Specialized Proresolving Mediators: Enhancing Nonalcoholic Steatohepatitis and Fibrosis Resolution

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Specialized Pro-resolving Mediators: enhancing nonalcoholic steatohepatitis and fibrosis resolution

Running title: NASH and SPM

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Abstract

The resolution of necroinflammation and fibrosis remains a primary clinical target in nonalcoholic steatohepatits (NASH), the most common chronic liver disease and a major cause of end-stage liver disease.Our understanding of the basic molecular mechanisms driving inflammation and fibrosis and their resolution in obesity-related conditions, including NASH, have led to the proposal of a novel, tractable therapeutic paradigm involving specialized pro-resolving mediators (SPMs)—namely lipoxins (LXs), resolvins (Rvs), protectins (PDs) and maresins (MaRs) . Growing evidence from cellular and *in vivo* animal models, as well as observational human data, suggests that the therapeutic potential of SPMs and their synthetic mimetics may expand to the regression of hepatic necroinflammatory and fibrotic changes in NASH. We review preclinical and clinical evidence linking SPMs to the pathogenesis of inflammation and fibrosis in NASH, as well as potential therapeutic use of these new molecules for the resolution of steatohepatitis and of fibrosis in NASH.

Introduction: enhancing resolution of inflammation and fibrosis

Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease in the world, encompasses a histological spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the latter characterized by necro-inflammation with variable degrees of fibrosis[1]. NASH can progress to cirrhosis and is projected to be the leading indication for liver transplantation, as a consequence of increasing disease occurrence and of the lack of an effective treatment[2]. As inflammation and fibrosis are central to the progression of NASH to cirrhosis, their resolution is a major therapeutic target[1].

Our knowledge of the resolution of tissue inflammation and fibrosis has evolved dramatically in recent years [3]. Regarding the inflammatory process, data from animal models and from isolated human cells showed that resolution of acute inflammation is not a passive phenomenon, occurring via a dissipation of pro-inflammatory signals, but an actively programmed biochemical process regulated by temporal biosynthesis of novel bioactive mediators, which belong to four distinct families, namely lipoxins (LXs), resolvins (Rvs), protectins (PDs) and maresins (MaRs)[4], collectively named "specialized pro-resolving mediators"(SPMs).

These SPMs are synthetized from omega-3 poly unsaturated fatty acids (PUFA) but, unlike their precursors eicosapentaenoic acid (EPA) and docosahexaenoic acid, (DHA), which act at the micromolar to millimolar range, exert their biological actions in the picomolar to nanomolar range, with concentrations as low as10nM producing a 50 percent reduction in PMN transmigration in models systems[4](see **Box 1**).

The production of these pro-resolving mediators is programmed early during the acute inflammatory response and primed by the synthesis ofProstaglandin E2 (PGE2) and PGD2, which at the site of infection upregulate the expression of 15-lipoxygenase (15-LOX)[5], that is required for the synthesis of pro-resolving LXs(e.g. LXA4)), Rvs and PDs, thereby switching the lipid mediator synthetic process from proinflammatory eicosanoids (prostaglandins, thromboxanes and

leukotrienes) to pro-resolving mediators [3,4](**Box 2**). Growing data expand the findings from acute inflammation to conditions characterized by chronic, low-grade inflammation like obesity and NASH[1], raising the possibility that targeting the defective resolution of inflammation could aid in the treatment of obesity-related liver disease metabolic dysregulation, and eventually fibrosis[6].

Parallel to the advances in inflammation, our knowledge of fibrosis has evolved from a paradigm of a static, irreversible condition to a dynamic process that can be reversed if the underlying fibrogenic stimuli are corrected and adequate pro-resolving cellular programs are activated [7,8] (**Box 3).** These programs are activated by the same molecules that are involved in inflammation resolution.

We will discuss the emerging role of these lipid molecules and pathways in regulating resolution of inflammation and fibrosis in NASH and the potential therapeutic implications of their modulation.

Biosynthetic pathways and receptors for SPMs

The term "specialized pro-resolving mediators" was originally coined by Charles N. Serhan and his collaborators to define the families of chemically and functionally distinct anti-inflammatory and pro-resolving lipid molecules synthesized from from both omega-6- (i.e. LXs) and omega-3- (i.e. resolvins, protectins and maresins) PUFA[3,5]. Using a lipidomics-based approach that combined liquid chromatography and tandem mass spectrometry (LC-MS/MS) to study exudates in in the murine dorsal air pouch model of inflammation, including zymosan sterile peritonitis, four families of SPMs were identified: lipoxins (LXs)[5]; resolvins (Rvs, derived from resolution phase interaction products), which were classified as either E-series Rvs (if derived from EPA) or D-series Rvs (if generated from DHA)[5]; protectins, and maresins (macrophage mediators in resolving inflammation), which also derive from DHA[9].

