	ALX/FPR2	Protects I/R liver injuries via Akt signaling	Tang *et al*., 2021
Adipose	RvD1	FPR2/ALX	Increases M2:M1 adipose tissue macrophage ratio	Hellmann *et al*., 2011
	RvD2	GPR18/DRV2	Increased UCP1 and PGC1α expression in BAT and increased whole body consumption	Pascoal *et al*., 2017
	RvD1	GPR32/DRV1	Decreased Anti-inflammatory activity*	Claria *et al*., 2012
	RvE1	ChemR23/ERV1	Regulation of NFKb and modulate IL-12 production	Arita *et al*., 2005
	RvE1	BLT1	Induces Pro-inflammatory activity	Claria *et al*., 2013
	RvE1	ChemR23/ERV1	Protect against obesity induced glucose disorder	Sima *et al*., 2018
	RvE2	BLT1	Inhibition of LTB4 mediated NF-κB activation	Arita *et al*., 2007
	LxA4	ALX/FPR2	Significantly increased adiponectin secretion under obese condition	Claria *et al*., 2012
	LxA4	GPR32	Inhibit IL-6 secretion and induce anti-inflammatory cytokine IL-10	Claria *et al*., 2012
	ω-3 PUFA	GPCR120	Regulation of TNF-α-induced inflammatory signalling	Oh *et al*., 2010
Blood vessel	RvD1	FPR2/ALX	Suppress lesional oxidative stress and necrosis	Fredman *et al*., 2016
	RvD2	Not studied	Halt necrotic expansion and macrophage accumulation	Viola *et al*., 2016
Neuron	RvD1	GPR32	Induce microglial phagocytosis for amyloid-β	Zhu *et al*., 2016
	PD1	Not studied	Decrease proinflammatory genes and increases antiapoptotic genes	Lukiw *et al*., 2005
	PD1	Not studied	Neuroprotection against proteotoxic and oxidative stress	Calandria *et al*., 2015b
	PD1	Not studied	Regulates NF-κB activity	Calandria *et al*., 2015a

tissue homeostasis, the steatotic liver undergoes progressive inflammations to develop nonalcoholic steatohepatitis (NASH), fibrosis, and ultimately cirrhosis (Neuschwander-Tetri, 2020). Lipotoxicity and release of endogenous damage-associated molecular patterns begin the hepatic inflammatory response by accumulation of leukocytes, including activated-neutrophils and macrophages (Koyama and Brenner, 2017). The relevance of compositional change of ω-6 and ω-3 PUFAs in patients with NASH suggested that specific lipid mediators could modulate the symptoms of progressive NASH (Puri *et al*., 2007).

Several studies have reported the role of eicosanoids, metabolites of inflammatory ω-6 arachidonic acid, in NASH diseases. Moreover, cyclooxygenase 2-mediated prostaglandin E2 production by Kupffer cells induced accumulation of hepatic triglycerides via cyclic adenosine monophosphate (cAMP) (Enomoto *et al*., 2000). In addition, leukotriene (LT) signaling exhibited a potential effect on the progression from steatosis to NASH (Araújo *et al*., 2018). In particular, 5-LOX, an enzyme involved in the synthesis of LT family members from arachidonic acid, was remarkably activated in patients and mouse models of NASH (Puri *et al*., 2009; Horrillo *et al*., 2010). Pharmacological and genetic ablation of the LT pathway consistently inhibited progression of high fat diet (HFD)-induced hepatic steatosis and inflammatory responses (Horrillo *et al*., 2010; Martínez-Clemente *et al*., 2010).

Considering the proresolving function of inflammatory lipid mediators, it is not surprising that SPMs, metabolites of ω-3 PUFAs, have a beneficial effect on the progression of NASH (Table 1). Indeed, the feeding of a ω-3-enriched diet ameliorated steatotic and inflammatory liver injury in mouse models (González-Périz *et al*., 2006, 2009). These hepatoprotective effects of a ω-3-enriched diet were involved in the production of SPMs including resolvins, protectins, and 17-HDHA. RvE1 reduced hepatic lipid levels and macrophage activation along with adiponectin-mediated improvement of adipose tissue homeostasis (González-Périz *et al*., 2009). 17-HDHA and protectin D 1 (PD1) mediated beneficial effects of ω-3 PU-

FAs by downregulation of tumor necrosis factor (TNF) release and DNA damage in the liver (González-Périz *et al*., 2006). In particular, RvD1 significantly attenuated the symptoms of steatohepatitis, including steatosis, fibrosis, oxidative stress, and inflammatory activations via inhibiting nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling in macrophages of mice models (Li *et al*., 2020). In addition, Kuang *et al*. (2016) reported that RvD1 and RvE1 decreased excessive activation of hepatic leukocytes in a concanavalin A-induced hepatitis model with mechanisms similar to NF-κB blockade (Kuang *et al*., 2016).

Among the SPMs, MaR1 is the most validated lipid mediator to protect against HFD-induced liver injuries. Moreover, MaR1 ameliorated liver steatosis via decreasing the expression of lipogenic enzymes. Treatment of MaR1 induced activation of AMP-activated protein kinase (AMPK) and its downstream factors that are associated with fatty acid oxidation and autophagy (Laiglesia *et al*., 2018b). Furthermore, MaR1 was observed to directly affect hepatocytes by increasing AMPK phosphorylation, and ultimately decreasing lipid accumulations and endoplasmic reticulum stress (Rius *et al*., 2017; Jung *et al*., 2018). In addition, MaR1 modulated the expression of fibroblast growth factor 21 (FGF21), a key growth factor in systemic metabolism, in cultured hepatocytes (Martinez-Fernandez *et al*., 2019). In a previous study, nuclear receptor RORα was identified as an important regulator of liver macrophage polarization to induce an anti-inflammatory M2 phenotype in NASH (Han *et al*., 2017). In addition to effects on hepatocytes, MaR1 contributed to enhancement of RORα-induced M2 polarization in liver macrophages, resulting in resolution of liver inflammation in NASH (Han *et al*., 2019). Interestingly, RORα was activated by direct binding of MaR1 as an endogenous lipid ligand, suggesting that the MaR1-RORα axis may link inflammation and metabolic dysfunction in the liver. Furthermore, MaR1 reduced hepatic ischemia–reperfusion injury and led to a large decrease in the necrotic area (Tang *et al*., 2021). Taken together, the ability of MaR1 to ameliorate NAFLD injuries could offer new therapeutic candidates to impede the progression from simple steatosis to NASH in fatty liver diseases.

