



Lipid Mediators in the Resolution of Inflammation

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Mounting of the acute inflammatory response is crucial for host defense and pivotal to the development of chronic inflammation, fibrosis, or abscess formation versus the protective response and the need of the host tissues to return to homeostasis. Within self-limited acute inflammatory exudates, novel families of lipid mediators are identified, named resolvins (Rv), protectins, and maresins, which actively stimulate cardinal signs of resolution, namely, cessation of leukocytic infiltration, counterregulation of proinflammatory mediators, and the uptake of apoptotic neutrophils and cellular debris. The biosynthesis of these resolution-phase mediators *in sensu stricto* is initiated during lipid-mediator class switching, in which the classic initiators of acute inflammation, prostaglandins and leukotrienes (LTs), switch to produce specialized proresolving mediators (SPMs). In this work, we review recent evidence on the structure and functional roles of these novel lipid mediators of resolution. Together, these show that leukocyte trafficking and temporal spatial signals govern the resolution of self-limited inflammation and stimulate homeostasis.

Resolution of an acute inflammatory response is the ideal outcome of this protective host response with return of the tissue to homeostasis (Majno and Joris 2004; Serhan et al. 2010). Lipid mediators are widely appreciated for their important roles in initiating the leukocyte traffic required in host defense (Cotran et al. 1999). These include the classic eicosanoids, prostaglandins (PGs) and leukotrienes (LTs) (Samuelsson et al. 1987; Samuelsson 2012), that stimulate blood flow changes, edema, and neutrophil influx to tissues (Flower 2006). Novel resolution-phase mediators that

possess potent proresolving actions were identified and named resolvins, protectins, and maresins. Further studies established that these three families as well as lipoxins function together with their aspirin-triggered (AT) forms (collectively termed specialized proresolving mediators [SPMs]) and are biosynthesized during active resolution (Serhan 2004; Serhan and Chiang 2013). The complete stereochemistry of each of the main SPMs is established and their potent actions confirmed via total organic synthesis (Serhan and Petasis 2011). Given increased availability of certain SPMs, a body of

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literature emerged that expands their potent proresolving and anti-inflammatory actions and functions originally identified for the SPMs. In this work, we review and update the roles and actions of the SPMs, focusing on recent results with resolvins, protectins, and maresins, in active resolution mechanisms.

Professor Rod Flower of the William Harvey Research Institute, University of London once recited the quotation from Juvenal, a Roman poet, to introduce these new concepts and findings: *Quis custodiet ipsos custodes?* Who will guard the guards themselves? Hence, this quote is apropos to begin this article focusing on novel chemical mediators of resolution. The guards, the innate immune system phagocytes, certainly require direction (Serhan 2004; Perretti and D'Acquisto 2009) in the form of chemoattractants and chemical signals to appropriately control their function(s) and permit clearance of microbes and cellular debris without tissue injury; the cardinal signs of resolution.

THE ORCHESTRA AND PLAYERS OF THE RESOLUTION PHASE

In the acute inflammatory response, some chemical signals are from exogenous microbial origins, whereas others are biosynthesized by the host in response to tissue injury and invasion (Cotran et al. 1999; Lawrence et al. 2002; Serhan et al. 2010). Among the chemical signals at the site of an acute inflammatory response (Buckley et al. 2013), those that originate from host essential fatty acids are of particular interest because of their nutritional regulation and the potential to design synthetic mimetics of these naturally optimized molecules (Serhan 2004). Prostaglandins and leukotriene B₄ are involved in the initiating steps that permit leukocytes and specifically neutrophils to leave, via diapedesis, postcapillary venules (Malawista et al. 2008; Serhan et al. 2010). We focused on mechanisms involved in endogenous anti-inflammation and its resolution (Serhan et al. 2000, 2002; Levy et al. 2001; Serhan 2004). Using a systems approach with LC-MS-MS (liquid chromatography-tandem mass spectrometry)–

based lipidomics, in vivo animal models, self-limited resolving inflammatory exudates, and functional assessment with isolated human leukocytes, we identified novel bioactive mediators produced in the resolution phase of acute sterile inflammation (Fig. 1) that activate new pro-resolving mechanisms (Serhan et al. 2000, 2002; Hong et al. 2003).

