Pro-resolving Lipid Mediators in Sepsis and Critical Illness.

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Abstract

Purpose of review: Sepsis is a life-threatening condition caused by a dysregulated host response to infection that remains a huge clinical challenge. Recent evidence indicates that bioactive lipid mediators derived from polyunsaturated fatty acids (PUFAs) termed specialized pro-resolving mediators (SPMs) are promising new candidates for treating critical illness.

Recent findings: We highlight herein the protective actions of SPMs in experimental sepsis, cardiac dysfunction as well as lung and cerebral injury, and discuss their mechanisms of action. We also emphasise that failed resolution responses and dysregulated SPM pathways may provide an explanation for the ongoing chronic inflammation in many diseases including chronic heart failure.

Summary: Importantly, monitoring plasma SPM profiles can predict patient outcomes in sepsis indicating their utility as new early biomarkers that may help stratify patients upon ICU admission.

Keywords: Sepsis, resolution, specialised pro-resolving mediators (SPMs), lung, heart.

Introduction

Resolution of acute inflammation is a biochemically active process, regulated by endogenous mediators that act in concert to switch off the inflammatory response and return the tissue to homeostasis. These include gaseous mediators such as hydrogen sulphide and nitric oxide, proteinaceous mediators such as annexin A1 and galectin-1 as well as lipid mediators derived from polyunsaturated fatty acids (PUFAs). This new genus includes lipoxins, resolvins, protectins and maresins, collectively coined specialized pro-resolving mediators (SPMs), which act as potent local resolution agonists. SPMs are enzymatically produced by a variety of cell types within the body and act upon specific G-protein coupled receptors (GPCRs) to evoke their bioactions. Some examples of their actions include limiting neutrophilic infiltration, enhancing phagocyte function and hence the clearance of microbial products and apoptotic cells, promoting macrophage phenotype switching and enhancing tissue repair. The discovery of SPMs has led to a new era of 'resolution pharmacology' whereby structure-function activity relationships of pro-resolving mediators and their receptor targets are being determined to aid the generation of novel therapeutics, providing a new mechanistic way to correct persistent inflammation by initiating resolution (1).

SPMs enhance bacterial clearance and survival from sepsis.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis kills over 52,000 people annually in the UK, and globally around 6 million a year and represents a major cause of death in hospitals. It remains a huge clinical challenge and hence there is an unmet need to identify new therapeutic opportunities to combat this fatal condition. In a study conducted by Dalli and colleagues, the temporal regulation of bioactive lipid mediators and pathway markers were assessed in peripheral blood of patients with sepsis. Furthermore, SPMs were correlated with patient outcomes and also clinical data to decipher whether they could be utilised as biomarkers or predictors of the disease course. In sepsis non-survivors, significantly higher inflammation-initiating mediators including prostaglandin F2α ($PGF_{2\alpha}$; 53.6±29.0 vs 3.3±1.2 pg/ml) and leukotriene B_4 (LTB_4; 2.2±1.1 vs. 0.9±0.3 pg/ml) as well as pro-resolving mediators including resolvin E1 (RvE1; 1.7±0.9 vs 0.3±0.2 pg/ml), RvD5 (4.9±2.7 vs 0.2±0.2 pg/ml), and 17*R*-protectin D1 (17*R*-PD1; 1.8±0.7 vs 0.3±0.3 pg/ml) were detected compared with patients surviving

sepsis. Systematic analysis of SPM profiles in septic patients with acute respiratory distress syndrome (ARDS) indicated that the amount of circulating 10*S*,17*S*-diHDHA (PDX) at day 3 was a better predictor of ARDS development than the APACHE II score (Figure 1). Importantly, the results indicate that PDX represents a new early biomarker that may help stratify patients upon ICU admission (2).

