

The Science of Inflammation Resolution: Specialized Pro-Resolving Mediators Evidence Summary

What are SPMs?

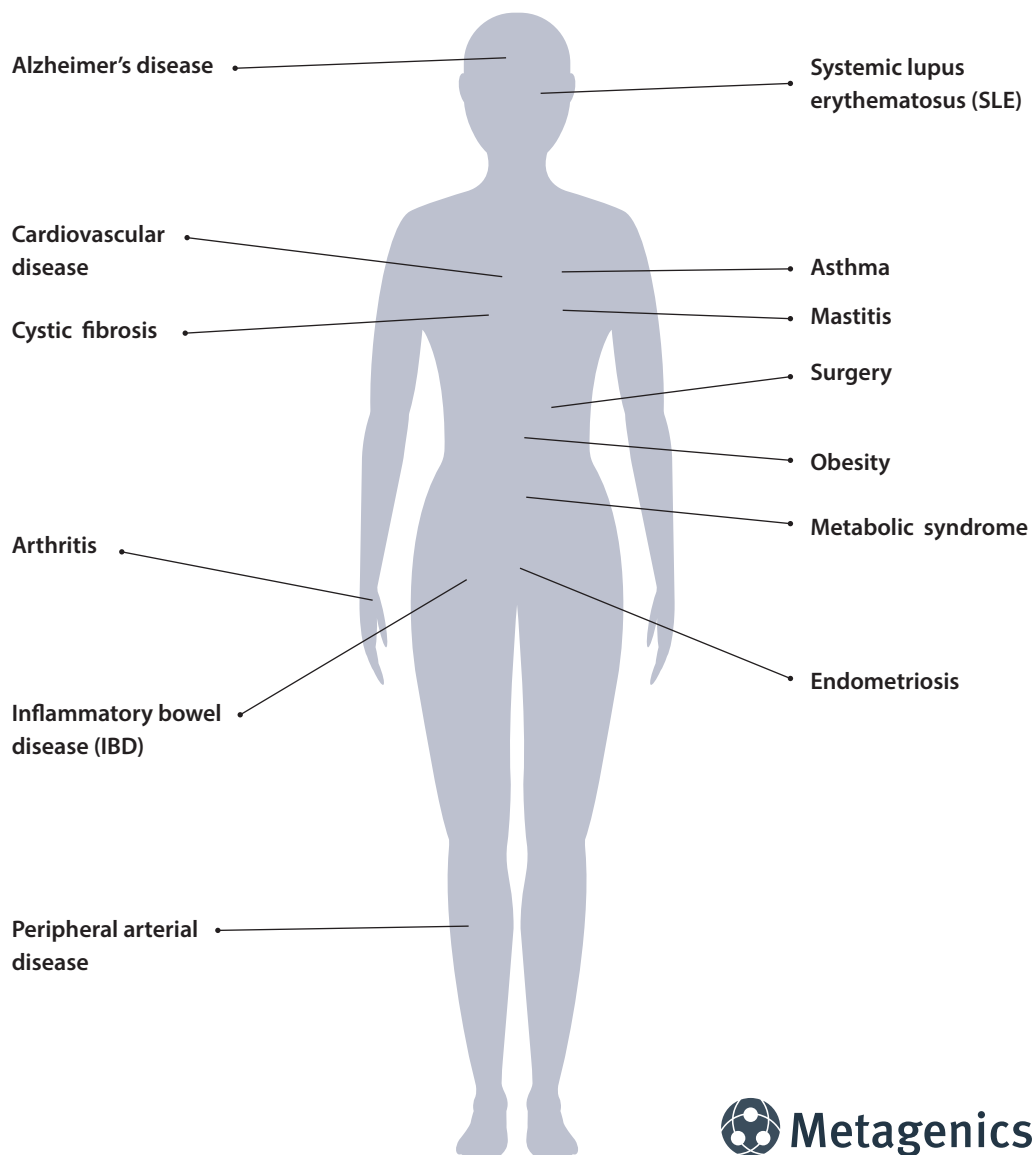
Specialized pro-resolving mediators (SPMs) are a group of lipid mediators that function as “resolution agonists” and actively coordinate the resolution of inflammation.¹ SPMs are produced naturally in the body from unsaturated fatty acids such as the omega-3 fatty acids eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). Although EPA and DHA are the precursors of SPMs, they do not have pro-resolving properties¹ and require multiple downstream enzymatic conversions to form 17-HDHA and 18-HEPE, which are further converted into D-series resolvins (RvDs) and E-series resolvins (RvEs) respectively.¹ Other groups of lipid mediators include lipoxins (LXs), maresins (MaRs), protectins (PDs), and neuroprotectins (NPDs) which work together to bring about the resolution of inflammatory cascade and return the tissue to homeostasis.¹ These SPMs also work as a counterbalance to proinflammatory signals, including proinflammatory lipid mediators such as prostaglandins (PGs) and leukotrienes (LTs).¹

For more information on SPMs and their role in inflammation resolution, please see “Science Review: Specialized Pro-Resolving Mediators.”

