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Review

Proresolving lipid mediators and liver disease☆

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ABSTRACT

Inflammation is a characteristic feature of virtually all acute and chronic liver diseases. It intersects different liver pathologies from the early stages of liver injury, when the inflammatory burden is mild-to-moderate, to very advanced stages of liver disease, when the inflammatory response is very intense and drives multiple organ dysfunction and failure(s). The current review describes the most relevant features of the inflammatory process in two different clinical entities across the liver disease spectrum, namely non-alcoholic steatohepatitis (NASH) and acute-on-chronic liver failure (ACLF). Special emphasis is given within these two disease conditions to gather the most relevant data on the specialized pro-resolving mediators that orchestrate the resolution of inflammation, a tightly controlled process which dysregulation commonly associates with chronic inflammatory conditions.

1. Introduction: the spectrum of chronic liver disease

Chronic liver disease is characterized by a continuous process of inflammation and injury of the liver parenchyma leading to fibrosis and cirrhosis with the severe disruption of the hepatic architecture. The final stages of liver cirrhosis, patients frequently develop the so called acute-on-chronic liver failure (ACLF), a severe syndrome characterized by extra-hepatic organ dysfunction and failure(s) resulting in high short-term mortality [1]. Chronic liver disease presents multiple etiologies including alcohol abuse, virus infection, toxins as well as autoimmune, genetic and metabolic disorders. The full spectrum of liver diseases offers the opportunity to investigate the inflammatory burden from very mild to very severe forms of presentation. In the following sections, we describe the most relevant features of the inflammatory process and its resolution in patients with non-alcoholic fatty liver disease (NAFLD) progressing to non-alcoholic steatohepatitis (NASH), who exhibit a "low-grade" inflammatory condition triggered by nutrient and metabolic surplus [2]. The most relevant features of the inflammatory process and its resolution will be also described for patients with advanced cirrhosis progressing to ACLF, in whom a very intense systemic hyper-inflammatory state leads to widespread tissue and organ injury [1].

2. NAFLD and NASH

NAFLD comprises a wide range of hepatic manifestations that are associated with features of the metabolic syndrome, especially obesity, insulin resistance, dyslipidemia and hypertension [3]. The incidence of NAFLD has increased in parallel with the obesity pandemic, being its global prevalence of 24% worldwide [4]. Pediatric NAFLD is also rising as consequence of more frequent childhood obesity [4]. NAFLD has also been reported in lean non-obese individuals, being its prevalence of 75% in patients with type 2 diabetes and of 50% in hypertensive individuals [5]. The clinical manifestations of NAFLD are very diverse and are under the influence of many risk factors such as metabolism, genetic background, diet and other environmental factors as well as the microbiome [4,6]. The common denominator of NAFLD is the presence of hepatic steatosis, which is the accumulation of fatty acids (FAs) in the form of lipid droplets rich in triglycerides (TAG) in the cytoplasm of hepatocytes

Abbreviations: 17-HDHA, 17-hydroxy-docosahexaenoic acid; 18-HEPE, 18-hydroxyeicosapentaenoic acid; ACLF, acute-on-chronic liver failure; AD, acute decompensation; CC, compensated cirrhosis; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FA, fatty acid; IL, interleukin; HFD, high fat diet; LOX, lipoxygenase; LPS, lipopolysaccharide; LT, leukotriene; LX, lipoxin; MaR, maresin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PD1, protectin D1; PG, prostaglandin; PMN, polymorphonuclear neutrophils; PUFA, polyunsaturated FA; RvD, resolvin D; SPM, specialized pro-resolving mediators; TAG, triglyceride; WAT, white adipose tissue.

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[6]. In these patients, the increase in the hepatic pool of FAs is the result of multiple factors including imbalanced hepatic synthesis and/or uptake and usage of these lipids. The main sources of FAs in this condition are extrahepatic TAG lipolysis in the visceral white adipose tissue (WAT) and de novo hepatic lipogenesis, which are commonly accompanied by reduced hepatic mitochondrial β-oxidation and lipid export through very low-density lipoproteins [3,7].

NAFLD frequently progresses to NASH, a condition in which lipid accumulation in the liver is accompanied by inflammation of this organ (Fig. 1). NASH is currently recognized as the most common chronic liver disease currently affecting 25% of the adult population [8,9]. The progression of NAFLD to NASH has classically been explained by the "two-hit hypothesis", in which the first hit is triggered by hepatic steatosis leading to increased vulnerability to other insults. The second hit is triggered by a wide range of injury factors, among them inflammatory cytokines released by Kupffer cells, adipokines released by WAT, increased oxidative stress and liver cell (hepatocyte) death, as well as mitochondrial dysfunction [10]. At present, the "two-hit hypothesis" has evolved into the "parallel multiple-hit hypothesis". According to this reformulated hypothesis, steatosis not necessarily precedes inflammation in all patients and the chronological appearance of the different injury hits vary from one patient to another, leading to different stages of NAFLD-NASH [11]. Therefore, NAFLD per se is already a pro-inflammatory condition and at the same time sustained hepatic inflammation is necessary for the progression to NASH. In addition to steatosis and inflammation, increased formation and accumulation of extracellular matrix proteins ultimately leading to hepatic fibrosis is commonly seen in patients with NASH. Fibrogenesis is usually activated by signals released by activated Kupffer cells and apoptotic hepatocytes, which induce phenotypical changes in hepatic stellate cells, which undergo myofibroblasts with the consequent exacerbated production of extracellular matrix components [8,12]. If the fibrogenic process remains highly active and the mechanisms blocking the remodelling of the extracellular matrix are insufficient, fibrosis can progress to liver cirrhosis. An approved therapy for NASH is not currently available, and therefore novel pharmacological strategies targeting inflammation and fibrosis in this disease condition are an unmet medical need [8,13].