Mitochondrial dysfunction has been suggested to play a critical role in the pathogenesis of sepsis. In a study conducted by Hao *et al.,* the authors aimed to explore the impact of maresin 1 (MaR1) on metabolic dysfunction in cecal ligation and puncture (CLP) induced sepsis model. MaR1 significantly increased the overall survival rate (58.33% versus 16.67%) and attenuated lung and liver injuries in septic mice. In addition, MaR1 markedly reduced the levels of proinflammatory cytokines (TNF-*α* and IL-6) and alleviated mitochondrial damage (3). In another study, MaR1 (100ng i.p.) significantly inhibited cytokine production, decreased peritoneal bacterial load, reduced neutrophil numbers, decreased lactic acid levels and upregulated cyclic AMP (cAMP), resulting in significantly decreased lung injury and enhanced survival (63%) in CLP-induced sepsis. Mechanistically, MaR1 was shown to inhibit reactive oxygen species (ROS) production by down-regulating nitric oxide (NOX) activity, and improving catalase (CAT) and superoxide dismutase (SOD) activity (4). Another interesting study from Zhuo and colleagues showed that RvD1 treatment (10ng/g body weight i.v.) increased survival in CLP-induced sepsis in mice. Moreover, RvD1 attenuated the degree of lung inflammation by suppressing signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB), extracellular signal-related kinase (ERK), and p38 activation through a mechanism partly dependent on the protein deacetylase sirtuin 1 (SIRT1) (5). To mimic intestinal infection and diarrhoea in infants, which represents a significant global cause of infant morbidity and mortality, infant mice were infected with *Citrobacter rodentium.* Strikingly, post-infection treatment with a single dose of RvD1 and RvD5 (100ng i.p) reduced bacterial loads, alleviated inflammation, and improved survival rates by 33% at 10 days post-infection. Importantly, treatment also protected from reinfection associated with *C. rodentium*-specific IgG responses comparable to adults (6) (Figure 2).

In a murine model of pneumonia, 15-epi-LXA_4 (100ng i.v.) inhibited lung neutrophil infiltration while enhancing bacterial clearance, indicating that this mediator is not immunosuppressive. This in line with other SPMs such as RvD1, RvD2, and MaR1 enhancing sepsis survival. Mechanistically, 15-epi-LXA_4 enhanced the synthesis of anti-microbial peptides cathelicidin/LL37 *(mCramp*) and bactericidal permeability-increasing protein, BPI (*mBPI*) within the lung and induced the NF-κB regulators A20 and single Ig IL-1R-related molecule (SIGIRR) to promote the resolution of pneumonia via its cognate receptor ALX/FPR2 (7).

Parenteral nutrition with omega-3 lipid emulsions (LEs) has proved beneficial for adult patients post gastrointestinal surgery, reducing infection rates and limiting hospital stay (8). Yet the benefits for critically ill patients are less clear (8) and further information on the mechanism of action of omega-3 LEs is required. Parenteral administration of LEs proved protective in a murine polymicrobial sepsis model, limiting hypothermia and weight loss leading to enhanced survival (9). Omega-3 LEs enhanced the levels of 15-hydroxy-eicosatetraenoic acid (15-HETE) along with the resolution mediators LXA_4, PDX and MaR1 in peritoneal lavage fluids, offering a molecular mechanism for improved survival from sepsis (9). A recent study investigated whether EPA could potentiate the beneficial effects of mesenchymal stromal cells (MSCs) in experimental sepsis. Mice received saline, adipose tissue-derived (AD)-MSCs or AD-MSCs preconditioned with EPA intravenously one day post-CLP. Mice treated with EPA-preconditioned AD-MSCs displayed reduced interstitial oedema, alveolar septal inflammation, collagen fibre content and neutrophilic infiltration leading to a significant reduction in lung injury. Additionally, EPA-preconditioned MSCs improved morphological abnormalities of the heart, liver, kidney and spleen, improving distal organ injury. Additionally, EPA preconditioning of MSCs resulted in increased secretion of bioactive lipid mediators RvD_1 and PGE_2 as well as IL-10, and TGF-β. These effects culminated in improved sepsis severity score and higher survival rates. This strategy could offer an alternate therapeutic approach, which enhances SPM levels to treat septic patients, (10).