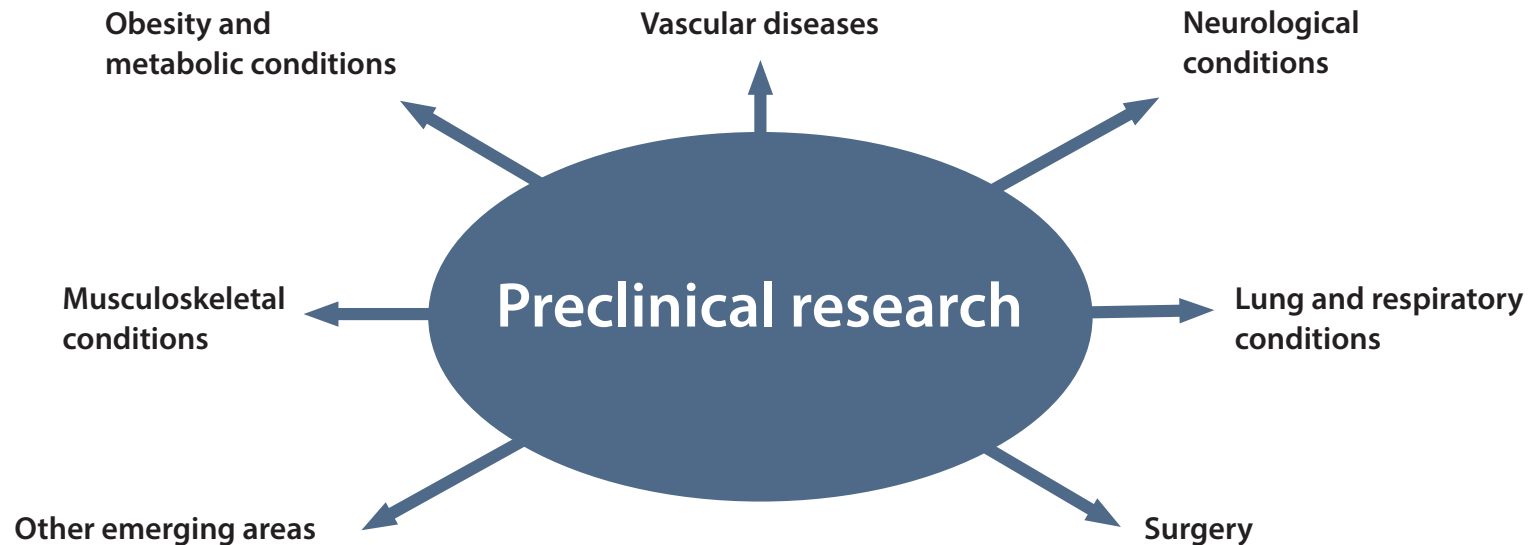
Human evidence of inflammation resolution deficit [Table 1]

Work over the past five years has greatly expanded our knowledge of different conditions associated with an inflammation resolution deficit in humans. Clinical work shows that, compared with healthy individuals, patients with many chronic inflammatory conditions have reduced levels of SPMs in circulation and in affected tissues. These data suggest that resolution support is needed to bring this critical resolution system into balance.

Conditions with reduced levels of SPMs in humans²⁻³⁵



Emerging areas of SPM research^{7,36-115}



This emerging research is defined largely by preclinical and human observational data and provides an indicator of which aspects of resolution science may continue to grow.

Preclinical and mechanistic data from animal and cell models is shining a light on the vast number of areas where SPMs have a role. Research is lighting up in these key areas:

- **Vascular disease:**³⁶⁻⁴⁵ atherosclerosis, myocardial infarction, aortic aneurysm, thrombosis
- **Obesity and metabolic conditions:**⁴⁶⁻⁵⁷ obesity, insulin resistance, diabetes, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver fibrosis
- **Surgery:**⁵⁸⁻⁶⁷ incisional wound healing, postoperative pain, infection, sepsis, allograft rejection
- **Neurological conditions:**⁶⁸⁻⁷⁹ postoperative cognitive decline, stroke, Alzheimer's disease
- **Musculoskeletal conditions:**⁸⁰⁻⁸³ arthritis, fibromyalgia
- **Lung and respiratory conditions:**⁸⁴⁻⁹¹ allergy-induced asthma, cystic fibrosis
- **Other emerging areas:**⁹²⁻¹¹⁵ kidney damage, psoriasis, dry eye, endometriosis, IBD