2.1. Lipid mediators and the onset of inflammation in NASH associated with obesity

The triggers of inflammation in patients with NAFLD progressing to NASH range from lipotoxicity to lipopolysaccharide (LPS) leaking from the gut as well as to the release of adipokines from visceral fat (Fig. 1) [2]. In fact, visceral adiposity has a direct impact on hepatic inflammation accelerating the progression from NAFLD to NASH. This is probably the consequence that both visceral WAT and liver have immediate access to a vast network of blood vessels that implicate a direct connection between these two organs. This connection is exemplified by the observation that the presence of "low-grade" inflammation in obese visceral WAT is a critical risk factor for the development of obesity-induced NASH [14,15]. This chronic, unresolved, "low grade" inflammatory state leads to increased WAT release of pro-inflammatory adipokines (i.e. leptin, interleukin (IL) 6, tumor necrosis factor (TNF) α and monocyte chemoattractant protein-1 (MCP-1)) accompanied by a reduction in the anti-inflammatory and insulin-sensitizing adipokine, adiponectin [14,15].

In addition to adipokines, inflamed WAT also releases bioactive lipid mediators that have a direct impact on other organs and tissues, especially on the liver. The ability of WAT to generate bioactive lipid mediators was first described in the late 1960s by Shaw and Ramwell who identified a group of carboxylic acids derived from the oxygenation of the omega-6- polyunsaturated fatty acid (PUFA) arachidonic acid (AA) in rat epididymal fat pads which were later identified as prostaglandins (PGs) [16]. Among these, PGE_2 was recognized as one of the most abundant lipid mediators in WAT with a role in the regulation of hormone-sensitive lipolysis [17]. In more recent times, PGE_2 was described as a regulatory factor of WAT inflammation and adaptive thermogenesis [18]. Overexpression of five-lipoxygenase (5-LOX) activating protein (FLAP) and increased production of leukotriene (LT) B_4 in WAT of patients and animals with obesity and insulin resistance was also described [19,20]. In this organ, LTB_4 activates NF-κB and stimulates the

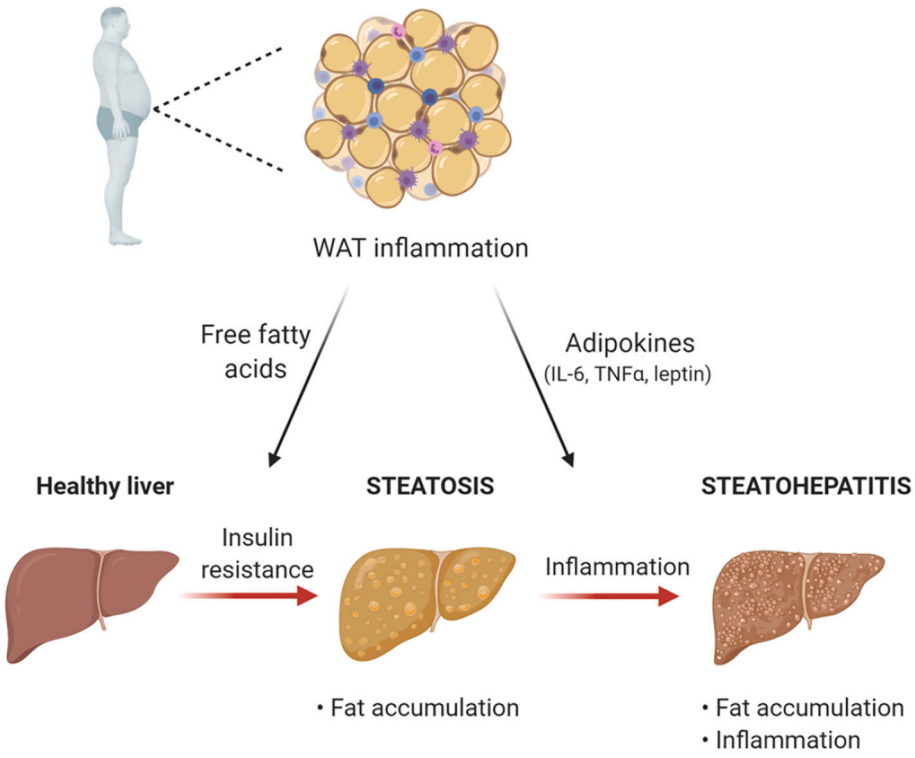

Fig. 1. Role of visceral white adipose tissue (WAT) inflammation in the pathogenesis of hepatic steatosis and steatohepatitis. Abdominal obesity, insulin resistance and WAT inflammation are crucial risk factors in the development of non-alcoholic fatty liver disease. The presence of chronic 'low grade' inflammation in WAT is associated with increased release of fatty acids and proinflammatory adipokines such as interleukin (IL)-6, tumor necrosis factor (TNF) α and leptin among others, which have a direct impact on liver pathophysiology, triggering insulin resistance, fat accumulation and inflammation in this organ.

release of the adipokines MCP-1 and IL-6, which directly connect WAT inflammation with insulin resistance and hepatic steatosis [20]. Furthermore, activation of the LTB_4 receptor BLT-1 in the liver was shown to promote hepatic insulin resistance [21]. Consistent with these findings, pharmacological inhibition of FLAP or genetic deletion of the BLT-1 receptor were associated with amelioration of insulin resistance and inflammation in this organ [20,22]. Moreover, overexpression of the 5-LOX pathway was reported in apolipoprotein E deficient ($ApoE^{-/-}$) mice, which spontaneously develop a liver phenotype characterized by steatosis, increased oxidative stress and induction of pro-inflammatory genes [23]. In these mice, genetic disruption of *ALOX5*, the gene coding for 5-LOX, offered protection against liver inflammatory injury induced by the administration of a high-fat diet (HFD) [24]. Mice double knockout mice for $ApoE^{-/-}$ and $5\text{-}LOX^{-/-}$ also showed improved insulin signaling secondary to reduced hepatic JNK phosphorylation and the normalization of insulin sensitivity [24]. Furthermore, hepatocytes isolated from these double knockout mice were protected against TNFα–induced apoptosis [25]. These experimental data have a translation to the clinic since patients with NASH exhibit increased formation of 5-LOX-derived products [25].