One in two patients with sepsis develop cardiac dysfunction and the severity of cardiac dysfunction is correlated with mortality in sepsis. Recent studies have revealed a protective role of transient receptor potential vanilloid receptor type (TRPV)-1 activation in models of sepsis. A low-dose LPS protocol

was selected to simulate the early stages of bacteremic sepsis. In WT mice, low-dose LPS had no effect on cardiac function, whereas TRPV1 null mice displayed profound cardiac dysfunction indicating an innate protective role of this receptor. Indeed, TRPV1 signaling by the endogenous agonist 20-hydroxyeicosatetraenoic acid (20-HETE), induced the release of neuropeptide and calcitonin gene-related peptide (CGRP), leading to cardioprotection in endotoxemia (11).

SPMs promote cardiac repair.

Cardiovascular disease is the leading cause of morbidity and mortality worldwide, causing almost a third of all global deaths. Current treatment strategies for heart failure after myocardial infarction are limited and non-curative, thus new therapeutics and further investigation into the pathophysiology of this process is warranted. Recent work assessed whether bioactive lipid mediators were generated at the site of the injured myocardium using an acute model of heart failure post-MI. A permanent coronary ligation model in C57/Bl6 mice was utilised to induce MI, causing decreased contractility index, marked wall thinning and necrosis of the infarcted left ventricle. Additionally, the splenic reservoir was assessed over the time course of the disease process to monitor leukocyte mobilisation. Prior to MI, SPMs were more abundant in the spleen than the left ventricle. Interestingly, 24h after coronary ligation, an increase in resolvins, protectins and maresin (RvD1, RvD3, RvD4, RvD5, RvD6, AT-RvD1, RvE2, PD1, MaR1, 7S,14S-diHDHA and 4S,14S-diHDHA) were detected in the infarcted myocardium, which correlated with a peak in neutrophils, and a depletion of leukocytes from the spleen. Gene expression analysis indicated that enzymes involved in SPM biosynthesis were higher in the infarcted LV compared to the spleen*; ALOX15* peaked within 24 hours post-MI and returned to naïve levels by day 5 post-MI, whilst *ALOX5* and *ALOX12* were gradually increased at d1 to d5 post-MI compared to d0 naïve controls. Resolving macrophages and N2 neutrophils ($Ly6G^+/CD206^+$) increased from day 1 and peaked at day 5 in the infarcted LV. Depletion of macrophages using clodronate liposomes was associated with decreased SPM biosynthesis in the heart, suggesting that leukocytes are mobilized from the spleen to the infarcted heart to generate SPMs to help resolve inflammation (Figure 2) (12) (13).

The following studies indicate that SPMs offer a valid therapeutic strategy for cardiac repair and prevention of organ dysfunction. Mice treated with 15-epi-lipoxin A_4 (1 µg/kg/day) either alone or fused

with liposomes displayed reduced LV and lung mass to body weight ratios and improved ejection fraction 5 days post myocardial infarction (14). RvD1 was tested for its ability to limit MI-induced cardiorenal syndrome (CRS). RvD1 (3 μg/kg/d; s.c., 3h after MI) promoted neutrophil clearance from the infarcted LV, and increased reparative macrophages ($F4/80^{+}/Ly6C^{low}/CD206^{+}$) 5 days after MI (Figure 2). Comprehensive miRNA expression analysis revealed that RvD1 prevents the significant alteration of numerous miRs in the infarcted LV area after MI and accelerates a healing response. RvD1 also attenuated MI-induced renal inflammation and preserved nephrin expression to limit CRS in a heart failure model (15).