Table 1: Human conditions with a resolution deficit component

Condition	Tissue or Fluid Assessed	SPM Evidence Summary
Alzheimer's disease	Brain tissue	<ul style="list-style-type: none"> In hippocampal tissue collected postmortem from individuals with Alzheimer's disease and individuals without dementia, levels of SPMs (LXA4, MaR1, and NPD1) were significantly lower in the Alzheimer's group.^{3,4} In the entorhinal cortex (an area affected early in disease progression) of Alzheimer's disease patients, levels of pro-resolving mediators (MaR1, PD1, and RvD5) were lower than age-matched controls, and levels of proinflammatory mediators (PGD2) were higher.⁵
	Cerebrospinal fluid	<ul style="list-style-type: none"> In a group of patients with Alzheimer's disease, a group with mild cognitive impairment and a group without objective impairment, higher concentrations of the SPM LXA4 in cerebrospinal fluid was associated with higher cognitive function scores assessed by the Mini-Mental State Examination (MMSE).³
Arthritis	Synovial fluid	<ul style="list-style-type: none"> In patients with inflammatory arthritis, higher levels of the SPM RvE2 in synovial fluid were inversely related to pain. In this group, higher total plasma SPM concentrations were related to lower levels of erythrocyte sedimentation rate (ESR), a general marker of inflammation.⁶ Total SPM content was higher in synovial fluid compared to healthy controls reflective of higher inflammatory burden. However, within the group with arthritis, higher levels of SPMs were associated with lower pain and inflammation.⁶
	Blood	<ul style="list-style-type: none"> Compared with healthy controls, patients with rheumatoid arthritis had significantly lower plasma levels of RvD3n-3 DPA.⁶ In this study, blood from the healthy controls differed from individuals with rheumatoid arthritis and was characterized by higher levels of resolvins (RvD3, RvD4, RvE3).⁷
Asthma	Alveolar macrophages	<ul style="list-style-type: none"> Compared with individuals with nonsevere asthma or nonasthmatics, alveolar macrophages from patients with severe asthma had lower production of the SPM LXA4 in response to an inflammatory challenge.²⁷
	Exhaled breath condensate	<ul style="list-style-type: none"> The ratio of the SPM LXA4 to the SPM LTB4 ratio decreased with increasing asthma severity, indicating that the balance between the pro-resolving and proinflammatory mediators was altered in more severe asthma to a less pro-resolving profile.²⁸ Another study identified that compared with healthy controls, levels of the pro-resolving mediator PD1 were also significantly lower in patients with asthma.²⁹
	Whole blood	<ul style="list-style-type: none"> Levels of the SPM LXA4 were reduced, and levels of the proinflammatory leukotrienes were increased in patients with asthma compared with healthy individuals.³⁰ Another study in children also demonstrated that LXA4 decreased in blood as asthma severity increased, with those with the highest asthma severity having the lowest circulating LXA4 concentrations. LXA4 was correlated with lung function (FEV-1) in this study.³¹
	Eosinophils	<ul style="list-style-type: none"> Compared with healthy controls, eosinophils collected from patients with asthma were shown to have a significantly reduced ability to produce the SPM PD1 following treatment with DHA.³²
	Bronchoalveolar lavage fluid	<ul style="list-style-type: none"> Individuals with severe asthma had significantly lower levels of the SPM LXA4 compared with patients with nonsevere asthma.³³
	Peripheral granulocytes	<ul style="list-style-type: none"> Levels of the SPM LXA4 were significantly reduced in circulating granulocytes of patients with more severe asthma, compared with patients with a less severe form of the condition.³³
	Urine	<ul style="list-style-type: none"> Compared with healthy controls, the levels of LXA4 in urine were significantly reduced in individuals with both aspirin tolerant and intolerant asthma.³⁴

Table 1: Human conditions with a resolution deficit component—cont'd.

Condition	Tissue or Fluid Assessed	SPM Evidence Summary
Cardiovascular disease	Carotid atherosclerotic plaques	<ul style="list-style-type: none"> In an analysis of carotid artery atherosclerotic plaques from human donors, vulnerable plaques were shown to have reduced concentrations of the SPM RvD1, and the ratio of total SPM concentrations to the proinflammatory lipid mediator LTB4 was reduced compared with stable plaque areas.⁸
	Blood	<ul style="list-style-type: none"> Patients with stable coronary artery disease assigned to either high-dose fish oil (providing 3.36g of EPA+DHA per day) or no fish oil treatment all showed an absence of resolvins (RvE1, RvD1, RvD2, RvD3, and RvD5) after one-year study. These SPMs had been previously shown to be present in healthy individuals.⁹ In patients with acutely symptomatic carotid disease, circulating levels of the SPM RvD1 was shown to be significantly lower than patients with asymptomatic high-grade carotid stenosis.¹⁰
Carotid intima media thickness	Saliva	<ul style="list-style-type: none"> The ratio of the SPM RvD1 to the proinflammatory lipid mediator LTB4 in saliva was an independent predictor of carotid intima media thickness assessed by ultrasound.¹¹ Individuals with a salivary RvD1:LTB4 ratio > 1 had a significantly lower intima media thickness than those in whom LTB4 prevailed.¹¹
Cystic fibrosis (CF)	Sputum and neutrophils	<ul style="list-style-type: none"> In adults and children with cystic fibrosis, the ratio of RvD1 to the proinflammatory cytokine IL-8 in sputum was correlated with FEV-1 (marker of lung function and CF severity). Those with lower RvD1:IL-8 (lower pro-resolving:higher proinflammatory) had reduced lung function.¹⁸ Lower levels of the SPM RvD1 in sputum was correlated with higher levels of proinflammatory cells and markers.¹⁸ In adults with cystic fibrosis, nondetectable levels of the SPM RvE1 in sputum was related to reduced lung function compared with those with detectable RvE1, though this trend did not reach statistical significance.¹⁹ A virulence factor secreted by <i>P. aeruginosa</i> has been shown to disrupt the production of lipoxins in human immune cells (neutrophils).²⁰
Endometriosis	Endometrial tissue	<ul style="list-style-type: none"> Endometrial tissue (obtained at time of surgery) from women with endometriosis was shown in two separate studies to have significantly lower concentrations of the SPM LXA4 compared to tissue from women without the condition.^{22,23} LXA4 was the only SPM measured in these studies.
Inflammatory bowel disease (IBD)	Colon	<ul style="list-style-type: none"> Compared with healthy controls, patients with IBD with ulcerative colitis were shown to have significantly lower levels of LXA4 in colonic mucosa.²⁴ In another study comparing colon tissues in patients with active colitis, patients in remission, and healthy controls, higher concentrations of the SPM LXA4 were seen in the tissue of patients in remission.²⁵ Another study identified an increase in both proinflammatory (LTB4, PGE2) and pro-resolving (RvD1, RvD2, RvD5) markers in colon tissue from patients with IBD relative to control, reflecting the high levels of background inflammation in this condition.²⁶
Mastitis	Human milk	<ul style="list-style-type: none"> Compared with breastmilk from healthy subjects, breastmilk from women with mastitis was higher in proinflammatory lipid mediators such as prostaglandins and leukotrienes.² Breastmilk from healthy women contained higher levels of SPMs including RvD1, RvD2, RvD3, MaR1, PD1, RvE2, LXA4, and LXB4.² When milk from both groups of women was used in a mouse model of inflammation, the breastmilk from the mastitis group had reduced ability to accelerate inflammation resolution.²