RESOLUTION OF ADIPOSE TISSUE INFLAMMATION: EFFECTS OF SPMS ON OBESITY-RELATED METABOLIC DYSFUNCTION

Serhan's research group examined human adipose tissue using liquid chromatography–tandem mass spectrometry-based lipidomics analysis and found that RvD1, RvD2, PD1, MaR1, and LXA4 are endogenous to human subcutaneous adipose tissue (Claria *et al*., 2013). Using anatomical location-dependent profile analysis, they also demonstrated that perivascular fat depots possess higher biosynthetic capacity of SPMs compared with subcutaneous adipose tissue (Claria *et al*., 2013). Furthermore, an analysis of pathologic conditions with regard to SPM levels demonstrated that 17-HDHA and PD1 are downregulated in patients with peripheral vascular disease, which is associated with the induction of cytokines such as monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and interleukin (IL)-10 (Claria *et al*., 2013). In human omental adipose tissue under nutritional stress, the levels of SPMs such as resolvins, lipoxins, and protectins were reduced with increased activity of IL-10 (Titos *et al*., 2016). An *in vivo* mouse study identified RvD1 and RvD2 as the major SPMs regulating the inflammatory responses in adipose tissue and demonstrated the reduction of RvD1, RvD2, and PD1 in adipose tissue from obese mice compared with that from lean mice (Claria *et al*., 2012). Another *in vivo* study demonstrated that dietary supplementation of ω-3 PUFAs improved thermogenic activity of brown and white adipose tissues in mice and that recruitment of thermogenic adipocytes was affected by local concentration of oxylipins, including SPMs (Ghandour *et al*., 2018). The positive correlation between thermogenic activity of human brown adipose tissue and levels of ω-3 fatty acid-derived SPMs (Kulterer *et al*., 2020) suggested the clinical relevance of the regulatory effects of SPMs in energy metabolism. We next summarize the recent research on the obesity-driven defects in biosynthesis of the major SPMs: resolvins, MaRs, lipoxins, and protectins.

Neuhofer *et al*. (2013) showed that obesity significantly reduces the levels of RvD1 in gonadal adipose tissue, along with an accumulation of adipose tissue inflammatory factors. RvD1 treatment in leptin receptor-deficient mice enhanced glucose tolerance and insulin sensitivity, together with reduced pro-inflammatory gene expression and crown-like structure formation in epididymal white adipose tissue (Hellmann *et al*., 2011). In inflamed human adipose tissue, RvD1 treatment increased MAPK activity and inhibited the activity of STAT-1 and related inflammatory genes without affecting the anti-inflammatory effects of IL-10 (Titos *et al*., 2016). Furthermore, RvD1 treatment modulated overactivation of STAT-3 phosphorylation at Tyr705 but maintained IL-10-induced anti-inflammatory response by inhibiting IL-6, IL-1β, IL-8, and TNF-α activity in adipose tissue (Titos *et al*., 2016). RvD1 and its precursor DHA were shown to classically polarize macrophages toward an M2-like phenotype by increasing M2 markers, such as IL-10, Arg1, Ym1, REALMα, and CD206, in adipose tissue of obese mice (Titos *et al*., 2011). Consequently, RvD1 protects against obesity-induced adipose tissue inflammation, insulin resistance, and metabolic liver disease (Titos *et al*., 2011). RvD1 treatment under calorie restriction status reduced the size of adipocytes in epididymal white adipose tissue, increased adiponectin levels, and reduced circulating leptin levels (Rius *et al*., 2014). In addition, depletion of RvD1 was related to obesity-associated osteoarthritis, wherein ω-3 PUFAs resulted in reduced expression of pro-inflammatory factors and induced M2 macrophage polarization (Sun *et al*., 2019).

A recent study demonstrated that RvE1 treatment prevented hyperinsulinemia and hyperglycemia in mice consuming a HFD. Moreover, the fasting glucose or insulin levels in RvE1 receptor (resolvin E1 receptor [ERV1]/ChemR23) knockout mice were not recovered by RvE1 treatment (Pal *et al*., 2020). Using transgenic mice that overexpressed human ERV1 in myeloid cells, Sima *et al*. (2018) demonstrated that ERV1 reduced body weight and provided protection against HFD-induced hyperglycemia. In addition, the administration of RvE1 reproduced the protective effects of ERV1 overexpression (Sima *et al*., 2018). In the same mouse model, endogenous production of SPMs such as RvD1, RvD4, RvD5, PD1, and LXA4 increased, indicating a significant contribution of ERV1 receptor signaling to the regulation of SPM production. Furthermore, RvE1 was identified to modulate the immune response via LTB4 receptor BLT1 in polymorphonuclear leukocytes, by inhibiting the pro-inflammatory response induced by LTB4 via blocking the mobilization of intracellular calcium and

NF-κB activation (Arita *et al*., 2007).

The anti-inflammatory effects of MaRs have been addressed in previous studies. MaR1 treatment reversed the effect of pro-inflammatory cytokine TNF-α and induced Akt phosphorylation in subcutaneous adipose tissue from patients with obesity as well as improved glucose homeostasis in obese mice (Martinez-Fernandez *et al*., 2020). Furthermore, MaR1 treatment in diet-induced obesity mice regulated FGF21 and its production in hepatocytes, resulting in improved glucose metabolism and insulin sensitivity. In addition, it reversed the HFD-induced downregulation of FGF21, FGFR1, and β-Klotho in white adipose tissue (Martinez-Fernandez *et al*., 2019). In another study with a similar mouse model, MaR1 treatment improved anti-inflammatory effects by reducing the levels of pro-inflammatory agents IL-1β and TNF-α in colonic mucosa of obese mice (Leon *et al*., 2020). In an *in vitro* study using mature 3T3L1 adipocytes, MaR1 treatment reversed the effect of TNF-α-induced lipolysis and autophagy by regulating phosphorylation of hormone sensitive lipase; moreover, it counteracted the cytokine-induced decrease of p62 and prevented the induction of autophagy flux (Laiglesia *et al*., 2018a). MaR1 treatment also promoted resolution of inflammation in adipose tissue in obese mice by reducing macrophage infiltration, downregulating M1 macrophage phenotype marker expression, reducing the levels of pro-inflammatory markers, and subsequently increasing expression of the anti-inflammatory adipokine adiponectin in white adipose tissue (Martinez-Fernandez *et al*., 2017).