Deep vein thrombosis (DVT) is a common cardiovascular disease that causes a major impact on quality of life and if missed or left untreated can lead to the development of life-threatening pulmonary embolism. A mouse model of DVT was utilised to test whether SPM could limit thrombus development. Mice were subjected to inferior vena cava stenosis leading to blood flow restriction and thrombus formation. Administration of RvD4 (3 μg i.v. via tail vein injection on days 1 and 4) significantly reduced thrombus burden (17% decrease in thrombus length on day 8 compared with the vehicle-treated group), enhanced leukocyte early apoptosis with significantly less neutrophils and increased pro-resolving monocytes in the thrombus. RvD4 also limited release of neutrophil extracellular trap (NETs), which are critical for DVT development, enhancing thrombus resolution (16).

It has recently been appreciated that chronic inflammation may persist not only because of excess pro-inflammatory mediators but also from defects in pro-resolving pathways (17). Chronic heart failure (CHF) is an example of this ongoing non-resolving inflammatory state. Elderly patients with CHF were found to have significantly lower plasma levels of RvD1 compared with healthy age-matched control subjects. Blood leukocytes from these patients displayed reduced 15-lipoxygenase activity and hence reduced biosynthesis of RvD1. They also expressed lower levels of a RvD1 receptor GPR32 rendering T cells less responsive to exogenous RvD1 treatment. Together these failed resolution responses may provide an explanation for the ongoing chronic inflammation in CHF patients (18). Defective Lipoxin A_4 and RvD1 production is also reported in patients with obstructive sleep apnea (19). It is well established that obstructive sleep apnea can be a major determinant of cardiovascular morbidity and mortality; leading to hypertension, ischaemic heart disease, cardiac arrhythmias and

stroke. In addition to defective SPM production, they also found reduced expression of the LXA_4/RvD1 receptor ALX/FPR2 on neutrophils from patients exhibiting sleep disordered breathing with hypertension (19), again suggesting defective resolution pathways (Figure 1).

SPMs protect from acute respiratory distress syndrome and lung injury.

Mechanical ventilation is a major life support for patients with severe illness, yet this can cause or aggravate acute lung injury leading to increased morbidity and mortality. The protective effects of RvD1 were investigated using a mouse model of ventilation at high tidal volume pressure (40 mL/kg, HV_T, 4h) to induce mechanical ventilation lung injury (VILI). RvD1 (500ng i.p) limited pathological damage to lungs, pulmonary oedema, leukocyte infiltration, and release of pro-inflammatory cytokines such as IL-1β, TNFα and IL-6 (20). Mechanistically, RvD1 enhanced heme oxygenase-1 (HO-1) expression, and decreased high mobility group chromosomal protein B1 (HMGB-1) expression (21). Mechanical ventilation can also induce pulmonary fibrosis, which contributes to the high mortality rate of acute respiratory distress syndrome (ARDS) whereby impaired fluid clearance in the lung results in an acute and lethal clinical syndrome. Importantly, RvD1 attenuated lung fibrosis and significantly reduced mechanical stretch-induced mesenchymal markers (vimentin and α-smooth muscle actin), whilst increasing epithelial markers (E-cadherin) (22). SPMs also promote alveolar fluid clearance by upregulating the epithelial sodium channel, Na,K-ATPase, cystic fibrosis transmembrane conductance regulator (CFTR), and aquaporins levels as reviewed in (23). In addition, RvE1 can restore TNF-α-induced mitochondrial dysfunction in human alveolar epithelial cells suggesting a beneficial effect of RvE1 in pulmonary diseases (24).

SPMs are neuroprotective.

Cerebral ischaemia/reperfusion (I/R) injury is a major contributing factor to a poor prognosis for ischemic stroke patients. Treatment of cerebral ischemia is limited, thus new neuroprotective therapies are needed. Omega-3 dietary supplements have been shown to improve the prognosis of patients with ischemic stroke, yet the protective mechanism remains to be fully elucidated. Induction of cerebral I/R by middle cerebral artery occlusion and reperfusion caused a significant reduction in the phosphorylation of 5-lipoxygenase and reduced endogenous RvD2 levels compared with sham-operated rats (25). Therefore, treatment with RvD2 (25, 50 and 100μg/kg) was tested in I/R-induced

brain injury, reducing cerebral infarction, inflammatory cytokines, oedema, and neurological dysfunction. Importantly, RvD2 (50μg/kg) was more effective than omega-3 treatment (oral gavage of 30% ω-3 fatty acids at 1g/kg/day) (25). In another study using a model of acute focal brain injury, RvD1 promoted functional recovery, reduced neuroinflammation via microRNA (miR)-146b- and miR-219a-1 and prevented neuronal cell death (26).