Focusing on self-limited resolving exudates also permitted a direct assessment of the host's responses that enables the return to homeostasis. For example, a key bioassay that proved critical in our initial studies focused on stopping human polymorphonuclear neutrophil (PMN) transmigration across vascular endothelial cells and mucosal epithelial cells (Serhan et al. 2000). We focused on neutrophils because they are among the first responders to injury, alarms, and microbial invasion. PMNs, given their high numbers, can amplify inflammation within tissues when inadvertently activated, causing collateral damage. Our hypothesis that endogenous chemical mediators are produced via cell–cell interactions within inflammatory exudates (i.e., pus) that control the size, magnitude, and duration of the inflammatory event proved to be the case and is relevant to human translation (Tabas and Glass 2013). Anti-PMN therapy (Takano et al. 1998) that limits tissue damage to control inflammation has increasing appeal. The milestones in resolution of inflammation from observation to active resolution, to new resolution therapeutics first in humans, are reviewed in Serhan (2011, 2014). In ancient medical texts of the 11th and 12th centuries, the notion of treating inflammation with resolvers to resolve disease is present (Avicenna, adapted by Laleh Bakhtiar, 1999). However, the concept was apparently lost until the structures and actions of endogenous resolution mediators were elucidated (Serhan et al. 2002). Within exudates resolving to homeostasis, the fundamental cellular processes impacted by SPMs, namely resolvins, protectins, and maresins, proved predictive of their actions in disease models in vivo, because cessation of PMN entry into tissue and the removal of dead PMNs are central to many disease pathologies in which uncontrolled inflammation is involved.

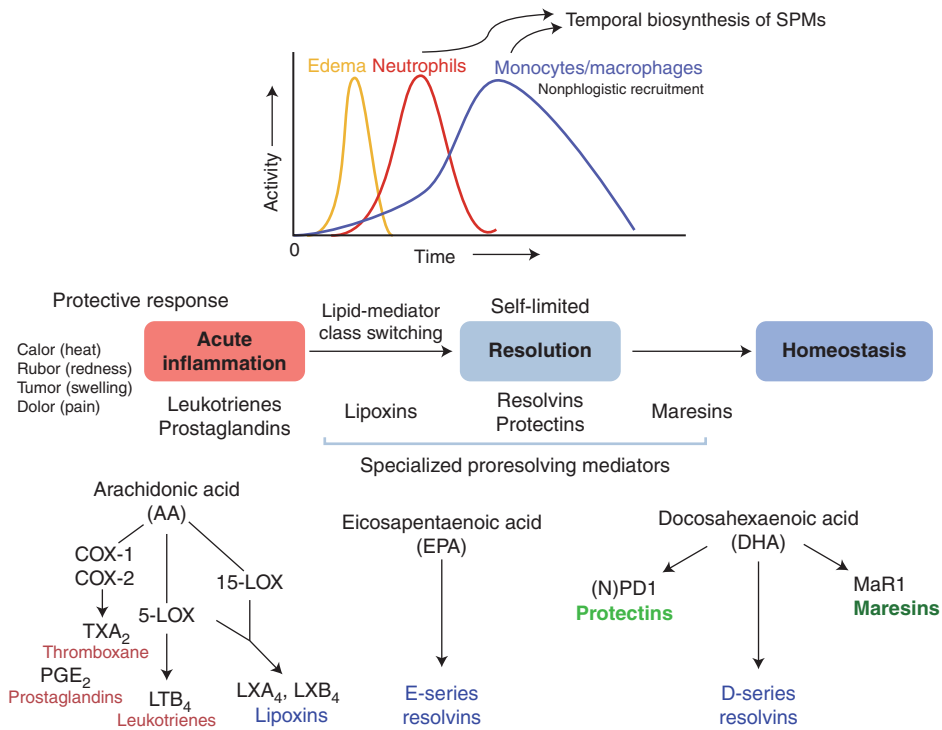


Figure 1. Lipid-mediator biosynthesis in exudate cell traffic in resolution of acute inflammation. Specialized proresolving mediators (SPMs) are generated during inflammation resolution and control the early events in acute inflammation such as edema formation, leukocyte trafficking, and functions (see text).