LXs

LXs are the first class of SPMs involved in the resolution phase of inflammation and include LXA4 and LXB4, both with potent antiinflammatory and pro-resolving activities. LXA4 is a trihydroxy-eicosatetraenoic acid generated by transcellular synthesis (i.e. through the cooperation of different cell types: a cell type synthesizes an intermediate that is further metabolized by a different nearby cell using their own enzymatic apparatus) from endogenous arachidonic acid(AA) through sequential LOX-LOX interactions[5](**Figure 1**). LXA4 biosynthesis is initiated from 15S-hydroxyeicosatetraenoic acid (15S-HETE) (produced by cells bearing 15-LOX activity, which is induced by the proinflammatory PGE2[4] 15S-HETE that is rapidly converted to LXA4 by leukocyte 5-LOX[5]. Of note, LXA4 (as well as resolvin) biosynthesis might be dependent on the nuclear integral membrane protein 5-lipoxygenase activating protein, or FLAP[10].
An alternative synthetic pathway for LXs is initiated when COX-2 is acetylated by aspirin: when aspirin inhibits PG formation in cells bearing the inducible COX-2, aspirin-acetylated COX-2 converts arachidonic acid into 15R-HETE, rather than the 15S enantiomer, which is further transformed by 5-LOX into 15-epi-LXs, also called "aspirin-triggered" LXs[11].
(**Figure 1**).

Overall, LXs act as "stop-signals" for inflammation and inhibit leukocyte chemotaxis, rolling, adhesion to and transmigration across endothelial monolayers in response to LTB4
They act through binding to A$ Lipoxin/Formyl-peptide receptor type 2(ALX/FPR2) receptor, a G-protein coupled receptor (GPCR) that together with GPR32 also signals for RvD1 and for the anti-inflammatory, proresolving peptide Annexin A1[12].

Rvs

The biosynthesis of the E-series resolvins is initiated when EPA is converted into 18Rhydro-EPE (18R-HEPE) by endothelial cells expressing aspirin-acetylated COX-2[13] (**Figure 1**). 18R-HEPE is then transformed by transcellular biosynthesis in neighboring 5-LOXcontaining leukocytes into RvE1 (5S,12R, 18R-trihydroxy-EPA) and RvE2 (5S, 18R-dihydroxy-EPA)[13]. RvE3 (17S, 18R dihydroxy-EPA) is generated via the 12/15-LOX pathway from 18RHEPE (**Figure 1**).

Moreover, a novel series of 18S-RvE1 (5S,12R, 18S-trihydroxy-EPA) and 18SRvE2 (5S, 18S-dihydroxy-EPA) derived from EPA have been identified using chiral LC-MS/MS-based lipidomics[14]. Of interest, biosynthesis of E-series resolvins can occur in the absence of aspirin treatment through the activity of the CYP450 system which can synthesize 18R-HEPE from EPA(**Figure 1**).

RvE1 signals through the GPCR ChemR23 and is also an endogenous receptor antagonist for the LTB4 receptor, BLT1[15], which allows cell type-specific actions: as a BLT1 antagonist it inhibits Nuclear Factor(NF)-kB activation and PMN trafficking to sites of inflammation, and as a ChemR23 agonist on mononuclear and dendritic cells it enhances efferocytosis and resolution of inflammation[16]. Consistently, in BLT1 knockout mice, anti-inflammatory actions of RvE1 were reduced when given at low doses (100 ng i.v.), while when given at higher doses (1.0 mg i.v.) RvE1significantly reduced PMN infiltration in a BLT1-independent manner[15].

Concerning DHA-derived SPMs, the biosynthesis of D-series resolvins is initiated by 15-LOX which transforms DHA into 17S-hydro(peroxy)-DHA (17S-H(p)DHA), which is further transformed by leukocyte 5-LOX into 7-hydroperoxy-17S-HDHA, and then converted into 7S, 8S-epoxide and finally hydrolyzed to either RvD1 (7S,8R, 17Strihydroxy-DHA) or RvD2 (7S,16R, 17S-trihydroxy-DHA)[3](**Figure 1**). Reduction of the 5-LOX derived hydroperoxide intermediate via a peroxidase also leads to the formation of RvD5 (7S, 17S-dihydroxy-DHA). Alternatively, lipoxygenation at the C-4 position by the enzyme 5-LOX forms 4-hydroperoxy-17SHDHA that is subsequently converted to RvD3 (4S,11R, 17S-trihydroxy-DHA), RvD4 (4S,5S, 17S-trihydroxy-DHA) and RvD6 (4S, 17Sdihydroxy-DHA). Endothelial cells expressing COX-2 acetylated by aspirin also transform DHAinto 17R-HDHA which is further converted by 5-LOX into the corresponding aspirin-triggered (AT)-resolvins[3]. RvD1 signals on the GPCR ALX/FPR2, while RvD2 binds GPR18.

PDs and MaRs

DHA can also be transformed by 15-LOX into a dihydroxy-containing DHA derivative named protectin D1 (PD1) (10R, 17S-dihydroxy-DHA) via an intermediate epoxide (**Figure 1).** Furthermore, lipoxygenation of DHA by 12-LOX originates a 14S-hydroperoxy-DHA intermediate that can be converted by epoxidation and/or hydrolysis into maresin (MaR) 1 (7R, 14Sdihydroxy-DHA) and MaR2 (13R, 14S-dihydroxy-DHA)[17] (**Figure 1**). MaR1 is slightly more potent at 1 nM than Resolvin D1 (RvD1) in stimulating Macrophage efferocytosis. Importantly MaR1 also accelerates surgical regeneration in planaria, increasing the rate of head reappearance. Indicating MaR1 is a potent SPM not only regulating noto only inflammation resolution but also tissue regeneration[18].