2.2. Lipid mediators and resolution of inflammation in NASH associated with obesity

The inability to resolve inflammation has emerged as a crucial factor in obesity-induced NASH [26]. During the last decades, the view of the resolution concept by the scientific community has evolved from being considered a mere passive process relying on the dissipation of pro-inflammatory mediators to be recognized as a highly active process orchestrated by the formation and actions of a specific set of endogenous specialized proresolving mediators (SPMs) [27]. The term SPMs embraces all the families of chemically and functionally distinct anti-inflammatory and pro-resolving lipid mediators derived from both omega-6- and omega-3-PUFAs. For example, human WAT has the capacity to generate lipoxin (LX) A_4 [28–30], which is a SPM generated by transcellular routes from endogenous sources of the omega-6-PUFA AA through sequential LOX-LOX interactions [31]. In addition to LXA_4, human WAT also has the capacity to generate SPMs derived from omega-3-PUFA [32]. Indeed, COX and LOX enzymes present in mouse and human WAT can convert eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) into potent bioactive lipid autacoids, termed resolvins (derived from resolution phase interaction products). Resolvins are classified as either resolvins of the E-series if the biosynthesis is initiated from EPA or resolvins of the D-series if they are generated from DHA [27,33]. Alternatively, DHA can be converted into protectins (PD1) and maresins (MaR1 and MaR2) and DPA can give rise to resolvins of the 13-series (RvTs) [33,34].

SPMs have dual roles as stop-signals for inflammation and activators of resolution of inflammation. SPMs exert anti-inflammatory actions within the nanomolar range at concentrations as low as 1 to 10 nM [27,33]. The anti-inflammatory properties are specific for each SPM. For example, LXA_4 inhibits leukocyte chemotaxis, rolling, adhesion to and transmigration across endothelial monolayers in response to LTB_4 [35]. RvE1 decreases neutrophil (PMN) infiltration and T cell migration, reduces TNFα and interferon (IFN) γ secretion, inhibits chemokine formation and blocks IL-1β-induced NF-κB activation [36]. RvD1 and RvD2 reduce inflammatory pain, block IL-1β expression induced by TNFα and limit PMN infiltration into inflamed brain, skin and peritoneum [37,38]. RvD2, in particular, has been shown to be a potent endogenous regulator of excessive inflammatory responses in mice with microbial sepsis (see below) [39]. In addition, RvD2 has been shown to down-regulate IL-1β expression, and to reduce ASC speck formation (a proxy of inflammasome assembly) and secretion of mature IL-1β in peritoneal and bone marrow-derived macrophages [40]. On the other hand, it has been reported that PD1 and MaR1 exert protective actions in acute models of inflammation by blocking PMN migration and infiltration into the inflammatory site [27,41]. In addition to their anti-inflammatory properties, SPM exert potent pro-resolving actions and expedite the resolution process also within the nanomolar range. In general, SPMs pave the way for monocyte differentiation into phagocytosing macrophages, facilitating the removal of dead or dying cells as well as bacterial clearance [42,43]. For example, RvE1 stimulates macrophage phagocytosis of apoptotic PMN and is a potent counter-regulator of L-selectin expression [36,44], meanwhile MaR1 stimulates macrophage phagocytosis and efferocytosis, which involves removal of dead or apoptotic cells by phagocytosing macrophages [41]. Interestingly, macrophage phagocytosis of apoptotic cells also leads to the biosynthesis of SPMs, which act in an autocrine manner to facilitate phagocytosis [45]. SPMs are also able to enhance phagocyte efflux from inflamed tissues to draining lymph nodes to aid in resolution [42].

Unbalanced formation of pro-resolving SPMs has been reported in obese individuals, a finding that advocate for the restoration of SPM levels as a potential therapy to counteract the inflammatory component of NASH associated with obesity [46]. For instance, by means of targeted lipidomics we have uncovered the presence of an impaired ratio between SPMs and pro-inflammatory LTs and PGs in WAT from obese individuals as compared to lean subjects [29]. A failure in the resolution program has also been described in the systemic circulation of obese individuals, who exhibit reduced leukocyte production of the SPM biosynthetic intermediate 17-hydroxy-DHA (17-HDHA) and unbalanced formation of SPMs, in particular of D-series resolvins, accompanied by enhanced production of pro-inflammatory lipid mediators such as LTB_4 [47]. At the experimental level, impaired formation of 17-HDHA, RvD1 and PD1 was reported in mice with HFD-induced obesity [28]. Similar deficits in SPMs were described in mice induced to obesity with an obesogenic diet and in genetically obese *ob/ob* and diabetic *db/db* mice [48–50].