Metchnikoff observed more than 100 years ago that neutrophils are ingested by tissue macrophages (“big eaters”) and that this clearance of neutrophils resolves tissue inflammation (Tauber and Chernyak 1991; Cotran et al. 1999). Subsequent decades of research identified the “go” signals (for example, complement components, cytokines, chemokines, and certain eicosanoids) that promote the recruitment of leukocytes from the blood to the inflamed tissue. Investigators believed that the removal of the inflammatory stimulus prevented the production of chemoattractants that promote leukocyte recruitment and that simple dilution of the chemoattractants prevented further leukocyte cell recruitment and that these passive events brought about the ending of inflammation.

Evidence that the resolution of inflammation is an active process came from our studies on acute self-limiting responses using a sys-

tems-based approach (Serhan et al. 2000, 2002; Levy et al. 2001; Hong et al. 2003). Results from these studies showed that, in resolving inflammatory exudates, cell–cell interactions lead to the biosynthesis of active signals that limit further neutrophil recruitment to the tissue (cessation of PMN influx) and enhance the engulfment of apoptotic neutrophils by macrophages, the two cardinal signs of resolution, promoting a return of the tissue to homeostasis. In active resolution, we uncovered a key process coined lipid-mediator class switching in exudates (see Fig. 1). That is, prostaglandins involved in the initiation phase of inflammation activate the translation of mRNAs encoding enzymes (Levy et al. 2001) that are needed for production of proresolvent mediators (lipoxins, resolvins, and protectins) during the resolution phase (Fig. 1). Low-dose aspirin jump-starts the resolution phase by triggering endogenous epimers of these SPMs (Serhan 2007), which is

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shown in animal disease (Chan and Moore 2010; Brancaleone et al. 2013) and in human skin blisters (Morris et al. 2009) and infantile eczema (Wu et al. 2013).

THE ENTRY OF OTHER SUBSTRATES IN RESOLUTION

We also learned that n-3 essential fatty acids are substrates within these inflammatory resolving exudates for the biosynthesis of potent anti-inflammatory and proresolving mediators (Serhan et al. 2002; Hong et al. 2003). Identification of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as precursors of mediators that activate proresolving mechanisms opened new avenues to consider for appreciating mechanisms underlying uncontrolled inflammation. It is worth noting that a large body of literature addressing the anti-inflammatory impact of EPA and DHA is present (for a recent review, see De Caterina 2011; Calder 2013); yet, the molecular mechanism(s) by which these essential nutrients exert their anti-inflammatory actions remained the subject of debate. DHA and EPA have many known critical functions in mammalian biology. Neither EPA nor DHA is produced by humans to any great extent, requiring their dietary intake (Calder 2013). DHA is an ancient molecule that has functional roles in brain and eye optimized by evolutionary pressure for its physical properties in membranes (Crawford et al. 2013). Uncovering novel chemical mediators that are biosynthesized within self-limited inflammatory responses with exudates in murine systems with functions on individual mammalian and human leukocytes has far-reaching implications (Fig. 1). Along these lines, n-3-derived SPMs are documented in humans in health and disease, including plasma, milk, adipose tissue, and synovial fluid (see Table 1 for details). For recent detailed reviews on resolvins, protectins, and maresins, interested readers are directed to the following: SPM biosynthesis (Bannenberg and Serhan 2010), actions (Recchiuti and Serhan 2012; Serhan and Chiang 2013), and total organic synthesis (Serhan and Petasis 2011). At this point, we address the initial observations of the SPM biosynthesis and activities

on phagocytes and in animal models of disease now confirmed in many laboratories (Tables 2 and 3).