A novel family of sulfido-conjugated components that share the biosynthetic pathway with maresin through the oxygenation of DHA at carbon 14 have been identified [19].Called maresin-conjugate in tissue regeneration (MCTR), they display potent wound repair and tissue regeneration properties. Similarly, novel 17-series sulfido-conjugated pathways, namely protectin sulfido-conjugates and resolvin sulfidoconjugates, were also identified in mouse and human spleens, self-resolving infectious exudates, human phagocytes and human sepsis plasma[20]. More recently, bioactive molecules derived from DPA, a third omega-3-PUFA standing between EPA and DHA, have been identified and called 13-series resolvins (RvTs), consist of four different compounds derived from DPA with a characteristic 22-carbon backbone with five double bonds[21].

NASH as a pro-resolution defective disorder

Adipose tissue dysfunction plays a key pathogenic role for liver injury in NASH [22], which encompasses a range of functional abnormalities ranging from unrestricted flow of lipotoxic free fatty acids from insulin resistant adipose tissue to the liver, to unbalanced pro-/anti-inflammatory adipokine and chemokine secretion, with prevalent secretion of pro-inflammatory Interleukin (IL)-1, Tumor Necrosis Factor(TNF)-α, Interleukin(IL)-6 and Monocyte Chemoattractant Protein (MCP)-1 and blunted secretion of anti-inflammatory adiponectin and IL10[1]. The effect of these

molecules on the liver causes the whole spectrum of functional and pathologic injury in NASH, including hepatic insulin resistance, hepatocyte apoptosis with the release of pro-inflammatory signalling molecules named damage-associaed molecular patterns (DAMPs), and Kupffer cell activation[1,23].

Activated Kupffer cells, which release proinflammatory and pro-fibrogenic cytokines[24]; and chemokines including CCL2, which promotes hepatic accumulation of bone marrow-derived, "classically activated" pro-inflammatory M1-polarized monocytes, and NKT cells[25]. Signals from Kupffer cells and injured hepatocytes, including reactive oxygen species (ROS) and Transforming Growth Factor(TGF)-β1, activate hepatic stellate cells(HSCs) to myofibroblasts, which start fibrogenesis[1,7] (**BOX 2**). Adipocytes in nearby adipose tissue also secrete CCL2, which further expands the local macrophage pool and promotes HSC activation, liver fibrosis[26] and adipose tissue inflammation and dysfunction[27].

A key driver of adipose tissue dysfunction and liver injury in NASH is a state of low-grade adipose tissue inflammation: adipocytes secrete chemokines and other proinflammatory signals that recruit proinflammatory cells, mainly M1-activated macrophages but also lympocytes, to adipose tissue[1,28]. The relevance of macrophage infiltration in the pathogenesis of NASH and adipose tissue inflammation is underscored by the finding that genetic or pharmacologic inhibition of the CCL2/CCR2 axis, which reduced the macrophage pool by 80% in the liver and by 40% in adipose tissue [29], ameliorated steatohepatitis, fibrosis, adipose tissue dysfunction and insulin resistance[30] in experimental NASH.

Mounting evidence places an inbalance between pro-inflammatory eicosanoids and SPM secretion/action in adipose tissue at the core of adipose tissue inflammation and dysfunction, and of resultant liver injury[6,31]: .white adipose tissue possesses all enzymes involved in eicosanoid synthesis, including phospholipase A2(PLA2), COX and 5-LOX, 5-LOX activating protein [FLAP], LTA4 hydrolase, and LTC4 synthase, as well as LT receptors (BLT-1, BLT-2, CysLT1, and CysLT2) and can produce and release eicosanoids, most prominently the COX product PGE2

and the 5-LOX product LTB4, which is the main LOX-derived metabolite in this tissue[31]. Human and experimental data link excessive production/action of these two eicosanoids to NASH pathogenesis and progression, and suggest the antagonization of these two eicosanoids may be an effective therapeutic strategy for NASH.

In methionine choline deficient (MCD) diet and high-fat diet (HFD)-induced NASH models, hepatic and adipose COX-2 activity is significantly upregulated, as a result of NF-κB and IL-1 axis activation, and correlates with the severity of steatohepatitis[32, 33, 34]. Several lines of evidence suggest PGE2 is a central mediator of the effects of COX-2 activation on liver disease in NASH. In cell cultures, PGE2 induces hepatocyte triglyceride accumulation and apoptosis, promotes Kupffer cell activation and adipocyte dysfunction [35, 36, 37, 38, 39]. In animal models of NASH, PGE2 promotes hepatic triglyceride storage[40], necro-inflammation and fibrosis by a variety of mechanisms: autophagy inhibition[41], enhancement of lipid droplet formation[42] and of adipogenesis[43], increased chemokine MCP-1 secretion and TGF-β1-induced HSC activation[44]**.** Finally, a tumor promoting role for PGE2 in obesity-related hepatocelular carcinoma and breast cancer has been recently proposed as a result of Prostaglandin E receptor 4(PTGER4)-mediated suppression of antitumor immunity and enhanced transcription of CYP-19, CYP-181 and aromatase-catalyzed estrogen biosynthesis[45].

Potential strategies to antagonize PGE2 action include inhibition of key enzymes involved in PGE2 synthesis, including PLA2 and COX-2, and PGE2 recentor antagonization.