2.3. Dietary and pharmacological interventions to restore resolution homeostasis in NASH

Different approaches have been tested to override impaired formation of SPMs in experimental obesity-induced NASH. The foremost approach was boosting SPM formation through the administration of diets rich in EPA and DHA, which are the parent precursors of a wide range of SPMs. Such an approach was used by our group by administering a diet enriched in EPA and DHA to obese *ob/ob* mice, in which these PUFA prevented the development of severe hepatic steatosis [49]. In this model, intraperitoneal injection of RvE1 conferred anti-steatotic protection, decreased serum ALT levels and consistently reduced hepatic F4/80 immunostaining, a marker of inflammatory infiltrate. Furthermore, RvE1 elicited significant insulin-sensitizing effects by inducing the expression of adiponectin, glucose transporter type 4 (GLUT-4), insulin receptor substrate 1 (IRS-1) and peroxisome proliferator-activated receptor (PPAR) γ in the perigonadal WAT depot of these obese mice [49]. In agreement with these findings, Pal et al. recently demonstrated in obese inbred mice that suppressed 18-hydroxyeicosapentaenoic acid (18-HEPE) levels in liver and WAT can be efficiently rescued by EPA administration [51]. In addition, RvE1 treatment was able to correct hyperinsulinemia and hyperglycemia in these mice [51]. Nevertheless, Depner et al. conducted studies demonstrating that DHA is more effective than EPA at preventing western diet-induced NASH in $Ldlr^{-/-}$ mice [52]. Consistent with this, the dietary supplementation of mice with DHA conferred significant protection against necroinflammatory liver injury [53]. In this study, increased hepatic formation of the DHA-derived lipid mediators 17-HDHA and PD1 was confirmed by high performance liquid chromatography-gas chromatography/mass spectrometry analysis. Moreover, incubation of hepatocytes with 17-HDHA significantly reduced DNA damage and oxidative stress induced by hydrogen peroxide [54]. Likewise, administration of the DHA-derived SPM RvD1 in combination with calorie restriction, which by itself lessened WAT and liver tissue weight and hepatic steatosis and insulin

resistance, markedly reduced the hepatic inflammatory component of obese mice with NASH, mainly by facilitating the hepatic resolution process and skewing liver macrophages from M1 to M2 proresolving phenotype [54]. Similar actions were described in WAT macrophages. Along these lines, Titos et al. provided evidence that RvD1 skewed WAT macrophages from a classical activation inflammatory profile (M1 phenotype) toward an alternatively anti-inflammatory M2-like state [55]. Consistent with this, Hellmann et al. confirmed reduction of macrophage-containing crown-like structures in WAT by RvD1 [50]. Administration of another DHA-derived SPM, MaR1, markedly improved insulin sensitivity and ameliorated liver steatosis by decreasing lipogenic enzymes, while inducing fatty acid oxidation genes and autophagy in mice with experimental obesity [56,57]. Furthermore, MaR1 was shown to promote phagocytic activity of the resident liver macrophages (i.e. Kupffer cells), a fundamental process in the active resolution of inflammation [58]. More recently, it has been demonstrated in mice with HFD-induced NASH that MaR1 enhances the transcriptional activity of retinoic acid-related orphan receptor alpha (RORα), a key regulator of M2 polarity in liver macrophages [59]. Finally, LXA_4, an omega-6-PUFA-derived SPM, was shown to exert protective effects against obesity-induced NASH by decreasing TNFα levels and M1 macrophages, while restoring $CD206^+$ M2 macrophages and reducing liver weight, serum ALT and hepatic TG levels [30]. Recently, LXA_4 was reported to reduce immune cell infiltration into the liver and to inhibit systemic inflammatory cytokines such as IL-1β, IL-6, IL-17, TNFα, and IFNγ in murine alcoholic hepatitis [60].

An alternative approach to the use of diets rich in omega-3 PUFAs to override the deficit of SPM formation in experimental NASH is the use of *fat-1* mice with transgenic expression of an omega-3 fatty acid desaturase that allows high content of omega-3-PUFA and a lower omega-6 to omega-3 ratio in body tissues [61,62]. Consequently, *fat-1* mice are endogenously enriched with omega-3-PUFA-derived SPMs [63]. In the context of liver disease, these mice were shown to be resistant to HFD-induced obesity associated NASH and to display less hepatic insulin resistance, steatosis, macrophage infiltration, necroinflammation and lipid peroxidation than paired-fed obese wild-type mice [62,64]. In addition, the liver transcriptome profile of *fat-1* mice was characterized by suppression of genes involved in inflammation, fatty acid uptake and lipogenesis [62,64]. Another approach to ensure optimal concentrations of SPM in tissue is the inactivation of enzymes mediating the catalysis of these lipid mediators. In tissues, SPMs such as LXA_4 as well as omega-3-derived epoxides are rapidly metabolized into inactive products by 15-PG-dehydrogenase/eicosanoid oxidoreductase and soluble epoxide hydrolase (sEH) [65], enzymes that are markedly up-regulated in obesity-induced NASH [28,64]. Finally, to increase the therapeutic half-life of SPMs and to provide prolonged biological actions and controlled release into target tissues, new strategies have emerged in the field of nanomedicine such as the incorporation of RvD1 into liposomes [66] and the encapsulation of LXA_4 in poly-lactic-*co*-glycolic acid microparticles [67].

The major challenge to promote resolution of inflammation through restoration of SPM levels in NASH remains in its clinical translation from the laboratory bench to the clinic bedside. The outcome of a recent trial in patients with NASH that received an omega-3-PUFA-rich diet for 6 months was the improvement of liver and plasma proteomic and lipidomic profiles and attenuation of endoplasmic reticulum (ER) stress [68]. Previously, a randomized control trial provided evidence that the supplementation of omega-3-PUFA to patients with NASH had an impact on the plasma lipid profile and liver histology [69]. In the WELCOME randomized control trial, 15 to 18-month treatment with DHA plus EPA (4 g/day) showed decreased liver fat and improved two histologically proven liver fibrosis biomarker scores [70]. Improvement of NASH was also observed in a clinical trial testing a highly purified EPA [71]. However, in a phase 2 trial, Sanyal and collaborators reported that the ethyl form of EPA significantly reduced levels of TAG compared to placebo but failed to exert any significant effect on the histologic features of NASH [72]. An important aspect to consider is that the response to omega-3-PUFA and SPMs is under the influence of the genetic background. For example, obese patients carrying a SNP variant in the gene encoding for the RvE1 receptor (i.e. ERV1/ChemR23 receptor) exhibit increased protein expression of this receptor in visceral WAT, which then associates with reduced levels of inflammatory cytokines/chemokines and lower TG/HDL ratio, a surrogate marker of insulin resistance and NASH [73]. The role of ERV1/ChemR23 in the regulation of the inflammatory burden in adipose tissue was confirmed in mice lacking the ERV1/ChemR23 gene which showed higher inflammatory gene expression in WAT [73].