Endogenous Anti-Inflammation and Proresolution Are Not Equivalent Processes

Each SPM possesses potent proresolving actions that are fundamental to resolution (Serhan 2004) including limiting or cessation of neutrophil tissue infiltration, counterregulation of chemokines and cytokines (Serhan et al. 2002; Hong et al. 2003), reduction in pain (Xu et al. 2010), and stimulation of macrophage-mediated actions, namely, phagocytosis of apoptotic PMNs and bacterial and debris clearance (Table 2) (Schwab et al. 2007; Chiang et al. 2012). The SPMs are multitarget agonists in that they each act on both PMNs and macrophages separately to stimulate resolution. Given this unique proresolving mechanism, resolvins and other SPMs each display potent actions in many animal disease models (Table 3). The actions of resolvins and all SPMs are stereochemically selective, reflecting their routes of biosynthesis and underlying their ability to activate receptors (G-protein-coupled receptor [GPCR]) that amplify and transduce their tissue response. Thus, establishing the complete stereochemical assignments for each resolvins, protectin, and maresin (SPM) family was key to confirming their novel leukocyte functions. Given their ability to stimulate resolution of inflammation without systemic immune suppression of host defense (Spite et al. 2009; Oh et al. 2011), we recognize that SPMs stimulate resolution of inflammation and bacterial infection (Serhan 2011; Chiang et al. 2012).

BIOSYNTHESIS, FUNCTION, AND STRUCTURAL ELUCIDATION

It was essential to confirm the proposed structures and novel potent actions for each of the resolvins and other SPMs (Figs. 2 and 3). To this end, a systematic approach was devised to match endogenous SPMs to those prepared by total organic synthesis (Serhan and Petasis 2011).

Table 1. Humans and SPMs

SPM	Disease/tissues	Formation
Lipoxins and aspirin-triggered lipoxins (ATLs)	Asthma	Higher urinary ATL levels in aspirin-tolerant asthma than in aspirin-intolerant asthma (Sanak et al. 2000; Levy et al. 2005; Yamaguchi et al. 2011) and regulate natural killer (NK) cell and innate lymphoid cell activation (Barnig et al. 2013; Peebles 2013)
	Alzheimer's disease (AD)	LXA ₄ levels are reduced in AD brain and CSF (Wang et al. 2014)
	Colitis	Elevated mucosal LXA ₄ promotes remission in individuals with ulcerative colitis (Vong et al. 2012)
	Type 2 diabetes	Increased plasma ATL with intake of pioglitazone (Gutierrez et al. 2012)
	Rheumatoid arthritis	LXA ₄ in synovial fluid from rheumatoid arthritis patients (Giera et al. 2012)
	Localized aggressive periodontitis (LAP)	Less LXA ₄ in LAP whole blood compared with healthy individuals (Fredman et al. 2011)
	Peripheral artery disease	Plasma levels of ATL are lower in patients with symptomatic peripheral artery disease (Ho et al. 2010)
	Adipose tissues	LXA ₄ identified in human adipocytes from obese patients (Clària et al. 2012)
Resolvins	Milk	Lipoxins and resolvins at very high levels in the first month of lactation (Weiss et al. 2013)
	Synovial fluid	RvD5 present in synovial fluid from rheumatoid arthritis patients (Giera et al. 2012)
	Blood (healthy volunteers)	Plasma RvD1 and RvD2 identified with oral omega-3 supplementation (Mas et al. 2012; Colas et al. 2014)
	Adipose tissues	RvD1 and RvD2 identified in human adipocytes from obese patients (Clària et al. 2012)
	Human plasma and milk	RvE1 identified in human plasma (Psychogios et al. 2011) and milk (Weiss et al. 2013)
	Multiple sclerosis	RvD1 was detected and up-regulated in serum and cerebrospinal fluid in the highly active group (Pruss et al. 2013)
	Human IgA nephropathy	RvE1 identified in patients supplemented with fish oil n-3 (Zivkovic et al. 2012)
Protectin	Asthma	PD1 in exhaled breath condensates in asthma exacerbation (Levy et al. 2007); decreased PD1 in eosinophils from patients with severe asthma compared with healthy individuals (Miyata et al. 2013)
	Embryonic stem cells	PD1 produced in embryonic stem cells (Yanes et al. 2010)
Maresins	Multiple sclerosis	NPD1 was detected in serum and cerebrospinal fluid in the highly active group (Pruss et al. 2013)
	Synovial fluid	MaR1 identified in synovial fluid from arthritis patients (Giera et al. 2012)