Conclusion

Mounting evidence indicates that SPM pathways are dysregulated in chronic inflammatory diseases including chronic heart failure and may explain disease persistence and failure to resolve. Whilst specific SPMs are increased in plasma from both sepsis non-survivors and ARDS patients, these may not be sufficient to counter the disease sequelae in these patients giving rise to a status of failed resolution. An alternative hypothesis could be that their cognate receptors are down-regulated, as observed in other diseases such as CHF, a hypothesis that warrant further investigation. Given their potent biological actions in promoting bacterial clearance as well as organ protection in animal models of sepsis, respiratory distress and heart failure, SPMs offer promising new therapeutics for critical illness. Indeed, development and testing of stable analogues and mimetics of SPMs with enhanced pharmacokinetics and pharmacodynamics is on-going and initial clinical evidence of protective actions of SPMs in human diseases is emerging (1).

Key Points

- SPMs promote the resolution of inflammation and increase survival in experimental sepsis.
- SPMs enhance host responses including bacterial clearance and do not cause immunosuppression.
- SPM profiling can predict septic patient outcomes.
- SPM pathways are dysregulated in chronic inflammatory diseases.

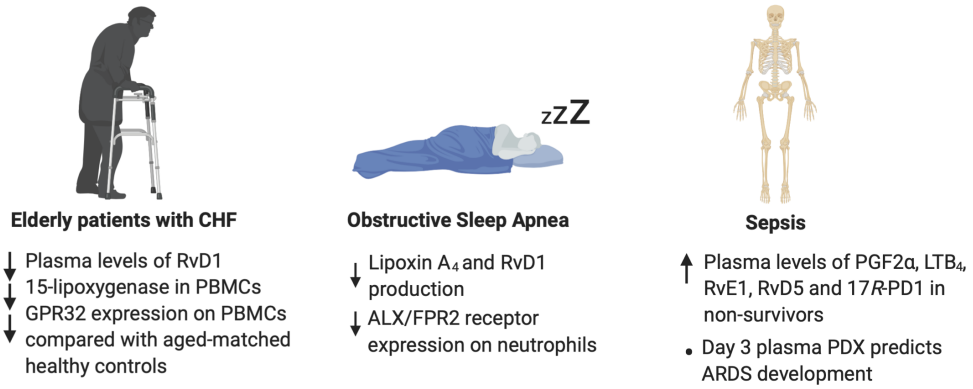

Figure 1. SPM are dysregulated in human pathology. Examples of dysregulated SPM and their receptors are shown in patients with chronic heart failure (CHF), people with obstructive sleep apnea and patients with sepsis. Importantly, monitoring plasma SPM profiles can predict septic patient outcomes and may help stratify patients upon ICU admission. *Abbreviations:* GPR32; G protein-coupled receptor 32, PBMC; peripheral blood mononuclear cells, LXA_4; lipoxin A4, RvD1; resolvin D1, ALX/FPR2; lipoxin A4/formyl peptide receptor 2, prostaglandin F2α; PGF2α, LTB_4; leukotriene B4, 17*R*-PD1; 17*R*-protectin D1.