2.4. SPM actions on ER stress

Because liver cells are highly susceptible to ER stress and ER stress plays a crucial role in the pathogenesis of NAFLD and NASH, a special section is dedicated to summarizing the effects of SPMs on hepatic ER stress. This view is consistent with the positive results obtained in ER stress in the recent omega-3-PUFA trial in patients with NASH described above [68]. A seminal study from our laboratory provided evidence in primary mouse hepatocytes and precision-cut liver slices that the DHA-derived SPM, MaR1 was able to down-regulate palmitate- and hypoxia-induced ER stress-associated genes ATF3, CHOP, BiP and Erdj4 (Fig. 2) [58]. In this study, a reduction in the number of TUNEL-positive apoptotic cells and a significant reduction in caspase 3/7 activity were observed in hepatocytes incubated in the presence of MaR1 [58]. Consistent with these findings, Jung et al. also found evidence that MaR1 was able to attenuate ER stress in HFD-fed obese mice by mechanism related to AMP-activated protein kinase (AMPK), thereby augmenting sarcoendoplasmic reticulum Ca2 + -ATPase 2b expression and suppressing lipid accumulation [74]. These authors subsequently demonstrated in the HepG2 cell line that another DHA-derived SPM, RvD1, was able to attenuate tunicamycin-induced ER stress and prevent caspase-3 activation and TAG accumulation [75]. Furthermore, the same group described similar actions for PDX, an isomer of PD1, which decreased phosphorylation of IRE-1 and eIF2α, downregulated CHOP expression, ameliorated hepatic steatosis and protected HepG2 cells from palmitate-induced ER stress [76].

3. Cirrhosis and ACLF

Cirrhosis is a progressive liver condition characterized by persistent hepatic inflammation, portal hypertension, extracellular matrix remodelling and intense deposition of collagen fibers leading to disorganization of the hepatic architecture and impaired liver function. The clinical course of liver cirrhosis can be divided into two stages, namely compensated and acutely decompensated (AD) cirrhosis. Compensated cirrhosis spans from the onset of liver cirrhosis to the first major complication, a period of time that can be longer than 10 years during which the patient remains asymptomatic or with minor symptoms, meanwhile liver injury and portal hypertension continue progressing [1,77]. AD cirrhosis is acutely manifested by the development of ascites (the accumulation of a large volume of fluid in the peritoneum), hepatic encephalopathy and variceal bleeding. More advanced complications of AD cirrhosis range from jaundice, higher susceptibility to bacterial infections, coagulopathy and hepatorenal syndrome. The estimated survival of a patient with AD cirrhosis is between 2 and 5 years [1,77]. AD cirrhosis is a reversible process, but these patients are at risk of suffering an additional acute deterioration due to a precipitating event (for example peritonitis) that might trigger ACLF development, the main cause of death in patients with cirrhosis [1,77]. ACLF is characterized by the manifestation of organ dysfunction and failure(s) across the six major organ systems (liver, kidney, brain, coagulation, circulation, and respiration) resulting in high short-term mortality [1,77]. The liver and the kidney are the most commonly affected organ systems followed by coagulation, brain, circulation and respiration. ACLF is classified in

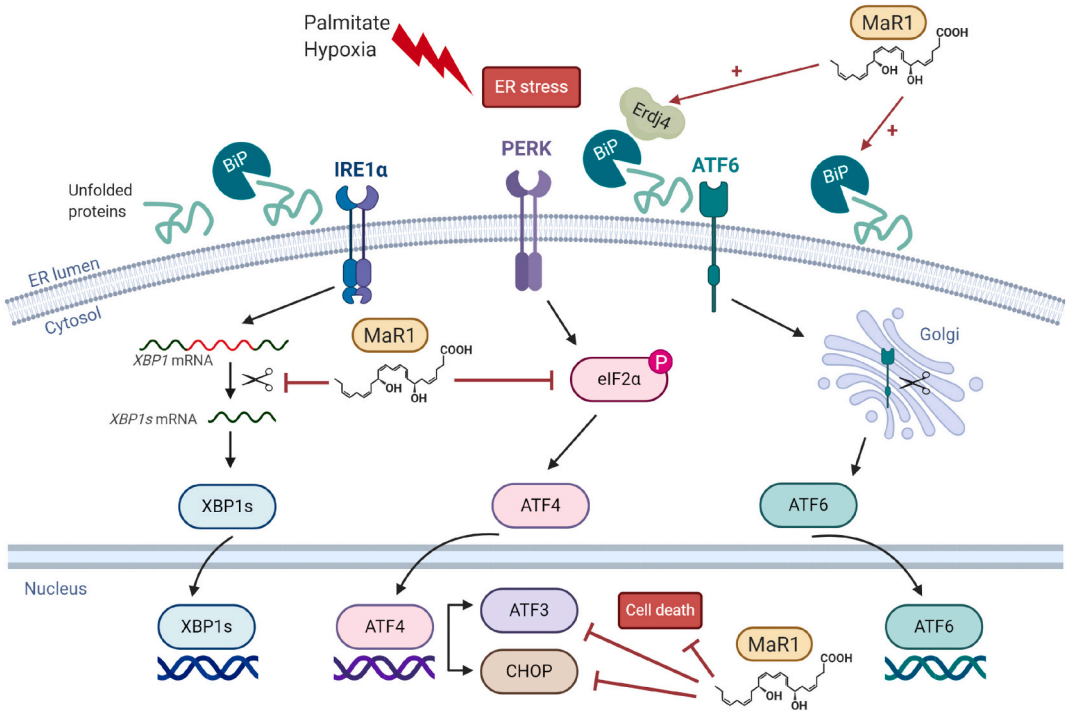

Fig. 2. Maresin 1 (MaR1) attenuates hepatic endoplasmic reticulum (ER) stress. In parenchymal liver cells (i.e. hepatocytes) pathogenic stimuli such as hypoxia and lipotoxicity (i.e. induced by the saturated fatty acid palmitate) disturb protein folding and activate the unfolded protein response, leading to ER stress. The specialized pro-resolving mediator (SPM) MaR1 prevents lipotoxicity-induced hepatocyte death by mechanisms related to the up-regulation of the chaperone BiP and the cochaperone Erdj4 at early stages of injury and down-regulation of the proapoptotic markers ATF3 and CHOP at later stages. MaR1 also blocks eIF2α phosphorylation and XBP1 splicing.