The mechanism of action of LXA4 was investigated in perigonadal adipose tissue of mice. LXA4 was found to induce the proresolving effect by inhibiting IL-6 secretion and enhancing IL-10 production. This finding suggested a protective effect of LXA4 in reprogramming of pro-inflammatory macrophages to a relatively proresolving phenotype and inhibiting the effect of inflammatory cytokines on adipose tissue inflammation, indicating a possible direct regulation of adipocyte insulin signaling pathways (Börgeson *et al*., 2012). Claria *et al*. (2012) identified the expression of LXA4 receptor FPR2/ALX in human adipose tissue. Furthermore, Börgeson *et al*. (2015) studied the role of lipoxins in preserving p62 and LC3-II levels in obese mice. They also reported that lipoxins regulate M1 to M2 macrophage phenotype conversion to induce resolution of inflammation in adipose tissue. Lipoxins demonstrate this protective effect independent of adiponectin secretion by reducing TNF-α expression and restoring annexin-1 level in the adipose tissue. Moreover, LXA4 administration in HFD mice can induce recovery from renal damage and inflammation due to NF-κB and ERK/P38 MAPK by inhibiting the phosphorylation of ERK/P38 MAPK (Tourki *et al*., 2020). In addition, pretreatment with a LXA4 antagonist was shown to worsen the inflammation and renal damage, suggesting that LXA4 activity in obese mice can decrease the inflammatory affects caused by NF-κB and ERK/P38 MAPK pathways (Tourki *et al*., 2020).

Administration of protectin DX (PDX), a double lipoxygenase derivative of docosahexaenoic acid, was found to reduce the increase in body weight and epididymal white adipose tissue mass, improve glucose tolerance, and improve insulin sensitivity (Piao *et al*., 2020).

ROLE OF SPMS IN LIPID METABOLISM DISORDERS IN ARTERIES AND NEURONS

Atherosclerosis is a complex human disease associated with inflammation and lipid metabolism dysfunction in arteries. Interestingly, imbalances between SPMs and pro-inflammatory mediators in the circulatory system are involved in prevalent atherosclerotic diseases. The ratio of SPMs to pro-inflammatory LTB4 was lower in the human carotid atherosclerotic regions, but the administration of RvD1 promoted recovery in the damaged areas (Fredman *et al*., 2016). Furthermore, exogenous treatment of RvD2 and MaR1 prevented atheroprogression via suppressing necrosis of endothelial cells and formation of collagen fibrous plaque (Viola *et al*., 2016). Nuclear localized 5-LOX generated pro-inflammatory LTs instead of proresolving lipoxins and human carotid atherosclerotic regions contained higher expression of nuclear 5-LOX compared with healthy regions (Spanbroek *et al*., 2003; Qiu *et al*., 2006). The impaired efferocytosis of vessel macrophages to produce SPMs on their own was found to be another possible mechanism underlying the imbalance of lipid mediators. However, the elevated expression of Mertk receptors to recognize apoptotic cells could support effective efferocytosis and production of SPMs in the artery (Fredman and Tabas, 2017). Therefore, investigation of anti-inflammatory SPMs is important to explore the pathological link between inflammation and lipid metabolism in atherosclerotic cardiovascular disease.

SPMs also modulate neuroinflammation and lipid metabolism-associated neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Alzheimer's disease is characterized by the excessive accumulation of amyloid-β in the brain. MaR1 and RvD1 alleviate neurodegeneration by promoting microglial phagocytosis of amyloid-β (Zhu *et al*., 2016). In particular, protectin D1 (PD1), produced by 15-LOX and 5-LOX, is a well-known lipid mediator that promotes the reduction of neurodegenerative injuries. The levels of PD1 were reduced in the hippocampus and temporal lobe of patients with Alzheimer's disease (Lukiw *et al*., 2005). Moreover, PD1 inhibited cell death and increased neural cell survival, which alleviated the symptoms of Alzheimer's and Parkinson's diseases (Lukiw *et al*., 2005; Stark and Bazan, 2011; Calandria *et al*., 2015b). PD1 also regulated the NF-κB cyclic response and showed anti-inflammatory effects (Calandria *et al*., 2015a). Although SPMs have shown protective effects for neural diseases, few clinical trials have been undertaken to explore the potential use of SPMs for Alzheimer's and Parkinson's diseases.

SPM RECEPTORS AND THEIR INTRACELLULAR SIGNALING

SPMs bind to G protein-coupled receptor (GPCR) family members and activate them. FPR2/ALX is expressed on a wide range of leukocytes and leads to pro- and anti-inflammatory effects (Fig. 2) (Chiang and Serhan, 2017). Lipoxins such as LXA4 and resolvins such as RvD1 and RvD3 can effectively activate FPR2/ALX receptor signaling. Moreover, anti-inflammatory and efferocytotic functions of RvD1 under peritonitis were inhibited when FPR2/ALX receptor signaling was defective (Krishnamoorthy *et al*., 2012). GPR32 is an orphan receptor predominantly expressed on human neutrophils, mono-