Table 1: Human conditions with a resolution deficit component—cont'd.

Condition	Tissue or Fluid Assessed	SPM Evidence Summary
Metabolic syndrome	Blood	<ul style="list-style-type: none"> When supplemented with high-dose fish oil (4 g, providing 2.4 g EPA+DHA/day) for 3 weeks, circulating levels of the D-series resolvins precursor 17-HDHA and the E-series resolvins precursor 18-HEPE increased less in individuals with metabolic syndrome compared with healthy controls.¹⁵
Obesity	Blood	<ul style="list-style-type: none"> In individuals with obesity, plasma levels of the resolvins precursors 17-HDHA and 18-HEPE, as well as levels of specific SPMs (LXA4, RvD2, and RvD4) were significantly lower compared with age-matched controls with lower BMI.¹⁶
	Immune cells	<ul style="list-style-type: none"> Circulating immune cells from individuals with obesity had a reduced ability to produce the D-series resolvins precursor 17-HDHA as well as resolvins when exposed to DHA. Treatment with 17-HDHA overrode this defect in the ability to produce resolvins.¹⁶
	Visceral adipose tissue	<ul style="list-style-type: none"> Visceral adipose tissue of individuals with obesity showed an imbalance between pro-resolving and proinflammatory mediators compared with controls with lower BMI. Specifically, the ratio of total SPMs to the proinflammatory mediator LTB4 and total SPMs to proinflammatory PGs were significantly lower in the group with obesity.¹⁷
Peripheral arterial disease	Adipose tissue	<ul style="list-style-type: none"> Adipose tissue isolated from patients with peripheral vascular disease had significantly reduced levels of the resolvins precursor 17-HDHA, as well as lower levels of the SPM PD-1 compared with age-matched controls.¹²
	Blood	<ul style="list-style-type: none"> Compared with healthy individuals, patients with peripheral arterial disease trended toward lower DHA- and DPA-derived resolvins in plasma. Patients with peripheral arterial disease had elevated leukotrienes and trended toward higher prostaglandins and thromboxane B₂. The ratio of plasma SPM to proinflammatory prostaglandins was significantly reduced in the peripheral arterial disease population.¹³
	HDL molecules	<ul style="list-style-type: none"> HDL molecules of patients with peripheral vascular disease exhibited a different proinflammatory/pro-resolving lipid mediator profile as compared to HDL of healthy controls.¹⁴
Surgery	Blood	<ul style="list-style-type: none"> In patients who underwent liver resection surgery, circulating levels of SPMs (LXA4 and RvD1) were shown to drop following surgery.²¹ LXA4 was reduced by 44%, 33%, and 28% on day 1, 3, and 5 postop, respectively. Similarly, RvD1 was reduced by 28%, 10%, and 5% on days 1, 3, and 5 postoperatively, respectively.²¹ Higher serum LXA4 and RvD1 were significantly and inversely correlated with the proinflammatory marker IL-6.²¹ Higher levels of IL-6 were associated with more postoperative complications.²¹
Systemic lupus erythematosus	Blood	<ul style="list-style-type: none"> Compared with individuals without the condition, patients with lupus had reduced levels of circulating RvD1.³⁵

Specialized pro-resolving mediator abbreviations: RvD, D-series resolvins; RvE, E-series resolvins; MaR, maresins; NPD, neuroprotectin; PD, protectin; LX, lipoxin; 17-HDHA, 17-hydroxydocosahexaenoic acid

Proinflammatory mediator abbreviations: PG, prostaglandin; LT, leukotriene

There are many publications highlighting the impact of specific SPMs in preclinical studies, which have shed light on the mechanisms of SPM action and the impact of inflammation resolution in these preclinical models. Tables 2-8 summarize the emerging preclinical evidence in a range of focus areas.