three grades of severity (ACLF-1, -2 and -3) according to the number of organ failures and may exhibit a variable course during hospitalization as it can follow a steady course or resolve, improve or worsen within few days. The CANONIC study, a prospective observational investigation in 1343 patients hospitalized for acute decompensation of cirrhosis, provided the first evidence-based definition of ACLF which includes the presence of organ failure(s) and a 28-day mortality risk of 15% or higher [78]. In Western countries, ACLF is particularly prevalent among young patients with alcoholic cirrhosis and in 60% of the cases develops in close association with potential precipitating events, mainly bacterial infections or active alcoholism. In Asian countries, ACLF is more commonly diagnosed in patients with hepatitis B-related cirrhosis who exhibit lower prevalence of extrahepatic organ failures.

3.1. *Lipid mediators and systemic inflammation in AD cirrhosis and ACLF*

The presence of a systemic hyperinflammatory state has been recognized as the main driver of widespread tissue and organ injury in patients with AD cirrhosis developing ACLF [79]. The observation that the higher the intensity of systemic inflammation, the higher the number of organ failures and short-term mortality in patients with AD cirrhosis [79], suggests a causal role for systemic inflammation in the pathogenesis of ACLF. The hyperinflammatory state in these patients is further intensified by the massive release of inflammatory and cytotoxic mediators such as proteases, oxidative molecules, cytotoxic cytokines and bioactive lipid mediators (PGs and LTs) (see below) that lead to immune-mediated tissue damage, a process that is known as immunopathology. Immunopathology is a term coined by pathologists to refer to the collateral tissue damage produced by the exacerbated activation of the immune system. The hyperinflammatory state in patients with AD cirrhosis frequently occurs in parallel with the presence of dysfunctional innate immune system at the physical, humoral and cell-mediated level [80]. As a consequence, the host defensive mechanisms of innate immune cells (i.e. neutrophils and monocytes) are severely impaired, rendering these patients immunocompromised and more vulnerable to precipitating events of organ failure, mainly infections [80]. This would explain why half of the patients who have AD cirrhosis and ACLF but no infection at hospital admission subsequently develop severe infections during hospitalization [81].

The formation and actions of lipid mediators, mainly eicosanoids, in patients with AD cirrhosis have been extensively studied in the past in the context of renal dysfunction [reviewed in 82]. In particular, PGE_2 and PGI_2 are powerful renal vasodilators and play a crucial role in the preservation of renal function under circumstances of low sodium diet, hemorrhagic hypovolemia and edematous conditions associated with impaired effective arterial blood volume such as congestive heart failure, nephrotic syndrome and especially AD cirrhosis [82]. In patients with AD cirrhosis, hyperproduction of PGs has the mission to counteract the increased activity of endogenous vasoconstrictors such as angiotensin II, norepinephrine and antidiuretic hormone, which in their attempt to compensate arterial hypotension produce an intense vasoconstriction of the renal vascular bed [82]. In contrast to the renal scenario, scarce information is available on the role of PGs and other bioactive lipid mediators in the context of systemic inflammation and immune function in AD cirrhosis. Recent studies have addressed this topic, providing some hints to the contribution of lipid mediators to the systemic inflammation and ramping immunosuppression in AD cirrhosis. For instance, O'Brien et al. have provided evidence that PGE_2 drives immunosuppression, thus potentially increasing the risk of infection in patients with AD cirrhosis [83]. This finding could not be confirmed in a targeted lipidomic analysis of 100 bioactive lipid mediators in more than 200 patients with AD cirrhosis with and without ACLF, plasma PGE_2 levels were found to be only moderately increased in patients with AD cirrhosis and without association with the presence or the risk of developing infections [84]. In this investigation, ACLF patients were shown to have elevated levels of pro-inflammatory and

vasoconstrictor eicosanoids including LTE_4 and $PGF_{2\alpha}$ (Fig. 3) [84]. Importantly, in ACLF patients, LTE_4 levels strongly correlated with IL-8 and the necrosis/apoptosis marker K18 [84]. Moreover, LTE_4 shaped a minimal plasma fingerprint that discriminated AD patients with ACLF from those without, distinguished ACLF grades and followed the clinical course of the disease (increased with worsening and decreased with improvement). Of interest, some lipid mediators derived from linoleic acid, an omega-6 PUFA precursor of AA, were identified to play a role in AD cirrhosis and ACLF. For instance, circulating levels of 9(10)-epoxy-9Z-octadecenoic acid (EpOME) and 12(13)-EpOME, which are indicators of poor bactericidal activity, were remarkably suppressed in ACLF patients [84].

In addition to being critical cellular components and a source of energy, structural lipids also work as signals for inter-organ communication and cell survival and most notably for shaping immune responses [85]. Indeed, lipid metabolism and immune responses are highly integrated and altered lipid composition interferes with immune regulation leading to immune-metabolic dysregulation and uncontrolled inflammation [86]. In addition, several lipid derivatives are important inflammatory mediators acting as intracellular signaling molecules [87]. Among these lipid derivatives, variations in the serum levels of ceramides are associated with hepatic decompensation and survival in patients with cirrhosis [88] and low levels of sphingosine-1-phosphate are predictive for increased mortality in these patients [89]. Along these lines, dysregulated formation of complex sphingolipids is characteristic of malnutrition in hospitalized patients with decompensated cirrhosis [90] and circulating extracellular vesicles carrying sphingolipid cargo have discriminating power for decompensated alcoholic cirrhosis and survival prediction [91].