Genetic group IV PLA2α deletion protected from high fat diet(HFD)-induced obesity and steatohepatitis and group IV PLA2α pharmacological inhibition with the orally active small molecule compound ASB14780 reversed established NASH and fibrosis[40]. Two other small molecule cPLA2 inhibitors, the ω3-PUFA derivatives AVX001 and AVX002, showed potent anti-inflammatory activity in vitro, and AVX001 was safe and effective in patients with mild-to-moderate psoriasis[46] but has not been evaluated in NASH.

Celecoxib, a selective COX-2 inhibitor, improved liver histology, adipose tissue inflammation and metabolic abnormalities in NASH[47, 48]. However, COX-2 inhibition might not be the safest and most effective strategy to treat chronic inflammation in NASH, for several reasons. First, PGE2 is required to trigger 15-LOX-mediated synthesis of LXA4, a SPM which is central for initiating inflammation resolution and switching macrophage phenotype from pro-inflammatory M1-to pro-resolving M2 [49]. Secondly, COX-2 contributes to the synthesis of protective PGI2 in endothelium and kidney and it is still debated if COX-2 inhibition increases cardiovascular disease (CVD) risk[50]. Under this instance, it is noteworthy that the PGE2 receptor-3 antagonist L-798106 improved adipose tissue pro-inflammatory gene activation, inflammation, insulin resistance and glucose homeostasis to a similar extent as COX-2 inhibitor celecoxib in rodent models of obesity and in cultured adipocytes[48]. These findings confirm that the effects of COX-2 activation on metabolic inflammation are largely PGE2-mediated and suggest that the off-target effects of COX-2 inhibition may be theoretically overcome by selective PGE2 receptor antagonism.

Similarly to PGE2, a key proinflammatory role has been demostrated for 5-LOX-mediated LTs in the liver and adipose tissue. Hepatic Kupffer cells constitutively express 5-LOX and synthesize LTB4 and cysteinyl-LT, the latter being also produced by hepatocytes through transcellular metabolism of LTA4 secreted by Kupffer cells[51]. 5-LOX-derived leukotrienes act in both paracrine and autocrine fashion to promote Kupffer cell viability and growth and HSC activation. A similar role for adipocyte 5-LOX in mediating adipose tissue inflammation has been found in experimental models of obesity-related NASH, where the adipose tissue and liver showed increased expression of 5-LOX and its products[**Errore. Il segnalibro non è definito.**]. In humans, the progression from healthy liver to NASH is paralleled by an increased formation of 5-lipoxygenase products[52].

In support of a causal role of 5-LOX/LT axis activation in liver injury, genetic deletion of 5-LOX protected from HFD-induced obesity and NASH[53, 54], and pharmacolicical inhibition of the 5-lOX or selective LTB4 receptor BLT-1 antagonism induced AMPK activation, down-regulated

NF-kB axis activation and reduced proinflammatorry cytokine/chemokine secretion and FFA release from adipose tssue, thereby improving hepatic and adipose insulin resistance, steatosis and necroinflammatory changes in NASH[**Errore. Il segnalibro non è definito.**,55]. On this basis, MN-001 (tipelukast), an orally available small molecule 5-LOX inhibitor, which acts also as LTD4 receptor antagonist and phosphodiesterases (PDE) 3/4 inhibitor, reduced inflammation and fibrosis and down-regulated expression of proinflammatory and profibrogenic genes in an advanced NASH model[56] and was FDA-approved for a Phase IIa RCT in NASH patients with advanced fibrosis[57].

Beside increased pro-inflammatory eicosanoid formation, new data suggest the increased formation of pro-inflammatory eicosanoids is accompanied by insufficient SPM levels in adipose tisue and in other metabolically active tissues, including the liver and skeletal muscle, thereby indicating that impaired tissue inflammation resolution ability is a generalized defect in obesity-related conditions like NASH[58]. In inflamed adipose tissue from genetically and diet-indced obese mice and from obese insulin resistant patients, the formation of SPM including RvD1, PD1, 17-HDHA and 18-HEPE was impaired, and the ratio between pro-inflammatory eicosanoids LTB4 and PGE2) and SPM levels, rather than the absolute levels of these mediators, correlated with the severity of inflammation and functional reregulation[59,60,61,62](**Table 1**).

Further corroborating a pathogenic role of SPM deregulation in obesity-related disorders, including NASH, decreased serum LXA4 levels and increased abdominal visceral fat area are independent predictors in a cohort of individuals at risk of developing metabolic syndrome[63].

Potential therapeutic role of SPMs for the treatment of inflammation and fibrosis in NASH

Based on the above-mentioned data, the restoration of normal proresolving ability could represent a novel therapeutic target for the treatment and reversal of inflammation and fibrosis in NASH.

Growing preclinical data support this perspective. RvD1 was the first SPM evaluated in cultured cells and in rodent models of diet-induced NASH. In cultured hepatocytes, pretreatment with RvD1 attenuated ER stress-induced apoptosis, Sterol Regulatory Element Binding Protein(SREBP)-1 expression and triglycerides accumulation[64], and in high fat diet-induced NASH, the addition of RvD1to calorie restriction reversed established steatohepatitis[65], reduced liver macrophage infiltration and shifted macrophages from an M1 to an M2 phenotype, and normalized the pro-inflammatory adipokine pattern in adipose tissue. These effects were accompanied by specific changes in hepatic miRNA signatures, suggesting these small, noncoding RNAs may mediate the proresolution activity of RvD1 at the post-transcriptional level[62], and were absent in macrophage-depleted precision-cut liver slices, indicating a crucial role of these cells in mediating RvD1 actions[62].