Table 2: Summary of preclinical animal and cell data related to vascular conditions

Condition	SPM Evidence Summary
Aortic aneurysm	<ul style="list-style-type: none"> The SPMs RvD1 and RvD2 attenuated the formation and progression of aortic aneurysm in mice.⁴³
Atherosclerosis	<ul style="list-style-type: none"> Treatment with the SPM RvE1 in rabbits with atherosclerosis lowered plasma hsCRP, reduced proinflammatory immune cells infiltrating vascular tissue, and reduced arterial plaque progression.³⁶ In mice with atherosclerosis, plaque progression and plaque instability were associated with lower levels of SPMs (RvD2 and MaR1) in the aorta.³⁷ Treatment with the SPMs MaR1 or RvD2 in mice with atherosclerosis shifted macrophages to an anti-inflammatory reparative phenotype, reduced the development of atherosclerotic plaque, and prevented the development of an unstable necrotic core.³⁷ Treatment with the SPM RvE1 in mice with atherosclerosis, with or without statins, attenuated atherogenesis.³⁸ Treatment with the SPM RvD1 in a mouse model of atherosclerosis slowed the progression of atherosclerosis, leading to smaller lesion size and a greater degree of plaque stability.⁸ Mechanistically, a range of SPMs has been shown to modulate mechanisms involved in atherosclerosis and neointima formation in response to vascular injury. In vascular endothelial cells, SPMs reduce inflammation and adhesion molecule expression and reduce leukocyte-vascular endothelial cell adhesion. In vascular smooth muscle cells, a range of SPMs has been shown to reduce monocyte adhesion to smooth muscle cells and reduce inflammation, migration, and proliferation of these cells.³⁹
Myocardial ischemia and reperfusion injury	<ul style="list-style-type: none"> In a rat model of myocardial ischemia and reperfusion injury, treatment with the SPM RvE1 prior to reperfusion reduced the infarct size.⁴⁰ In a mouse model of myocardial infarction (MI), treatment with the SPM RvD1 improved ventricular function and reduced post-MI fibrosis.⁴¹ Treatment with the SPM RvE1 of mice post-MI improved cardiac function, reduced proinflammatory cytokines within injured heart tissue and protected cardiomyocytes from apoptosis.⁴²
Thrombosis	<ul style="list-style-type: none"> The SPM MaR1 reduced the release of proinflammatory and prothrombotic factors from platelets while maintaining their hemostatic function.⁴⁴ In two burn injury mouse models, administering the SPM RvD2 postburn prevented dermal vascular thrombosis.⁴⁵

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvins; RvE, E-series resolvins; MaR, maresins

Table 3: Summary of preclinical animal and cell data related to obesity and metabolic conditions

Condition	SPM Evidence Summary
Insulin resistance and diabetes	<ul style="list-style-type: none"> • Treatment with the SPM RvD1 in mice with obesity and diabetes improved glucose tolerance and reduced fasting blood glucose.⁴⁶ • Treatment with the SPM RvE1 in mice with obesity improved insulin sensitivity through an increase in AMPK-adiponectin signaling and an upregulation of glucose transport and insulin receptor signaling.⁵¹ • 17-HDHA (D-series resolvin precursor) treatment showed insulin-sensitizing effects and improved adiponectin expression and glucose tolerance in a mouse model of obesity and diabetes (<i>db/db</i> mice).⁴⁸ • In models of diet and genetic obesity (<i>ob/ob</i> mice), the SPM MaR1 treatment improved insulin tolerance test, indicating increased insulin sensitivity.⁵⁰
Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> • Treatment with the E-series resolvin precursor 18-HEPE and the D-series resolvin precursor 17-HDHA in mice with obesity and nonalcoholic fatty liver disease improved circulating adiponectin and resistin concentrations and reduced inflammatory markers in liver tissue.⁵² • Treatment with the SPM MaR1 in mice with obesity was shown to protect liver cells from lipotoxicity-induced cell damage and endoplasmic reticulum stress, both of which are hallmarks of NAFLD.⁵³ • Treatment with the SPM MaR1 in mice with obesity-induced fatty liver reduced liver triglyceride content and liver weight and reduced lipogenic enzymes in liver tissue and increased pathways related to fatty acid oxidation and autophagy.⁵⁴ • The SPM RvE1 reduced liver triglyceride accumulation in a mouse model of obesity (<i>ob/ob</i> mice).⁵¹
Nonalcoholic steatohepatitis (NASH) and liver fibrosis	<ul style="list-style-type: none"> • Treatment with the SPM RvD1 in mice with steatohepatitis increased adiponectin and reduced proinflammatory macrophage infiltration into the liver.⁵⁵ • The SPM RvD1 promoted an anti-inflammatory M2 phenotype and reduced liver inflammation. RvD1 treatment led to expression of a specific microRNA signature, which was related to cytokine and inflammatory signaling.⁵⁵ • In a mouse model of liver fibrosis induced by <i>Schistosoma japonicum</i> infection, the SPM RvE1 reduced cytokine expression in the liver and lowered indicators of fibrosis (laminin, hyaluronic acid, procollagen type III, type IV collagen).⁵⁶ • The SPM MaR1 was shown to protect mice from development of diet-induced NASH in a retinoic acid-related orphan receptor alpha (RORα) manner. RORα is involved in macrophage polarization and is dysregulated in NASH.⁵⁷
Obesity	<ul style="list-style-type: none"> • In mice with obesity, the SPMs RvD1,^{46,47} RvD2,⁴⁷ and the D-series resolvin precursor 17-HDHA⁴⁸ reduced the influx of proinflammatory cells and reduced the expression of proinflammatory markers in adipose tissue. • The SPMs RvD1⁴⁹ and MaR1⁵⁰ promoted an “M2 anti-inflammatory” macrophage phenotype within adipose tissue in a rodent model of obesity, leading to a reduction in proinflammatory cytokines. • In human visceral adipose tissue and macrophages, treatment with the SPM RvD1 limited inflammatory cytokine expression.¹⁷ • In models of diet and genetic obesity (<i>ob/ob</i> mice), the SPM MaR1 increased adiponectin in adipose tissue.⁵⁰