3.2. Lipid mediators and resolution of systemic inflammation in AD cirrhosis and ACLF

Blood levels of FAs have been reported to be increased in patients with AD cirrhosis and ACLF [92]. However, among the fatty acid repertoire, the total pool of PUFAs (including free as well as those esterified in triglycerides, phospholipids and cholesterol esters) is invariably reduced in patients with AD and ACLF [84]. This suppression is not seen when the analysis only considers the free circulating PUFA and not the total content, which more accurately represents the actual PUFA pool in the circulation [93]. Furthermore, AD patients with ACLF exhibit a remarkable unbalance between omega-6 and omega-3 PUFA families (higher AA (omega-6) to EPA (omega-3) ratio), which is a surrogate marker of systemic inflammation and/or a deficit of resolution [84]. Consistent with the view of impaired resolution in AD cirrhosis, our group described in the late 90s a deficit of LXA_4 formation in coincubations of PMN and platelets from patients with AD cirrhosis as compared to those from healthy subjects [94]. In addition, a defective chemotactic response to LTB_4 was identified in PMN from patients with AD cirrhosis, an abnormality that likely contributes to the characteristic bacterial killing dysfunction existent in this condition that poses these patients at higher risk of recurrent infections [94]. More recently, reduced levels of LXA_5, a pro-resolving SPM derived from EPA were also demonstrated to be reduced in patients with AD cirrhosis and ACLF [84]. In these patients, plasma LXA_5 levels negatively correlated with IL-8 and the necrosis/apoptosis marker [84]. Importantly, China et al. described in a feasibility study analyzing the potentiality of human serum albumin infusions to restore immune function in patients with AD cirrhosis and ACLF (the ATTIRE trial), that these patients can be categorized into two distinct phenotypes according to their lipid mediator profile [95]. Specifically, by investigating plasma lipid mediator profiles for essential

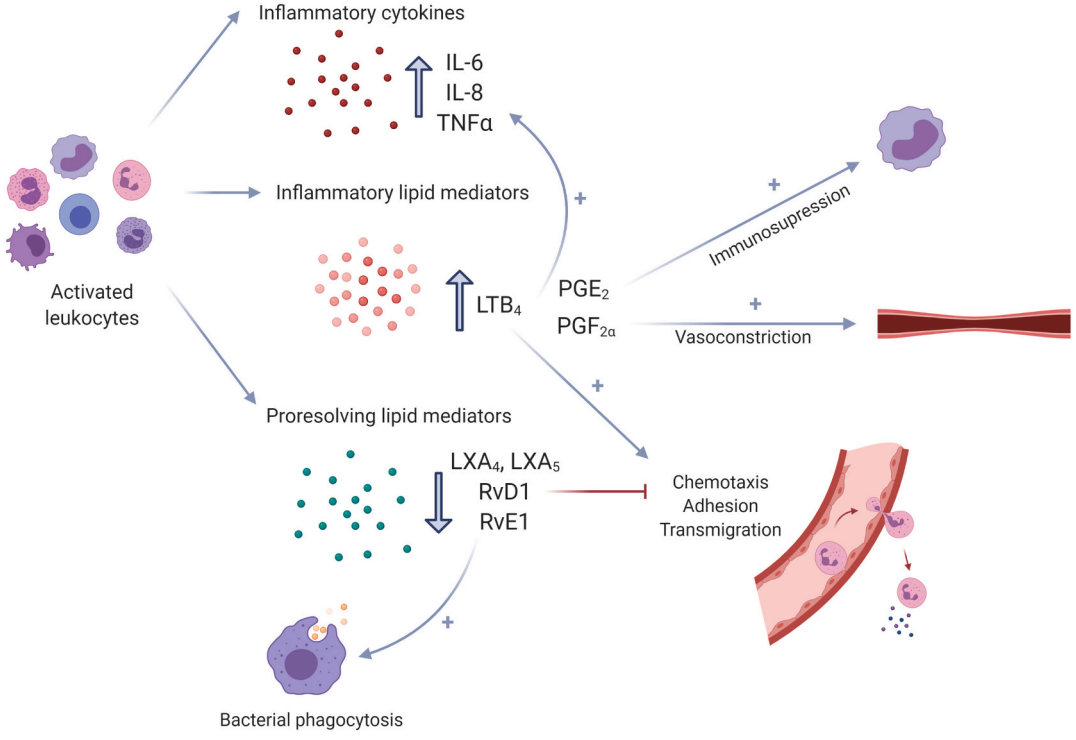

Fig. 3. Imbalanced formation of pro-inflammatory and pro-resolving lipid mediators in leukocytes from patients with AD cirrhosis and ACLF. Activated leukocytes in the systemic circulation of patients with AD cirrhosis and ACLF produce a massive release of soluble bioactive mediators including pro-inflammatory cytokines and lipid mediators, such as leukotrienes and prostaglandins with potent pro-inflammatory, immunosuppressive and vasoconstrictor properties. In these patients, elevated concentrations of these inflammatory mediators occur in parallel with decreased levels of specialized pro-resolving lipid mediators such as lipoxins and resolvins carrying potent anti-inflammatory and pro-resolution properties. These lipid mediators not only promote the resolution of inflammation but also trigger bacterial clearance. IL-6: interleukin-6, IL-8: interleukin-8, TNFα: tumor necrosis factor α, LTB_4: leukotriene B_4, PGE_2: prostaglandin E_2, $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$, LXA_4: lipoxin A_4, LXA_5: lipoxin A_5, RvD1: resolvin D1, RvE1: resolvin E1.

fatty acid–derived SPMs, these authors identified that patients with AD and ACLF segregated into two distinct groups of patients. One group exhibited a hypoactivated profile with reduced concentrations of several pro-resolving and inflammation-initiating mediators including PD1, LXA_4, PGs, TXB_2 and LTB_4, whereas the other showed a hyperactivated status with increased production of these lipid mediators [95]. The latter group had elevated white blood cell count and higher temperature and cytokine and CRP levels accompanied by increased plasma LPS concentration. A distinct trend between inflammation-initiating and resolution pathways have also been identified between surviving and non-surviving patients with AD cirrhosis, indicating that patient survival is also associated with a shifted profile in the levels of SPMs [96]. Further studies are needed to determine the pathophysiological significance of these findings.