Other SMPs have also yielded interesting results in diet-induced NASH: LXA4, RvE1, Protectin D1 (PD1) and Maresin D1(MaR1) improved adipose tissue inflammation and insulin resistance and hepatic fat infiltration and insulin resistance and reduced hepatocyte ER stress-induced apoptosis through Akt and AMPK activation and c-Jun N-terminal kinase (JNK) inhibition; and PD1 and MaR1 increased expression of adiponectin, a key anisteatotic, anti-inflammatory and antifibrogenic adipokine to a similar extent as thiazolidinediones[66, 67, 68 ,69 70].

In HFD-induced rodent models of NASH and in cultured primary hepatocytes Kupffer cells and adipocytes, MaR1 administered at physiological, nanomolar concentrations prevented palmitate- and hypoxia-induced ER stress and apoptosis by inducing a specific miRNA signature and enhanced Kupffer cell phagocytosis[71].

Collectively, these mechanisms underlied the improvement in steatosis and steatohepatitis observed with SPM administration in diverse diet-induced models of NASH[63-69].

Beside attenuating inflammatory response, SPMs expedited its resolution by enhancing monocyte migration, macrophage polarization into a pro-resolving M2 phenotype[72], promoting macropage autophagy[73] and clearance of apoptotic hepatocytes and cellular debris

(efferocytosis). Collectively, these properties of SPM converged to restore a normal hepatic and adipose tissue architecture and homeostasis.Importantly, SPM demostrated also potent anti-fibrotic properties preclinically: Resolvin D1, Resolvin E1, Protectin DX and Maresin 1 atenuated fibrosis progression and, more intriguingly, also attenuated established fibrosis in diverse preclinical models of hepatic, renal and pulmonary fibrosis[74, 75, 76], at least in part through suppressing and reversing TGF-β1/Smad2/3-induced epithelial-to-mesenchimal transition (EMT) of epithelial cells, which provide up to 40% of extracellular matrix-deposing myofibroblasts, and restoring a normal tissue levels of Matrix metalloproteinase(MMPs), which contribute to ECM resorption[76,77,78,79.]

The antifibrotic potential of SPMs in NASH remains unexplored to date. Furthermore, the optimal pharmacological strategy to ensure pharmacological concentrations of these SPMs in target tissues needs to be defined, as SPMs are rapidly inactivated by eicosanoid oxidoreductases. Several pharmacological strategies to prolong SPMs biological activity and enhance selective delivery of SPMs to target organs, are being investigated.

Benzo-diacetylenic-17R-RvD1-methyl ester (BDA-RvD1) is a synthetic, oxidoreductase-resistant RvD1 analogue which showed a 3.5-fold higher potency than natural compound in protecting lungs from ischemia-reperfusion injury[80],

Nanomedicine techniques yielded the incorporation of SPMs into liposomes (Lipo-RvD1)[81], which are cleared by macrophages and may therefore accumulate in the liver, and SPM encapsulation in poly-lactic-co-glycolic acid(PLGA) microparticles[82], in order to preserve their biological activities and provide controlled release.Treatment with LXA4 encapsulared in PLGA microparticles accelerated wound healing of dorsal rat skin ulcers[82], while a RCT evaluating safety and efficacy of RX10045, a synthetic RvE1 analog, on dry eye disease, has been completed (ClinicalTrials.gov Identifier:: NCT00799552).

Concluding Remarks

The resolution of necroinflammation and fibrosis remains a primary clinical target in NASH, the most common chronic liver disease and a major cause of end-stage liver disease. Our evolving understanding of lipotoxicity[83] the basic molecular mechanisms driving inflammation and fibrosis[84] and their resolution in obesity-related conditions, including NASH,, have led to the proposal of a novel, tractable therapeutic paradigm i.e. SPM-promoted resolution. As growing evidence from cellular and *in vivo* animal models, as well as observational human data, suggest that the therapeutic potential of SPMs and their synthetic mimetics may expand to the regression of hepatic necroinflammatory and fibrotic changes in NASH. Further issues remain (see **Outstanding Questions**).

The reason for reduced SPM levels in obesity-related NASH needs also to be elucidated, Several potential underlying causes may underlie such deficit. The most obvious factor is a reduced tissue PUFA content resulting from Western diet-induced deregulated hepatic and adipose tissue Δ5- and Δ6-desaturase activity and desaturation capacity, resulting in an unbalanced ω-6 to ω-3 PUFA ratio[85, 86]. Furthermore, an accelerated SPM inactivation in obesity may also contribute: consitently, 15-PG-dehydrogenase/eicosanoid oxidoreductase, a key enzyme in SPM inactivation, and soluble epoxide hydrolase (sEH), the enzyme that hydrolyzes omega-6 and omega-3 epoxides into inactive diols, are up-regulated in obese adipose tissue[60, 87]. Elucidating the dominant mechanism of SPM inactivation may have important therpeutic implications, sos blocking genralized SPM catabolism may be more effective than single SPM supplementation**.**

Figure legends

Figure 1 Pathways for SPMs biosynthesis

Omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) are released from membrane phospholipids mainly by phospholipase A2 (PLA2) activity. Cyclooxygenase (COX) 1 and 2 convert the omega-6-PUFA arachidonic acid (AA) into prostaglandins (PGs) such as PGE2, while 5-lipoxygenase (5-LOX) interacting with 5-LOX activating protein (FLAP) generate the unstable epoxide intermediate leukotriene (LT) A4, which is further converted into LTs such as LTB4, from AA.