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvin; RvE, E-series resolvin, MaR, maresin; 17-HDHA, 17-hydroxydocosahexaenoic acid; 18-HEPE, 18-hydroxyeicosapentaenoic acid

Table 4: Summary of preclinical animal and cell data relevant to surgery

Condition	SPM Evidence Summary
Allograft rejection	<ul style="list-style-type: none"> <li data-bbox="436 212 2007 277">• In a mouse model of corneal transplant, the SPM RvE1 improved allograft survival, reduced infiltration of neutrophils into corneal cells, and reduced numbers of Th1/Th17 cells in the area as well as reducing proinflammatory mediators within the site.⁶⁶ <li data-bbox="436 282 2007 318">• The SPM RvE1 prolonged renal allograft survival in mice.⁶⁷
Infection	<ul style="list-style-type: none"> <li data-bbox="436 342 2007 378">• The SPMs RvD1, RvD5, and PD1 enhanced human macrophage and PMN containment of <i>E. coli</i>.⁶¹ <li data-bbox="436 383 2007 418">• Treatment with the SPMs RvD1 and RvD5 reduced bacterial count and prevented hypothermia in a mouse model of <i>E. coli</i>-induced peritonitis.⁶¹ <li data-bbox="436 423 2007 459">• The SPM RvD1 enhanced antibiotic (ciprofloxacin) effects in <i>E. coli</i> peritonitis, accelerating the onset of resolution and shortening overall time to resolution.⁶¹ <li data-bbox="436 464 2007 529">• The SPMs RvD1, RvD5, and PD1 also reduced bacterial counts of <i>S. aureus</i> in a mouse model of peritonitis⁶¹ and enhanced the antibacterial action of antibiotic (vancomycin).⁶¹ <li data-bbox="436 534 2007 599">• The SPM RvE1 enhanced neutrophil containment of <i>C. albicans</i> and increased neutrophil fungicidal activity,⁶² and in a mouse model of systemic candidiasis, RvE1 reduced circulating fungal counts.⁶²
Insulin resistance and diabetes	<ul style="list-style-type: none"> <li data-bbox="436 612 2007 647">• The SPMs RvD1^{59,60} and RvD2⁶⁰ reduced postoperative pain in mouse surgery models.
Postoperative pain	<ul style="list-style-type: none"> <li data-bbox="436 699 2007 735">• The SPMs RvD1,⁵⁸ RvE1,^{45,58} and RvD2^{45,58} reduced the time of wound closure significantly in a mouse incisional injury model.
Sepsis	<ul style="list-style-type: none"> <li data-bbox="436 764 2007 829">• In models of microbial sepsis (cecal ligation and puncture), treatment with the SPMs RvD1⁶³ and RvD2⁶⁴ increased survival rate, enhanced bacterial clearance, and reduced proinflammatory cytokines. <li data-bbox="436 834 2007 899">• Treatment with the SPM MaR1 improved survival rates and decreased proinflammatory cytokines and enhanced bacterial clearance in a model of cecal ligation and puncture-induced sepsis.⁶⁵

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvin; RvE, E-series resolvin, MaR, maresin; PD, protectin

Table 5: Summary of preclinical animal and cell data related to neurological conditions