This approach was necessary because SPMs are isolated in pure form in only small quantities from exudates (picogram to nanogram range), are locally active, and are inactivated via further metabolism (Arita et al. 2006; Clària et al. 2012). These transient and small quantities preclude direct NMR analysis. The original identification of the D-series resolvins reported the structural

elucidation of several distinct bioactive structures that stopped PMN influx and migration, denoted resolvin D1 through resolvin D6, from resolving self-limited murine exudates. Their biosynthetic pathway(s) were established with isolated human leukocytes (Figs. 2 and 3), and potent *in vivo* actions were determined in murine (Table 3) as well as human inflammation (Ser-

Table 2. Host defense: Enhanced phagocytosis and the roles of SPMs

	Phagocytosis in vivo	PMN	Macrophages
LXA ₄	STZ (Schwab et al. 2007)		Apop PMN (Godson et al. 2000; Schwab et al. 2007)
ATL	Apop PMN (El Kebir et al. 2009) <i>Escherichia coli</i> (El Kebir et al. 2009) Multimicrobial sepsis/CLP (Walker et al. 2011)		Serum-treated zymosan (Schwab et al. 2007) Latex beads (Schwab et al. 2007) <i>E. coli</i> (Prescott and McKay 2011)
RvE1	STZ (Schwab et al. 2007) HSV-1 (Rajasagi et al. 2011) <i>E. coli</i> (Seki et al. 2010; El Kebir et al. 2012)	<i>Candida albicans</i> (Haas-Stapleton et al. 2007)	Apop PMN (Schwab et al. 2007; Oh et al. 2011) Serum-treated zymosan (Schwab et al. 2007; Ohira et al. 2010; Oh et al. 2011) Latex beads (Schwab et al. 2007) <i>E. coli</i> (Oh et al. 2011)
18S-RvE1			Apop PMN (Oh et al. 2011) Serum-treated zymosan (Oh et al. 2011) <i>E. coli</i> (Oh et al. 2011)
RvE2			Serum-treated zymosan (Oh et al. 2011)
PD1	STZ (Schwab et al. 2007) Apop PMN (El Kebir et al. 2009) <i>E. coli</i> (Chiang et al. 2012)	<i>E. coli</i> (Chiang et al. 2012)	Serum-treated zymosan (Schwab et al. 2007) Apop PMN (Schwab et al. 2007) Latex beads (Schwab et al. 2007) <i>E. coli</i> (Chiang et al. 2012)
RvD1	<i>E. coli</i> (Chiang et al. 2012) Apop PMN (Hsiao et al. 2013)	<i>E. coli</i> (Chiang et al. 2012)	Serum-treated zymosan (Krishnamoorthy et al. 2010) Apop PMN (Krishnamoorthy et al. 2010) <i>E. coli</i> (Chiang et al. 2012)
AT-RvD1			<i>E. coli</i> (Palmer et al. 2011) IgG-OVA-coated beads (Rogerio et al. 2012)
RvD2	Multimicrobial sepsis/CLP (Spite et al. 2009)	<i>E. coli</i> (Spite et al. 2009)	Serum-treated zymosan (Spite et al. 2009)
RvD3			Serum-treated zymosan (Dalli et al. 2013a)
AT-RvD3			Apop PMN
RvD5	<i>E. coli</i> (Chiang et al. 2012)	<i>E. coli</i> (Chiang et al. 2012)	<i>E. coli</i> (Chiang et al. 2012)
MaR1			Serum-treated zymosan (Serhan et al. 2009)
MaR2			Apop PMN (Serhan et al. 2012; Deng et al. 2014)

ATL, aspirin-triggered lipoxins; STZ, serum-treated zymosan; CLP, common lymphoid progenitors.

han et al. 2002; Morris et al. 2009; Wu et al. 2009, 2013).