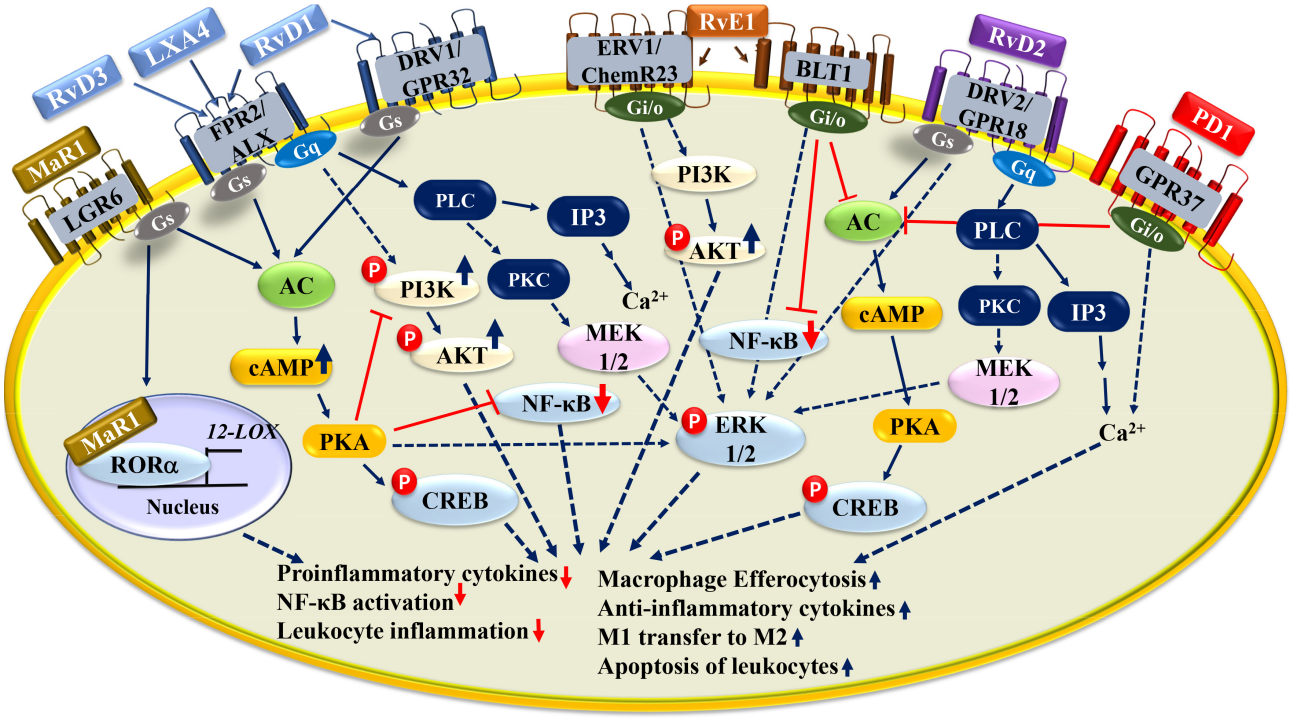

Fig. 2. SPM receptors and associated intracellular signaling pathways. SPMs signal through specific G-protein coupled receptors (GPCRs). RvD1, RvD3 and LXA4 are agonist for ALX/FPR2 and its activity leads to PKA activation to phosphorylate CREB promoting production of anti-inflammatory cytokines, macrophage polarization. RvD1 also influences AKT phosphorylation via PI3K pathway to inhibit NF-kB mediated pro-inflammatory effects. It also enhances ERK1/2 phosphorylation via MEK1/2 to induce anti-inflammatory effects. RvD2 works through DRV2, leading to ERK1/2 or PLC pathway to promote resolution. RvE1 is an agonist for ChemR23 and BLT1. The ChemR23-RvE1 downstream signaling activates AKT phosphorylation, inhibiting NF-kB inflammatory effects. PD1-GPR37 mechanistic actions also found to block PKA activation. MaR1 acts via two distinct receptors, LGR6 and RORα. MaR1 activates RORα transcriptional activity, leading to M2 polarization and 12-LOX expression, an enzyme required for MaR1 syntheis. MaR1 activates LGR6-mediated cAMP signaling to promote macrophage efferocytosis and resolution.

cytes, adipose tissue, and endothelial cells. RvD1, RvD3, and RvD5 activate the cellular response via this receptor. Although RvD1 has a higher affinity for GPR32 than for FPR2/ALX, the former is not expressed in rodents. This finding indicated that the function of RvD1 in rodents is mainly mediated via FPR2/ALX signaling (Schmid *et al*., 2016; Chiang *et al*., 2019a). Chimerin receptor 1 (ChemR23 or ERV1) is expressed on immune cells, including monocytes, macrophages, natural killer cells, and dendritic cells. ERV1 was identified as a surface receptor for RvE1 among the GPCRs (Arita *et al*., 2005). RvE1 treatment reduced IL-12 production and dendritic cell trafficking, but these effects were eliminated by ERV1 siRNA (Arita *et al*., 2005). GPR37 is mostly expressed on brain cells and macrophages and is associated with neurological diseases, such as Parkinson's disease (Lopes *et al*., 2015). Especially, GPR37 was revealed to PD1 receptors, and PD1-induced anti-inflammatory effects were reduced in GPR37 knockout mice (Bang *et al*., 2018). Recently, the receptors for MaR1 were identified in two studies. First, LGR6, a human leucine-rich repeat containing GPCR, was identified as a stereoselective receptor of MaR1 for efferocytotic functions (Chiang *et al*., 2019b). Second, MaR1 could act as an endogenous ligand for nuclear receptor RORα, which modulates M2 polarization of macrophages and induces anti-inflammatory effects (Han *et al*., 2019). The functions of MaR1 differed at different time points: LGR6-mediated phagocyte action was rapid but RORα-mediated M2 polarization was moderately slow. These findings underlie the potential signaling of intracellular functions of SPMs as well as surface GPCRs. Furthermore, PPARγ is a possible potent nuclear receptor for other SPMs, including PD1 and RvD1, to mediate anti-inflammatory responses (Zhao *et al*., 2011; Liao *et al*., 2012).

THERAPEUTIC POTENTIAL OF SPMS IN DISEASES WITH LIPID METABOLISM DISORDERS

SPMs showed high potential to ameliorate diverse inflammatory and lipid-related diseases in preclinical animal models (Table 2). However, few clinical trials of SPMs have been performed, although some SPMs demonstrated significant anti-inflammatory effects, because the stability of SPMs is low due to their complex physiochemical nature and structure (Arita *et al*., 2006). A synthetic analog of RvE1, RX-10045, was synthesized by Resolvyx Pharmaceuticals. It was tested regarding ocular inflammation diseases, and a phase 2 randomized trial was recently completed (Clinicaltrials.gov; NCT02329743). In addition, a combination of DHA metabolite SPMs, including 17-HDHA, 18-HEPE, and 14-HDHA, called Lipinova, demonstrated resolution of inflammation after orthopedic sur-

Table 2. Potential therapeutic effects of SPM on tissue dysfunction

SPMs	Dosage	Experimental model	Resolution	Ref
RvE1	1.2 ng/g (4 days)	Ob/ob mice	Reduces liver steatosis and macrophage activation	González-Périz *et al.*, 2009
RvD1	300 ng	C57BL/6J under 4 weeks of MCD diet	Decreases expression of inflammatory genes and stress markers for restoring NASH	Li *et al.*, 2020
MaR1	50 ug/kg	Ob/ob and HFD-fed (3 months) mice	Ameliorates hepatic triglycerides and fasting glucose levels	Laiglesia *et al.*, 2018b
MaR1	5 ug/kg	HFD-fed (3 months) mice	Reduces liver fibrosis	Han *et al.*, 2019
MaR1	20 ng	Ischemic/reperfusion injury	Lowered liver injuries including necrosis	Tang *et al.*, 2021
RvE1	300 ng	C57BL/6J under 5 weeks of HFD	Restored glucose level in obese mice	Pal *et al.*, 2020
MaR1	50 ug/kg (3 h)	Diet induced obesity mice	Induced Akt phosphorylation for better insulin sensitivity	Martinez-Fernandez *et al.*, 2020
MaR1	2 mg/kg (10 days)	Genetic obese mice	Blocks the activity of TNFa, IL-1b pro-inflammatory action, and upregulates adiponectin and Glut-4, Akt phosphorylation	Martinez-Fernandez *et al.*, 2017
LxA4	LXA_4 (5ng/g) or benzo-LXA_4 (1.7 ng/g)	C57BL/6J and C57BL/6J adiponectin$^{-/-}$ mice under 3 month of HFD	Block adipose tissue inflammation and increases insulin sensitivity	Börgeson *et al.*, 2015
RvD1	100 ng	LDLR knockout mice	Reduces fibrous cap in vessels	Fredman *et al.*, 2016