Condition	SPM Evidence Summary
Alzheimer's disease	<ul style="list-style-type: none">• Lower levels of SPMs were identified in brain tissue of mice with Alzheimer's disease compared with controls.⁷⁰• Treatment with the SPMs RvE1 and LXA4 alone or in combination reduced neuroinflammation and decreased measures of amyloid beta (Aβ) pathology in a mouse model of Alzheimer's disease.⁷⁰• The SPMs MaR1 and RvD1 reduced Aβ-induced inflammation in human microglia.⁵• The SPM MaR1 treatment stimulated microglial uptake of Aβ.⁵• The SPM LXA4 reduced inflammation induced by Aβ in the cortex and hippocampus of mice.⁷¹
Brain and spinal cord injury	<ul style="list-style-type: none">• The SPM LXA4 reduced blood-brain barrier permeability postinjury, attenuated brain edema, and reduced lesion volume in a mouse model of traumatic brain injury. LXA4 also reduced proinflammatory marker expression in this mouse model.⁷⁷• The SPM RvD1 had a neuroprotective effect, promoted functional recovery, and reduced inflammatory-induced neuronal cell death in remote brain regions in a rodent model of focal brain injury (hemicerbellectomy).⁷⁸• The SPM MaR1 accelerated inflammation resolution, improved locomotor recovery, and reduced secondary injury progression in a mouse model of spinal cord injury.⁷⁹
Hemorrhagic stroke	<ul style="list-style-type: none">• Treatment with the SPM LXA4 following subarachnoid hemorrhage decreased brain water content after 24 hours and improved neurological function and scores on learning and memory tests 21 days after the event in rats.⁷⁵ In this model, the SPM LXA4 also ameliorated cerebrovascular endothelial dysfunction.⁷⁶
Ischemic stroke	<ul style="list-style-type: none">• Treatment with the SPM LXA4 in a rat model of cerebral ischemia and reperfusion injury reduced infarct size, reduced inflammatory marker expression in the cerebral cortex, and led to improved neurological functioning.⁷²• Administration of the SPM MaR1 in a mouse brain ischemia and reperfusion model reduced infarct volume size and neurological defects and also alleviated proinflammatory effects.⁷³• Treatment with the SPM RvD2 treatment in a rat model of cerebral ischemia and reperfusion injury reduced neuron and brain microvascular endothelial cell death.⁷⁴
Postoperative pain	<ul style="list-style-type: none">• The SPM MaR1 protected against a reduction in tight-junction protein postsurgery and prevented blood-brain barrier opening in a mouse orthopedic surgery model.⁶⁸• Treatment with the SPMs MaR1⁶⁸ and RvD1⁶⁹ protected hippocampal memory function and prevented cognitive impairments postsurgery in a mouse model of orthopedic surgery.

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvins; RvE, E-series resolvins; MaR, maresins; LX, lipoxins

Table 6: Summary of preclinical animal and cell data related to musculoskeletal conditions

Condition	SPM Evidence Summary
Arthritis	<ul style="list-style-type: none"><li data-bbox="420 227 2005 292">• Treatment with the SPM RvD1 in mice with obesity-associated osteoarthritis reduced inflammatory immune cell infiltration and diminished the progression of arthritis in the knee.⁸¹<li data-bbox="420 300 2005 365">• Treatment with the SPM RvD1 in mice with rheumatoid arthritis attenuated arthritis severity, edema, and immune cell infiltration and also shortened the interval to remission. PGE2 was reduced, and cartilage regeneration was induced by the RvD1 treatment.⁸²<li data-bbox="420 373 2005 438">• In a separate study in a mouse rheumatoid arthritis model, the SPM RvD1 prevented bone resorption and paw inflammation, as well as bone and joint destruction.⁸³<li data-bbox="420 446 2005 479">• The SPM RvD3 was shown to reduce arthritis severity and joint inflammation in a mouse model of arthritis.⁷
Fibromyalgia	<ul style="list-style-type: none"><li data-bbox="420 490 2005 555">• In a mouse model of fibromyalgia, acute administration of the SPMs RvD2 and AT-RvD1 reduced mechanical allodynia, thermal sensitization, and chronic treatment prevented depressive-like behavior in mice.⁸⁰<li data-bbox="420 563 2005 628">• Chronic treatment with the SPMs RvD2 and AT-RvD1 was shown to prevent 5-HT reduction in total brain and reverse glutamate increase in spinal cord and brain.⁸⁰

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvins; RvE, E-series resolvins; MaR, maresins; LX, lipoxins

Table 7: Summary of preclinical animal and cell data related to lung and respiratory conditions

Condition	SPM Evidence Summary
Allergy-induced asthma	<ul style="list-style-type: none"> <li data-bbox="422 228 1986 293">• In a mouse model of allergy-induced asthma, treatment with the SPM RvE1 reduced airway immune cell infiltration and reduced proinflammatory cytokines and IgE response to allergen. Airway hyperresponsiveness and mucous were also reduced.^{84,85} <li data-bbox="422 298 1986 363">• In mice with allergic rhinitis or asthma, the SPM LXB4 significantly reduced airway inflammation, mucus, and hyperresponsiveness. Mast cell degranulation was also reduced.⁸⁶ <li data-bbox="422 368 1986 433">• The SPM MaR1 treatment reduced lung inflammation markers and increased generation of Treg cells, which acted to suppress proinflammatory cytokine expression in a mouse model of allergy-induced asthma.⁸⁷ <li data-bbox="422 438 1986 503">• In a model of aerosol allergen-induced asthma, mice treated with the SPM PD1 before aerosol challenge showed reduced airway eosinophil and T-lymphocyte recruitment, reduced airway mucous, reduced proinflammatory markers, and reduced airway hyperresponsiveness to aerosol challenge.²⁹ <li data-bbox="422 508 1986 573">• In an allergy-induced asthma mouse model, treatment with the SPM RvD1 reduced airway eosinophils and mucus and accelerated resolution of airway hyperresponsiveness to stimulus.⁸⁸ <li data-bbox="422 578 1986 643">• Administration of the SPM RvE1 after the final challenge accelerated airway inflammation resolution and promoted a reduction in the number of proinflammatory immune cells in the airway.⁸⁹
Cystic fibrosis	<ul style="list-style-type: none"> <li data-bbox="422 651 1986 716">• In a mouse model of cystic fibrosis, the SPM RvD1 improved airway pathogenesis, enhanced phagocytic and bacterial killing capacity of alveolar macrophages, and reduced proinflammatory cytokine expression.⁹⁰ <li data-bbox="422 721 1986 826">• The SPM RvD1 treatment of mice with <i>P. aeruginosa</i> infection (the key bacterial agent of cystic fibrosis lung infections) reduced PMN infiltration and proinflammatory cytokines, increased macrophage and PMN clearance of bacteria and reduced bacterial load, reduced time to infection and inflammation resolution, and reduced mucus.⁹¹