LTA4 is also converted by 12-LOX into lipoxin (LX) A4. The coordinated activities of 15-LOX, which produces 15S-hydroxyeicosatetraenoic acid (15S-HETE), and 5-LOX also give rise to LXA4. Alternatively, formation of 15R-HETE by aspirin (ASA)-acetylated COX-2 results in the biosynthesis of 15-epi-LXA4. On the other hand, the omega-3-PUFA docosahexaenoic acid (DHA) is converted by 15-LOX into 17S-hydroxy-DHA (17S-HDHA), which is subsequently transformed by 5-LOX into resolvins of the D series. Additionally, 17S-HDHA can be converted by epoxidation hydrolysis into protectin D1 (PD1). Moreover, DHA is transformed by 12-LOX into 14S-hydroxy-DHA (14S-HDHA), the precursor of maresin (Mar) 1 and 2.

The omega-3-PUFA eicosapentaenoic acid (EPA) can also be converted by either ASA-acetylated COX-2 or CYP450 activities into 18R-hydroxy-EPE (18R-HEPE), which is subsequently transformed by 5-LOX into RvE1and RvE2. Conversion of 18R-HEPE via 15-LOX gives rise to RvE3. Lipid mediators generated from AA, DHA and EPA exert autocrine and paracrine actions by binding to specific G-protein coupled receptors present in the surface of the cell membrane.

Figure 2.

Panel A

Eicosanoids and Specialized Pro-resolving Mediators(SPMs) derived from arachidonic acid(AA), eicosapentaenoic acid(EPA) and docosahexaenoic acid(DHA).

AA is metabolized by cyclooxygenases (COX) 1/2 to prostaglandins(PGs) and thromboxanes(TXs) and by 5-lipoxygenase (5-LOX) to leukotrienes (LTs) which are involved in the initiation of the inflammatory response (red colour).

Hydroxyeicosatetraenoic acids (HETEs) and lipoxins are also synthesized from arachidonic acid by 5-, 12- and 15-LOX and cytochrome (Cyt) P450.

Eicosapentaenoic acid is metabolized to 3-series PGs by COX and 3-series TXs by 5-LOX (weak pro-inflammatory properties, orange colour) and to E-series resolvins (anti-inflammatory and pro-resolving actions, green colour) by CYP450 and 5-LOX.

Resolvins of the D-series, protectins and maresins are derived from docosahexaenoic acid.

Lipoxins, resolvins, protectins and maresins have anti-inflammatory and pro-resolving actions.

Panel B.

The receptors for eicosanoids and SPMs.

Prostaglandins, Thromboxanes and Leukorienes elicit a proinflammatory response by binding and activating their receptors, including Prostaglandin E2 receptor type 2,3 and 4 (EP2/3/4), B-leukotriene 1 and " receptor(BLT1/2) and Cysteinyl leukotriene 1 and 2(CysLT1/2) receptors.

LXA4 is a central switching signal for inflammation, as is stops LTB4-induced leukocyte chemotaxis by binding CysLT1 and BLT1 receptors and inhibiting LT-induced intracellular Calcium influx, and it initiates inflammation resolution by binding A$ Lipoxin/Formyl-peptide receptor type 2(ALX/FPR2) receptor, a G-protein coupled receptor (GPCR) that together with GPR32 also signals for RvD1 and for the anti-inflammatory, proresolving peptide Annexin A1.

Other known GPCRs for SPMs include GPR32 for RvD1, ChemR23 for RvE1 and FPR18 for RvD2.

Table 1. Main SPMs and molecular targets and cellular effects

Series	**Mediator**	**Receptor**	**Cellular pathway**	**Biological effect**
A4-series LXs	LXA4 15-epi-LXA4	ALX/FPR2	**Macrophage:** MAPK/HSP 27 activation→↑ IL10	Anti-inflammatory & Pro-resolving
E-series Resolvins	RvE1, RvE2, RvE3	ChemR23	**Adipocyte**: ↑ AMPK phosphorylation ↑ adiponectin expression ↑ PPAR-γ expression ↑ IRS-1/IRS-2 ↑ GLUT-2/-4 **Epithelium:** ↓EMT transition **Macrophage:** ↑PI3K/Akt and Raf/ERK signaling pathway	Anti-inflammatory & Pro-resolving ↑ insulin sensitivity ↓ fibrogenesis ↑efferocytosis and shift to M2 pro-resolving phenotype
		BLT1(antagonist)	**Neutrophil:** [NF-kB activation	↓ PMN recruitmen
D-series resolvins	RvD1, RvD2, RvD3, RvD4, RvD5, RvD6	ALX/FPR2 GPR32	**Adipocyte:** ↑ AMPK and Akt phosphorylation ↑ PPAR-γ expression ↑ adiponectin expression **Hepatocyte:** ↓ ER stress-induced JNK activation →↓ apoptosis and Tg accumulation **Epithelium:** ↓EMT transition ↑MMP-9 secretion→↓ECM resorption	Anti-inflammatory & Pro-resolving ↑ adipose and hepatic insulin sensitivity ↓ steatohepatitis
Protectins	PD1	?	**Adipocyte:**	↑ insulin sensitivity