gery (Clinicaltrials.gov; NCT03434236). Furthermore, some synthetic analogs of SPMs showed high potency in reducing inflammatory responses. A synthetic benzo-diacetylenic-17R-RvD1-methyl ester (BDA-RvD1) significantly reduced acute recruitment of neutrophils in ischemia–reperfusion-induced lung injury and enhanced phagocytosis (Orr *et al.*, 2015). A benzo-fused ring-modified LXA4 analog (BLXA4-ME) showed proresolving properties and is currently under clinical trials for a topical rinse treatment of gingivitis (Clinicaltrials.gov; NCT02342691). In addition to SPM mimetics, GPCR agonists, especially for the receptor FPR2/ALX, are extensively being developed for clinical trials. AR234245 (Arena Pharmaceuticals) was the first developed synthetic agonist of FPR2/ALX. After the development of AR234245, many pharmaceutical and academic groups have endeavored to develop other FPR2/ALX agonists. ACT-389949 (Actelion Pharmaceuticals) was the first-in-class candidate of anti-inflammatory GPCR agonists to show good safety and toleration in healthy subjects during clinical trials (Stalder *et al.*, 2017). Recently, a clinical trial for peripheral artery diseases with dietary administration of SPM emulsion was endeavored, and the outcomes will be posted soon (Clinicaltrials.gov; NCT02719665).

SPMs and their corresponding receptors have been targeted to develop therapeutic strategies for the resolution of inflammation and its consequent diseases. However, even after 20 years since SPMs were first identified, no clinically usable drugs have been successfully developed for the therapeutic strategy involving GPCRs and SPM mimetics. Numerous GPCRs have been identified for SPMs, but the downstream signaling is complex and evokes multiple responses, and a lack of in-depth knowledge regarding these physiological responses hampers the exploration of GPCRs for clinical use. Recently, new mechanisms of SPM actions were identified, and it was reported that SPMs can enter cells and directly bind with nuclear receptors as agonistic ligands (Han *et al.*, 2019). Many nuclear receptors interact with lipid mediators as endogenous ligands, such as PPARα–LT, HNF4α–linoleic acid, RORβ–stearic acid, and RORα–MaR1 (Holzer *et al.*, 2017). These mechanisms could broaden the clinical usage of SPMs because the use of nuclear receptors for treatment of human diseases is being established.

CONCLUSIONS

SPMs have the potential to attenuate or prevent chronic inflammatory diseases with lipid metabolism disorders through resolution of the feedback loop of inflammatory stimulations and metabolic dysfunctions. SPMs can trigger anti-inflammatory processes by binding and activating GPCRs and nuclear receptors. Currently, however, the understanding of SPMs and their receptor signaling pathways is limited. Thus, identification and characterization of specific receptors and intracellular signaling pathways for each SPM that are intricately linked to the pathogenesis of lipid metabolism disorders would provide new insights to overcome the hurdles in therapeutic application of SPMs. Due to the high potency of SPMs for resolution of acute and chronic inflammations, clinical SPM therapy for inflammatory and lipid metabolism-related diseases could soon be established.

CONFLICT OF INTEREST

The authors declare no competing interest.

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REFERENCES

Araújo, A. C., Wheelock, C. E. and Haeggström, J. Z. (2018) The eicosanoids, redox-regulated lipid mediators in immunometabolic disorders. *Antioxid. Redox Signal.* **29**, 275-296.

Arita, M., Bianchini, F., Aliberti, J., Sher, A., Chiang, N., Hong, S., Yang, R., Petasis, N. A. and Serhan, C. N. (2005) Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J. Exp. Med.* **201**, 713-722.

Arita, M., Oh, S. F., Chonan, T., Hong, S., Elangovan, S., Sun, Y. P., Uddin, J., Petasis, N. A. and Serhan, C. N. (2006) Metabolic inactivation of resolvin E1 and stabilization of its anti-inflammatory actions. *J. Biol. Chem.* **281**, 22847-22854.

Arita, M., Ohira, T., Sun, Y. P., Elangovan, S., Chiang, N. and Serhan, C. N. (2007) Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. *J. Immunol.* **178**, 3912-3917.

Bang, S., Xie, Y. K., Zhang, Z. J., Wang, Z., Xu, Z. Z. and Ji, R. R. (2018) GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. *J. Clin. Invest.* **128**, 3568-3582.

Börgeson, E., Johnson, A. M., Lee, Y. S., Till, A., Syed, G. H., Ali-Shah, S. T., Guiry, P. J., Dalli, J., Colas, R. A., Serhan, C. N., Sharma, K. and Godson, C. (2015) Lipoxin A4 attenuates obesity-induced adipose inflammation and associated liver and kidney disease. *Cell Metab.* **22**, 125-137.

Börgeson, E., McGillicuddy, F. C., Harford, K. A., Corrigan, N., Higgins, D. F., Maderna, P., Roche, H. M. and Godson, C. (2012) Lipoxin A4 attenuates adipose inflammation. *FASEB J.* **26**, 4287-4294.

Buckley, C. D., Gilroy, D. W. and Serhan, C. N. (2014) Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity* **40**, 315-327.

Calandria, J. M., Asatryan, A., Balaszczuk, V., Knott, E. J., Jun, B. K., Mukherjee, P. K., Belayev, L. and Bazan, N. G. (2015a) NPD1-mediated stereoselective regulation of BIRC3 expression through cREL is decisive for neural cell survival. *Cell Death Differ.* **22**, 1363-1377.

Calandria, J. M., Sharp, M. W. and Bazan, N. G. (2015b) The docosanoid neuroprotectin D1 induces TH-positive neuronal survival in a cellular model of Parkinson's disease. *Cell. Mol. Neurobiol.* **35**, 1127-1136.