Specialized pro-resolving mediator (SPM) abbreviations: RvD, D-series resolvins; RvE, E-series resolvins; MaR, maresin; PD, protectin

Table 8: Summary of preclinical animal and cell data in other emerging areas

Condition	SPM Evidence Summary
Dry eye	<ul style="list-style-type: none"> Members of the resolvin, lipoxin, protectin, and maresin SPM families have been identified in human tears.¹⁰¹ Treatment with the SPMs RvE1,¹⁰² RvD1,^{103,104} and RvD2¹⁰⁵ in rat conjunctival goblet cells was shown to stimulate glycoconjugate secretion. In human goblet cells, the SPM RvD1 treatment stimulated mucin secretion.¹⁰⁴
Endometriosis	<ul style="list-style-type: none"> Treatment with the SPM RvD1 in rats with endometriosis reduced vascular permeability of ectopic endometrial tissue. This is important, as vascular permeability of this ectopic tissue is thought to be related to inflammation and contributes to sensory sensitivity and pain.¹⁰⁶ The SPM RvD1 reduced vaginal hypersensitivity in a rat model of endometriosis.¹⁰⁶ In a mouse model of endometriosis, treatment with the SPM LXA4 inhibited the growth of endometrial lesions.¹⁰⁷ In a separate study, the SPM LXA4 reduced inflammatory markers (IL-1β and IL-6, PGE2) and markers of angiogenesis (VEGF) in a mouse model of endometriosis.¹⁰⁸ Treatment with the SPM LXA4 in mice with endometriosis attenuated aromatase expression and attenuated estrogen signaling and the expression of estrogen-regulated genes involved in cell proliferation.¹⁰⁸ This multilevel modulation by the SPM LXA4 of pathways relevant to endometriosis pathogenesis resulted in reduced lesion growth and progression.¹⁰⁸
IBD	<ul style="list-style-type: none"> The D-series resolvin precursor 17-HDHA treatment in mice with colitis reduced colonic epithelial damage and prevented weight loss.¹⁰⁹ Treatment with the SPM MaR1 in mice with colitis reduced colon damage^{110,111} and proinflammatory cells and markers in intestinal tissue,^{110,111} improved iron status,¹¹⁰ and protected against body weight loss.¹¹¹ Treatment with the SPM RvE1 before the onset of colitis was shown to increase survival,¹¹² protect against body weight loss,^{112,113} reduce proinflammatory cell infiltration and proinflammatory gene expression,¹¹²⁻¹¹⁴ and protect against intestinal tissue damage in a mouse model of colitis.¹¹²⁻¹¹⁴ DPA-derived SPMs (PD1 and RvD5) prevented loss of colon length, reduced mucosal ulceration, and reduced colon damage while reducing proinflammatory cytokine expression and granulocyte infiltration in a mouse model of colitis.²⁶ The SPMs RvD2 and AT-RvD1 reduced body weight loss and colon damage and reduced proinflammatory cell infiltration and proinflammatory cytokine expression in a mouse model of colitis.¹¹⁵
Kidney damage	<ul style="list-style-type: none"> The SPM LXA4 treatment in mice with obesity-induced chronic kidney disease reduced glomerular expansion, mesangial matrix, and urinary H2O2.⁹² <i>In vitro</i>, the SPM MaR1 protected kidney cells' inflammation and upregulation of pathways involved in fibrosis as a result of high glucose conditions.⁹³ The SPM MaR1 treatment in a mouse model of acute kidney injury (renal ischemia and reperfusion) reduced renal dysfunction and tissue damage and lowered inflammation and oxidative stress.⁹⁴ Treatment with the SPMs RvD1 and PD1 in a mouse model of acute kidney injury reduced proinflammatory immune cell infiltration and resulted in less functional and morphological kidney injury. D-series resolvins also reduced interstitial fibrosis caused by the injury.⁹⁵ In a mouse obstructed kidney model, the SPM RvE1 had an antifibrosis effect.⁹⁶
Psoriasis	<ul style="list-style-type: none"> Treatment with the SPMs RvD1 or RvD5 in human keratinocytes reduced expression of the proinflammatory cytokine (IL-24).⁹⁷ Topical application of the SPM MaR1 in a psoriasis-like mouse model reduced swelling and reduced IL-23 receptor and IL-17α expression.⁹⁸ The SPMs RvE1⁹⁹ and RvD1¹⁰⁰ both reduced inflammatory cell infiltration, reduced the expression of proinflammatory markers, and reduced pathological skin changes in mouse models of psoriasis.

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