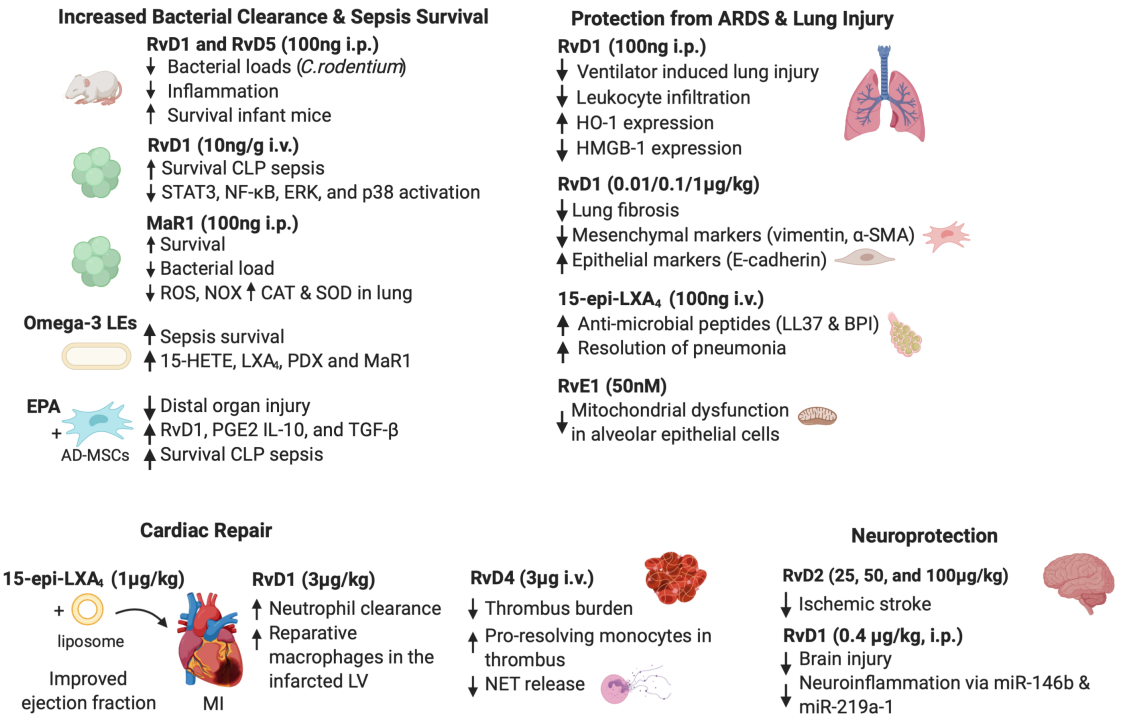

Figure 2. SPM are protective in experimental models of inflammation and critical illness. Protective actions of SPMs in experimental sepsis, cardiac dysfunction as well as lung and cerebral injury are shown. *Abbreviations:* RvD1; resolvin D1, RvD2; resolvin D2, RvD5; resolvin D5, RvE1; resolvin E1, MaR1; maresin 1, PDX; protectin DX/10*S*,17*S*-diHDHA, STAT3; signal transducer and activator of transcription 3, NF-κB; nuclear factor kappa light-chain-enhancer of activated B cells, ERK; extracellular signal-related kinase, ROS; reactive oxygen species, NOX; nitric oxide, CAT; catalase, SOD; superoxide dismutase, IL-10; interleukin 10, omega-3 LEs; omega-3 lipid emulsions, 15-HETE; 15-hydroxy-eicosatetraenoic acid, LXA_4; Lipoxin A_4, EPA; Eicosapentaenoic acid, AD-MSCs; adipose tissue-derived mesenchymal stromal cells, PGE_2; prostaglandin E2, IL-10; interleukin 10, TNF-α; tumour necrosis factor alpha, CLP; cecal ligation and puncture, 15-epi-LXA_4; 15-epi-lipoxin A_4, MI; myocardial infarction, LV; left ventricle, RvD4; resolvin D4, NET; neutrophil extracellular trap, HO-1; heme oxygenase 1, HMGB-1; high mobility group protein 1, α-SMA; alpha-smooth muscle actin, cathelicidin/LL37 (mCramp); BPI; bactericidal permeability-increasing protein, miR; micro RNA.

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