Chiang, N., Barnaeva, E., Hu, X., Marugan, J., Southall, N., Ferrer, M. and Serhan, C. N. (2019a) Identification of chemotype agonists for human resolvin D1 receptor DRV1 with pro-resolving functions. *Cell Chem. Biol.* **26**, 244-254.e4.

Chiang, N., Libreros, S., Norris, P. C., de la Rosa, X. and Serhan, C. N. (2019b) Maresin 1 activates LGR6 receptor promoting phagocyte immunoresolvent functions. *J. Clin. Invest.* **129**, 5294-5311.

Chiang, N. and Serhan, C. N. (2017) Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. *Mol. Aspects Med.* **58**, 114-129.

Claria, J., Dalli, J., Yacoubian, S., Gao, F. and Serhan, C. N. (2012) Resolvin D1 and resolvin D2 govern local inflammatory tone in obese fat. *J. Immunol.* **189**, 2597-2605.

Claria, J., Nguyen, B. T., Madenci, A. L., Ozaki, C. K. and Serhan, C. N. (2013) Diversity of lipid mediators in human adipose tissue depots. *Am. J. Physiol. Cell Physiol.* **304**, C1141-C1149.

Dalli, J. and Serhan, C. N. (2012) Specific lipid mediator signatures of human phagocytes: microparticles stimulate macrophage efferocytosis and pro-resolving mediators. *Blood* **120**, e60-e72.

Enomoto, N., Ikejima, K., Yamashina, S., Enomoto, A., Nishiura, T., Nishimura, T., Brenner, D. A., Schemmer, P., Bradford, B. U., Rivera, C. A., Zhong, Z. and Thurman, R. G. (2000) Kupffer cell-derived prostaglandin E(2) is involved in alcohol-induced fat accumulation in rat liver. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279**, G100-G106.

Fredman, G., Hellmann, J., Proto, J. D., Kuriakose, G., Colas, R. A., Dorweiler, B., Connolly, E. S., Solomon, R., Jones, D. M., Heyer, E. J., Spite, M. and Tabas, I. (2016) An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. *Nat. Commun.* **7**, 12859.

Fredman, G. and Tabas, I. (2017) Boosting inflammation resolution in atherosclerosis: the next frontier for therapy. *Am. J. Pathol.* **187**, 1211-1221.

Ghandour, R. A., Colson, C., Giroud, M., Maurer, S., Rekima, S., Ailhaud, G., Klingenspor, M., Amri, E. Z. and Pisani, D. F. (2018) Impact of dietary omega3 polyunsaturated fatty acid supplementation on brown and brite adipocyte function. *J. Lipid Res.* **59**, 452-461.

González-Périz, A., Horrillo, R., Ferre, N., Gronert, K., Dong, B., Moran-Salvador, E., Titos, E., Martinez-Clemente, M., Lopez-Parra, M., Arroyo, V. and Clària, J. (2009) Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvins and protectins. *FASEB J.* **23**, 1946-1957.

González-Périz, A., Planagumà, A., Gronert, K., Miquel, R., López-Parra, M., Titos, E., Horrillo, R., Ferré, N., Deulofeu, R., Arroyo, V., Rodés, J. and Clària, J. (2006) Docosahexaenoic acid (DHA) blunts liver injury by conversion to protective lipid mediators: protectin D1 and 17S-hydroxy-DHA. *FASEB J.* **20**, 2537-2539.

Han, Y. H., Kim, H. J., Na, H., Nam, M. W., Kim, J. Y., Kim, J. S., Koo, S. H. and Lee, M. O. (2017) RORα induces KLF4-mediated M2 polarization in the liver macrophages that protect against nonalcoholic steatohepatitis. *Cell Rep.* **20**, 124-135.

Han, Y. H., Shin, K. O., Kim, J. Y., Khadka, D. B., Kim, H. J., Lee, Y. M., Cho, W. J., Cha, J. Y., Lee, B. J. and Lee, M. O. (2019) A maresin 1/RORα/12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. *J. Clin. Invest.* **129**, 1684-1698.

Hellmann, J., Tang, Y., Kosuri, M., Bhatnagar, A. and Spite, M. (2011) Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. *FASEB J.* **25**, 2399-2407.

Holzer, G., Markov, G. V. and Laudet, V. (2017) Evolution of nuclear receptors and ligand signaling: toward a soft key-lock model? *Curr. Top. Dev. Biol.* **125**, 1-38.

Horrillo, R., González-Périz, A., Martínez-Clemente, M., López-Parra, M., Ferré, N., Titos, E., Morán-Salvador, E., Deulofeu, R., Arroyo, V. and Clària, J. (2010) 5-lipoxygenase activating protein signals adipose tissue inflammation and lipid dysfunction in experimental obesity. *J. Immunol.* **184**, 3978-3987.

Jung, T. W., Kim, H. C., Abd El-Aty, A. M. and Jeong, J. H. (2018) Maresin 1 attenuates NAFLD by suppression of endoplasmic reticulum stress via AMPK-SERCA2b pathway. *J. Biol. Chem.* **293**, 3981-3988.

Koyama, Y. and Brenner, D. A. (2017) Liver inflammation and fibrosis. *J. Clin. Invest.* **127**, 55-64.

Krishnamoorthy, S., Recchiuti, A., Chiang, N., Fredman, G. and Serhan, C. N. (2012) Resolvin D1 receptor stereoselectivity and regulation of inflammation and proresolving microRNAs. *Am. J. Pathol.* **180**, 2018-2027.

Kulterer, O. C., Niederstaetter, L., Herz, C. T., Haug, A. R., Bileck, A., Pils, D., Kautzky-Willer, A., Gerner, C. and Kiefer, F. W. (2020) The presence of active brown adipose tissue determines cold-induced energy expenditure and oxylipin profiles in humans. *J. Clin. Endocrinol. Metab.* **105**, dgaa183.

Kuang, H., Hua, X., Zhou, J. and Yang, R. (2016) Resolvin D1 and E1 alleviate the progress of hepatitis toward liver cancer in long-term concanavalin A-induced mice through inhibition of NF-κB activity. *Oncol. Rep.* **35**, 307-317.

Laiglesia, L. M., Lorente-Cebrian, S., Lopez-Yoldi, M., Lanas, R., Sainz, N., Martinez, J. A. and Moreno-Aliaga, M. J. (2018a) Maresin 1 inhibits TNF-alpha-induced lipolysis and autophagy in 3T3-L1 adipocytes. *J. Cell. Physiol.* **233**, 2238-2246.