			↑ AMPK phosphorylation ↑ adiponectin expression ↑ PPAR-γ expression ↑ IRS-1/IRS-2 ↑ GLUT-2/-4 **Epithelium:** ↓EMT transition ↑MMP-9 secretion→ ↓ ECM resorption	Anti-inflammatory & Pro-resolving
Maresins	MaR1 MaR2	?	**Hepatocyte:** ↑ anti-ER stress and anti-apoptotic miRNA signature **Kupffer cells:** ↑ palmitate- and hypoxia-induced phagocytosis **Adipocyte:** ↓ palmitate- and hypoxia-induced ER stress ↑ AMPK and Akt phosphorylation ↑ PPAR-γ expression ↑ adiponectin expression ↓ lipolysis ↑ autophagy **Epithelium**: ↓EMT transition ↑MMP-9 secretion→↓ECM resorption	↑ insulin sensitivity Anti-inflammatory & Pro-resolving ↓ fibrosis
Protectin D			Macrophage: M2 phenotype shift	anti-inflammatory & Pro-resolving

Abbreviations: SREBP-1c: sterol regulatory element-binding protein 1c; ChREBP: carbohydrate response element binding protein; JNK: c-Jun N-terminal kinase;

ransporter 2; POMC: proopiomelanocortin; TGF: transforming growth factor; AMPK:

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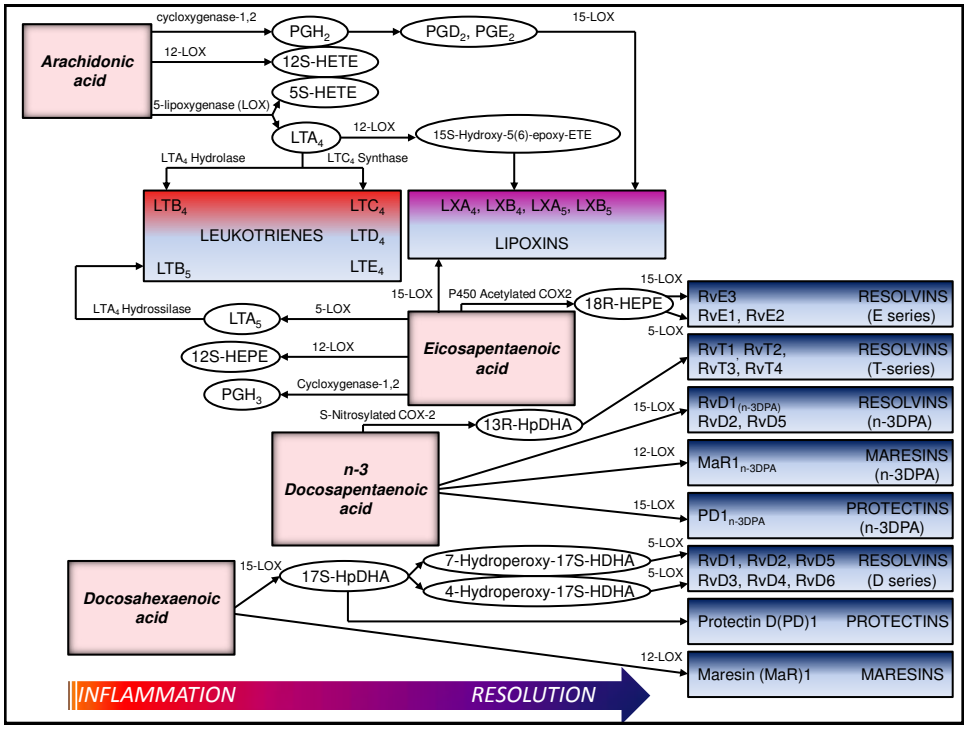
Arachidonic acid
cycloxygenase-1,2
PGH2
PGD2, PGE2
15-LOX
12-LOX
12S-HETE
5S-HETE
5-lipoxygenase (LOX)
LTA4
12-LOX
15S-Hydroxy-5(6)-epoxy-ETE
LTA4 Hydrolase
LTC4 Synthase
LTB4
LTC4
LEUKOTRIENES
LTD4
LTB5
LTE4
LXA4, LXB4, LXA5, LXB5
LIPOXINS
15-LOX
P450 Acetylated COX2
18R-HEPE
RvE3
RvE1, RvE2
RESOLVINS (E series)
LTA4 Hydrossilase
LTA5
5-LOX
Eicosapentaenoic acid
12S-HEPE
12-LOX
PGH3
Cycloxygenase-1,2
S-Nitrosylated COX-2
13R-HpDHA
RvT1, RvT2, RvT3, RvT4
RESOLVINS (T-series)
RvD1(n-3DPA)
RvD2, RvD5
RESOLVINS (n-3DPA)
n-3 Docosapentaenoic acid
MaR1n-3DPA
MARESINS (n-3DPA)
PD1n-3DPA
PROTECTINS (n-3DPA)
Docosahexaenoic acid
17S-HpDHA
7-Hydroperoxy-17S-HDHA
4-Hydroperoxy-17S-HDHA
RvD1, RvD2, RvD5
RvD3, RvD4, RvD6
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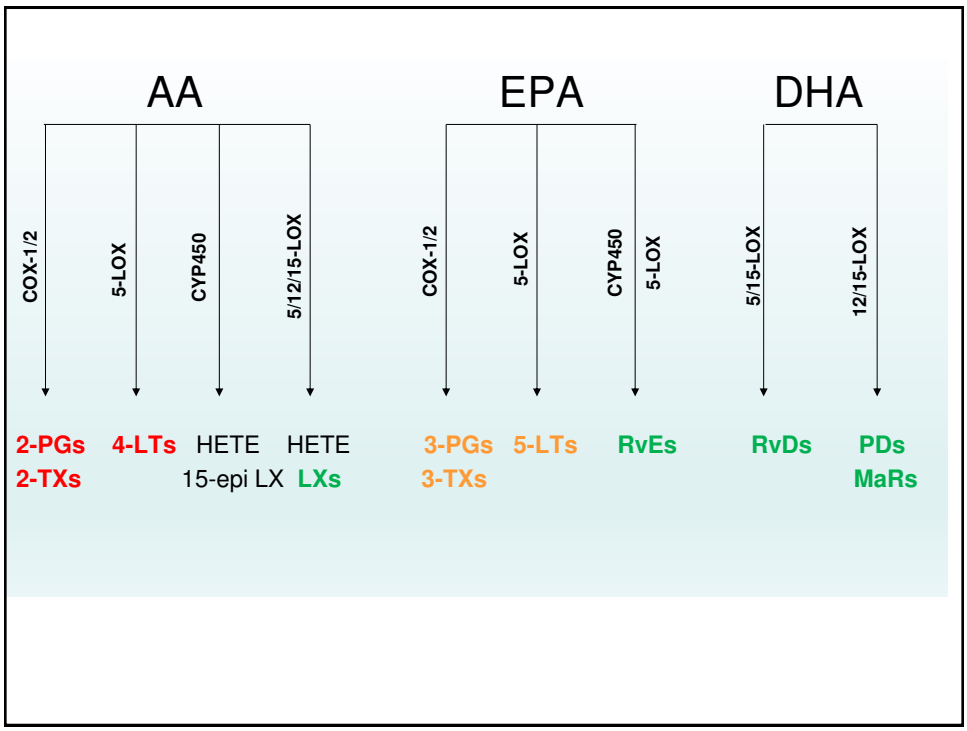
PROTECTINS
Maresin (MaR)1
MARESINS
INFLAMMATION
RESOLUTION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5/15-LOX
12/15-LOX
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2-TXs
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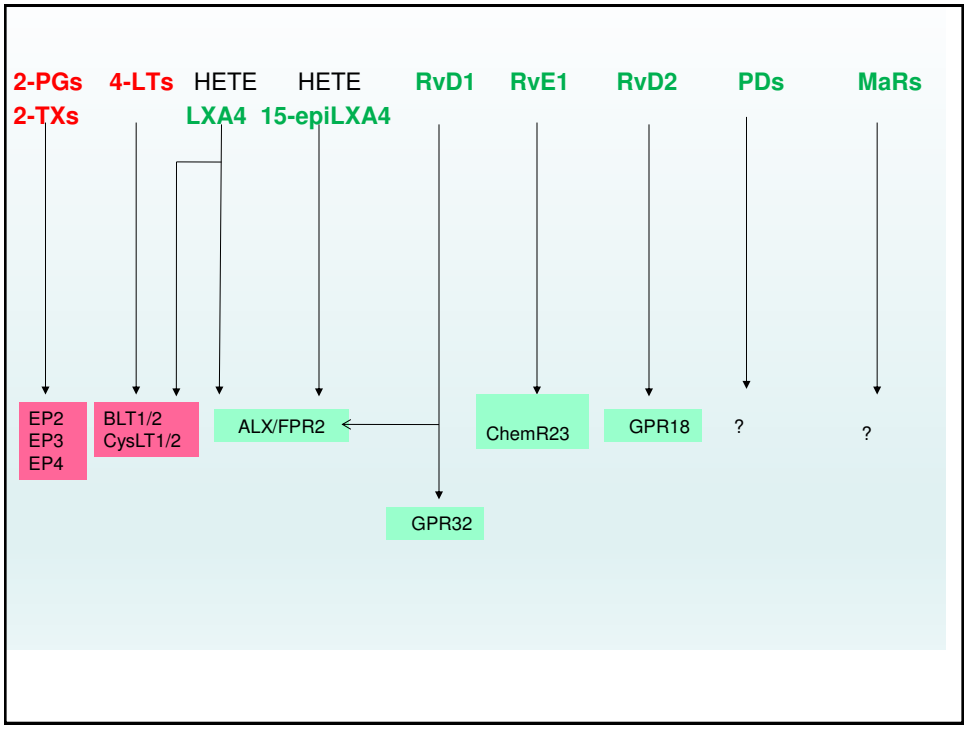
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RvE1
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EP2
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EP4
BLT1/2
CysLT1/2
ALX/FPR2
ChemR23
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GPR32