Patients with AD cirrhosis who develop the ACLF syndrome exhibit some features with similar characteristics to severe sepsis. These features include exuberant systemic inflammation with acute activation of the innate immune system and metabolic impairment in peripheral organs associated with reduced mitochondrial oxidative phosphorylation resulting in decreased energy production, alterations that culminate in the acute development of organ failure(s) [97]. Therefore, although not much information about SPMs is currently available for ACLF, some lessons can be learned from sepsis. For example, a specific lipid mediator signature comprised by inflammatory-initiating eicosanoids including $PGF_{2\alpha}$ and LTB_4 together with SPMs, including RvE1, RvD5 and 17R-PD1, showed discriminatory power between surviving and not surviving septic patients [98]. At the experimental level, in the caecal ligation and puncture (CLP) method in mice, RvD1 improved survival by preventing excessive activation of the inflammatory response [99]. Similar results were reported for RvD1 in the LPS-D-galactosamine model of septic shock [100]. In the CLP model, RvE1 attenuated polymicrobial sepsis-induced cardiac dysfunction, MarR1 attenuated mitochondrial dysfunction and RvD2 attenuated inflammation and increased survival [39,101,102]. Among the different organ dysfunctions in sepsis, RvD1 and PD1 were shown to mitigate acute kidney injury whereas LXA_4 mitigated acute lung injury [103,104]. An important aspect to consider is that RvD1, RvD2 and RvE1 have been shown to reduce bacterial load and to increase clearance of bacteria by phagocytes, thus inducing organ protection and prolonging survival [39,101,105]. Furthermore, specific SPMs are temporally and differentially regulated during infections and, in addition to enhance infection containment, they lower antibiotic requirements for bacterial clearance [4]. Taken together, these data indicate that pro-resolving lipid mediators are positioned as potential candidates to efficiently terminate and resolve unremitting inflammation in critically ill conditions.

4. Summary and future perspectives

Liver diseases are characterized by different degrees of inflammation, from the very moderate such as that present in patients with NASH, to the very intense such as that manifested by patients with ACLF. A common finding in these two disease conditions is the lack of an appropriate response in the mechanisms orchestrating the resolution of inflammation (the key findings in the field of resolution in chronic liver disease are summarized in Table 1). In these patients, it is of utmost importance to find an appropriate intervention that effectively restores the resolution capacity and reduces excessive inflammation without putting at risk the host defense mechanisms, thus avoiding immunosuppression. Therefore, SPMs and other lipid mediators, which enhance resolution of inflammation without inducing immunosuppression, are gaining traction as potential therapeutic agents available to resolve inflammation in patients with chronic liver disease.

Table 1
List of key findings related to the role of SPMs in chronic liver diseases.

Evidence level and authors	Key finding	References
Cell cultures		
González-Périz et al.	17-HDHA reduces DNA damage and oxidative stress in hepatocytes	[53]
Rius et al.	MaR1 protects hepatocytes from lipotoxic- and hypoxia-induced ER stress	[58]
Jung et al.	MaR1 and RvD1 reduce ER stress and triglyceride accumulation in a human hepatocyte cell line (HepG2)	[74,75]
Han et al.	MaR1 induces proresolving actions in liver macrophages	[59]
Animal models		
González-Périz et al.	RvE1 alleviates obesity-induced insulin resistance and hepatic steatosis	[49]
Hellmann et al.	RvD1 reduces adipose tissue macrophage inflammation and insulin sensitivity in obese mice	[50]
Clària et al.	Impaired formation of SPMs in white adipose tissue of mice with diet-induced obesity progressing to NASH	[28]
Börgeson et al.	LXA_4 ameliorates white adipose tissue inflammation and associated liver disease in obese mice	[30]
Pal et al.	Rescue of liver 18-HEPE levels by EPA administration in obese inbred mice. Role for RvE1 in correcting metabolic dysfunction.	[51]
Depner et al.	DHA is more effective than EPA in preventing western diet-induced NASH	[52]
Rius et al.	RvD1 accelerates resolution of obesity-induced NASH	[54]
Laiglesia et al.	MaR1 mitigates liver steatosis in obese mice	[56]
Queck et al.	LXA_4 ameliorates inflammation in mice with alcoholic hepatitis	[60]
Transgenic animal models		
White et al.	Transgenic *fat-1* mice enriched in omega-3 fatty acids have better resolution capacity in insulin-sensitive tissues and organs, including the liver	[63]
López-Vicario et al.	*Fat-1* mice exhibit reduced hepatic insulin resistance, steatosis and necroinflammation	[62,64]
Human studies		
Titos et al.	Impaired SPM signaling in white adipose tissue of obese individuals at risk of NASH development	[29]
López-Vicario et al.	Unbalanced formation of SPMs by peripheral leukocytes from obese individuals at risk of NASH development	[47]
Clària et al.	Deficit of leukocyte LXA_4 formation in patients with AD cirrhosis	[94]
López-Vicario et al.	Reduced levels of LXA_5 in patients with ACLF	[84]
China et al.	Reduced levels of PD1 and LXA_4 are related to hypoactivated immunity in patients with ACLF	[95]
Becares et al.	Altered SPM profile in patients with ACLF is associated with survival	[96]

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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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