Laiglesia, L. M., Lorente-Cebrián, S., Martínez-Fernández, L., Sáinz, N., Prieto-Hontoria, P. L., Burrell, M. A., Rodríguez-Ortigosa, C. M., Martínez, J. A. and Moreno-Aliaga, M. J. (2018b) Maresin 1 mitigates liver steatosis in ob/ob and diet-induced obese mice. *Int. J. Obes. (Lond.)* **42**, 572-579.

Leon, I. C., Quesada-Vazquez, S., Sainz, N., Guruceaga, E., Escote, X. and Moreno-Aliaga, M. J. (2020) Effects of Maresin 1 (MaR1) on colonic inflammation and gut dysbiosis in diet-induced obese mice. *Microorganisms* **8**, 1156.

Lumeng, C. N. and Saltiel, A. R. (2011) Inflammatory links between obesity and metabolic disease. *J. Clin. Invest.* **121**, 2111-2117.

Li, J., Deng, X., Bai, T., Wang, S., Jiang, Q. and Xu, K. (2020) Resolvin D1 mitigates non-alcoholic steatohepatitis by suppressing the TLR4-MyD88-mediated NF-κB and MAPK pathways and activating the Nrf2 pathway in mice. *Int. Immunopharmacol.* **88**, 106961.

Liao, Z., Dong, J., Wu, W., Yang, T., Wang, T., Guo, L., Chen, L., Xu, D. and Wen, F. (2012) Resolvin D1 attenuates inflammation in lipopolysaccharide-induced acute lung injury through a process involving the PPARγ/NF-κB pathway. *Respir. Res.* **13**, 110.

Lopes, J. P., Morató, X., Souza, C., Pinhal, C., Machado, N. J., Canas, P. M., Silva, H. B., Stagljar, I., Gandía, J., Fernández-Dueñas, V., Luján R., Cunha, R. A. and Ciruela, F. (2015) The role of parkinson's disease-associated receptor GPR37 in the hippocampus: functional interplay with the adenosinergic system. *J. Neurochem.* **134**, 135-146.

Lukiw, W. J., Cui, J. G., Marcheselli, V. L., Bodker, M., Botkjaer, A., Gotlinger, K., Serhan, C. N. and Bazan, N. G. (2005) A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J. Clin. Invest.* **115**, 2774-2783.

Martínez-Clemente, M., Ferré, N., González-Périz, A., López-Parra, M., Horrillo, R., Titos, E., Morán-Salvador, E., Miquel, R., Arroyo, V., Funk, C. D. and Clària, J. (2010) 5-lipoxygenase deficiency reduces hepatic inflammation and tumor necrosis factor alpha-induced hepatocyte damage in hyperlipidemia-prone ApoE-null mice. *Hepatology* **51**, 817-827.

Martinez-Fernandez, L., Gonzalez-Muniesa, P., Laiglesia, L. M., Sainz, N., Prieto-Hontoria, P. L., Escote, X., Odriozola, L., Corrales, F. J., Arbones-Mainar, J. M., Martinez, J. A. and Moreno-Aliaga, M. J. (2017) Maresin 1 improves insulin sensitivity and attenuates adipose tissue inflammation in ob/ob and diet-induced obese mice. *FASEB J.* **31**, 2135-2145.

Martinez-Fernandez, L., Gonzalez-Muniesa, P., Sainz, N., Escote, X., Martinez, J. A., Arbones-Mainar, J. M. and Moreno-Aliaga, M. J. (2020) Maresin 1 regulates insulin signaling in human adipocytes as well as in adipose tissue and muscle of lean and obese mice. *J. Physiol. Biochem.* **77**, 167-173. .

Martinez-Fernandez, L., Gonzalez-Muniesa, P., Sainz, N., Laiglesia, L. M., Escote, X., Martinez, J. A. and Moreno-Aliaga, M. J. (2019) Maresin 1 regulates hepatic FGF21 in diet-induced obese mice and in cultured hepatocytes. *Mol. Nutr. Food Res.* **63**, e1900358.

Neuhofer, A., Zeyda, M., Mascher, D., Itariu, B. K., Murano, I., Leitner, L., Hochbrugger, E. E., Fraisl, P., Cinti, S., Serhan, C. N. and Stulnig, T. M. (2013) Impaired local production of proresolving lipid mediators in obesity and 17-HDHA as a potential treatment for obesity-associated inflammation. *Diabetes* **62**, 1945-1956.

Neuschwander-Tetri, B. A. (2020) Therapeutic landscape for NAFLD in 2020. *Gastroenterology* **158**, 1984-1998.e3.

Oh, D. Y., Talukdar, S., Bae, E. J., Imamura, T., Morinaga, H., Fan, W., Li, P., Lu, W.J., Watkins, S. M. and Olefsky, J. M. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **142**, 687-698.

Orr, S. K., Colas, R. A., Dalli, J., Chiang, N. and Serhan, C. N. (2015) Proresolving actions of a new resolvin D1 analog mimetic qualifies as an immunoresolvent. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **308**, L904-L911.

Pascoal, L. B., Bombassaro, B., Ramalho, A. F., Coope, A., Moura, R. F., Correa-da-Silva, F., Ignacio-Souza, L., Razolli, D., de Oliveira, D., Catharino, R. and Velloso, L. A. (2017) Resolvin RvD2 reduces hypothalamic inflammation and rescues mice from diet-induced obesity. *J. Neuroinflammation* **14**, 5.

Pal, A., Al-Shaer, A. E., Guesdon, W., Torres, M. J., Armstrong, M., Quinn, K., Davis, T., Reisdorph, N., Neufer, P. D., Spangenburg, E. E., Carroll, I., Bazinet, R. P., Halade, G. V., Clària, J. and Shaikh, S. R. (2020) Resolvin E1 derived from eicosapentaenoic acid prevents hyperinsulinemia and hyperglycemia in a host genetic manner. *FASEB J.* **34**, 10640-10656.

Park, J., Langmead, C. J. and Riddy, D. M. (2020) New advances in targeting the resolution of inflammation: implications for specialized pro-resolving mediator GPCR drug discovery. *ACS Pharmacol. Transl. Sci.* **3**, 88-106.

Piao, S., Du, W., Wei, Y., Yang, Y., Feng, X. and Bai, L. (2020) Protectin DX attenuates IL-1beta-induced inflammation via the AMPK/NF-kappaB pathway in chondrocytes and ameliorates osteoarthritis progression in a rat model. *Int. Immunopharmacol.* **78**, 106043.

Puri, P., Baillie, R. A., Wiest, M. M., Mirshahi, F., Choudhury, J., Cheung, O., Sargeant, C., Contos, M. J. and Sanyal, A. J. (2007) A lipidomic analysis of nonalcoholic fatty liver disease. *Hepatology* **46**, 1081-1090.

Puri, P., Wiest, M. M., Cheung, O., Mirshahi, F., Sargeant, C., Min, H. K., Contos, M. J., Sterling, R. K., Fuchs, M., Zhou, H., Watkins, S. M. and Sanyal, A. J. (2009) The plasma lipidomic signature of nonalcoholic steatohepatitis. *Hepatology* **50**, 1827-1838.

Qiu, H., Gabrielsen, A., Agardh, H. E., Wan, M., Wetterholm, A., Wong, C. H., Hedin, U., Swedenborg, J., Hansson, G. K., Samuelsson, B., Paulsson-Berne, G. and Haeggström, J. Z. (2006) Expression of 5-lipoxygenase and leukotriene A4 hydrolase in human atherosclerotic lesions correlates with symptoms of plaque instability. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 8161-8166.

Rius, B., Duran-Güell, M., Flores-Costa, R., López-Vicario, C., Lopategi, A., Alcaraz-Quiles, J., Casulleras, M., Lozano, J. J., Titos, E. and Clària, J. (2017) The specialized proresolving lipid mediator maresin 1 protects hepatocytes from lipotoxic and hypoxia-induced endoplasmic reticulum stress. *FASEB J.* **31**, 5384-5398.

Rius, B., Titos, E., Moran-Salvador, E., Lopez-Vicario, C., Garcia-Alonso, V., Gonzalez-Periz, A., Arroyo, V. and Claria, J. (2014) Resolvin D1 primes the resolution process initiated by calorie restriction in obesity-induced steatohepatitis. *FASEB J.* **28**, 836-848.

Schmid, M., Gemperle, C., Rimann, N. and Hersberger, M. (2016) Resolvin D1 polarizes primary human macrophages toward a proresolution phenotype through GPR32. *J. Immunol.* **196**, 3429-3437.

Serhan, C. N. (2017) Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. *Mol. Aspects Med.* **58**, 1-11.

Serhan, C. N., Clish, C. B., Brannon, J., Colgan, S. P., Chiang, N. and Gronert, K. (2000) Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *J. Exp. Med.* **192**, 1197-1204.

Sima, C., Montero, E., Nguyen, D., Freire, M., Norris, P., Serhan, C. N. and Van Dyke, T. E. (2018) Author correction: ERV1 overexpression in myeloid cells protects against high fat diet induced obesity and glucose intolerance. *Sci. Rep.* **8**, 4143.

Spanbroek, R., Grabner, R., Lotzer, K., Hildner, M., Urbach, A., Ruhling, K., Moos, M. P., Kaiser, B., Cohnert, T. U., Wahlers, T., Zieske, A., Plenz, G., Robenek, H., Salbach, P., Kuhn, H., Radmark, O., Samuelsson, B. and Habenicht, A. J. (2003) Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. *Proc. Natl. Acad. Sci. U.S.A.* **100**, 1238-1243.

Spite, M., Clària, J. and Serhan, C. N. (2014) Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. *Cell Metab.* **19**, 21-36.

Stalder, A. K., Lott, D., Strasser, D. S., Cruz, H. G., Krause, A., Groenen, P. M. and Dingemanse, J. (2017) Biomarker-guided clinical development of the first-in-class anti-inflammatory FPR2/ALX agonist ACT-389949. *Br. J. Clin. Pharmacol.* **83**, 476-486.

Stark, D. T. and Bazan, N. G. (2011) Neuroprotectin D1 induces neuronal survival and downregulation of amyloidogenic processing in Alzheimer's disease cellular models. *Mol. Neurobiol.* **43**, 131-138.

Sun, A. R., Wu, X., Liu, B., Chen, Y., Armitage, C. W., Kollipara, A., Crawford, R., Beagley, K. W., Mao, X., Xiao, Y. and Prasadam, I. (2019) Pro-resolving lipid mediator ameliorates obesity induced osteoarthritis by regulating synovial macrophage polarisation. *Sci. Rep.* **9**, 426.

Tang, D., Fu, G., Li, W., Sun, P., Loughran, P. A., Deng, M., Scott, M.

J. and Billiar, T. R. (2021) Maresin 1 protects the liver against ischemia/reperfusion injury via the ALXR/Akt signaling pathway. *Mol. Med*. **27**, 18.

Titos, E., Rius, B., Gonzalez-Periz, A., Lopez-Vicario, C., Moran-Salvador, E., Martinez-Clemente, M., Arroyo, V. and Claria, J. (2011) Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. *J. Immunol.* **187**, 5408-5418.

Titos, E., Rius, B., Lopez-Vicario, C., Alcaraz-Quiles, J., Garcia-Alonso, V., Lopategi, A., Dalli, J., Lozano, J.J., Arroyo, V., Delgado, S., Serhan, C. N. and Clària, J. (2016) Signaling and immunoresolving actions of resolvin D1 in inflamed human visceral adipose tissue. *J. Immunol.* **197**, 3360-3370.

Tourki, B., Kain, V., Shaikh, S. R., Leroy, X., Serhan, C. N. and Halade, G. V. (2020) Deficit of resolution receptor magnifies inflammatory leukocyte directed cardiorenal and endothelial dysfunction with signs of cardiomyopathy of obesity. *FASEB J.* **34**, 10560-10573.

Viola, J. R., Lemnitzer, P., Jansen, Y., Csaba, G., Winter, C., Neideck, C., Silvestre-Roig, C., Dittmar, G., Döring, Y., Drechsler, M., Weber, C., Zimmer, R., Cenac, N. and Soehnlein, O. (2016) Resolving lipid mediators Maresin 1 and Resolvin D2 prevent atheroprogression in mice. *Circ. Res.* **119**, 1030-1038.

Zhao, Y., Calon, F., Julien, C., Winkler, J. W., Petasis, N. A., Lukiw, W. J. and Bazan, N. G. (2011) Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPARγ-mediated mechanisms in Alzheimer's disease models. *PLoS ONE* **6**, e15816.

Zhu, M,. Wang, X., Hjorth, E., Colas, R. A., Schroeder, L., Granholm, A. C., Serhan, C. N. and Schultzberg, M. (2016) Pro-resolving lipid mediators improve neuronal survival and increase Aβ42 phagocytosis. *Mol. Neurobiol.* **53**, 2733-2749.