Recently, the stereochemical structures of resolvin D1 (RvD1; 7*S*,8*R*,17*S*-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid), its AT 17*R*-epimer (Sun et al. 2007), RvD2 (resolvin D2, 7*S*,16*R*,17*S*-trihydroxy-4*Z*, 8*E*,10*Z*,12*E*,14*E*,19*Z*-docosahexaenoic acid) (Spite et al. 2009), AT-protectin D1 (PD1; protectin D1/neuroprotectin D1, 10*R*,17*S*-dihydroxy-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-docosahexaenoic acid) (Ser-

han et al. 2011), and maresin 1 (MaR1; maresin 1, 7*R*,14*S*-dihydroxy-docosa-4*Z*,8*E*, 10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid) (Serhan et al. 2012) were each assigned, as well as their biosynthetic-related isomers, and several made commercially available.

Recently, we also establish the complete stereochemistry of RvD3 (resolvin D3, 4*S*,11*R*,17*S*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid) (Fig. 3) and its AT-RvD3 (4*S*,11*R*,17*R*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-

Table 3. Update on SPM actions in disease models

Disease	SPM	Bioaction
Alzheimer's disease (AD)	RvD1	Stimulates phagocytosis of A β by AD macrophages (Mizwicki et al. 2013)
Burn wound	RvD2	Prevents secondary thrombosis and necrosis (Bohr et al. 2013)
Chronic pancreatitis	RvD1	Reverses allodynia (Feng et al. 2012)
Diabetic wounds	RvD1	Accelerates wound healing (Tang et al. 2013)
Dermatitis	RvE1	Ameliorates dermatitis (Kim et al. 2012)
Pulmonary inflammation	RvE1	Promotes apoptosis and accelerates airway resolution (Seki et al. 2010)
Peripheral nerve injury	RvE1	Inhibits neuropathic pain (Xu et al. 2013)
Obesity	RvD1, RvD2	Govern inflammatory tone (Clària et al. 2012)
Allergic airway response	RvD1, AT-RvD1, RvE1, PD1	Promote resolution (Levy et al. 2007; Haworth et al. 2011; Rogerio et al. 2012)
Amyotrophic lateral sclerosis	RvD1	Inhibits inflammation (Liu et al. 2012)
Acute lung injury	AT-RvD1	Reduces mucosal inflammation (Eickmeier et al. 2013)
Fibrosis	RvE1, RvD1	Inhibit kidney fibrosis (Qu et al. 2012)
Bacterial infection	RvD1, RvD5, PD1	Increase survival and lower antibiotic requirement (Chiang et al. 2012)
Peritonitis	RvD1	Limits PMN recruitment and accelerate resolution (Recchiuti et al. 2011; Norling et al. 2012)
Dry eye	RvE1 and analog	Protect from goblet cell loss (de Paiva et al. 2012); improves tear production (Li et al. 2010)
Tissue regeneration	RvE1, MaR1	Promote tissue regeneration in planaria (Serhan et al. 2012)
Pain	MaR1, RvD1, AT-RvD1, RvD2, RvE1	Control inflammatory pain (Bang et al. 2010, 2012; Xu et al. 2010; Park et al. 2011; Serhan et al. 2012)
Adipose tissue inflammation	RvD1	Elicits macrophage polarization and promote resolution (Titos et al. 2011)
Localized aggressive periodontitis	RvE1	Rescues impaired phagocytosis (Fredman et al. 2011)
Colitis	RvD1, RvD2, RvE1	Prevent colitis (Ishida et al. 2010; Bento et al. 2011)
Temporomandibular joint inflammation	AT-RvD1	Limits PMN infiltration to CFA-inflamed TMJ (Norling et al. 2012)
Arthritis	AT-RvD1	Antihyperalgesic (Lima-Garcia et al. 2011)
Postoperative pain	RvD1	Prevents and reduces pain (Huang et al. 2011)
Postsurgical cognitive decline	AT-RvD1	Improves postoperative decline and attenuates memory neuronal dysfunction (Terrando et al. 2013)
Endotoxin shock	RvD1	Suppresses septic mediators (Murakami et al. 2011)
HSV-keratitis	RvE1	Controls ocular inflammatory lesions (Rajasagi et al. 2011)
Allograft rejection	RvE1	Preserves organ function (Levy et al. 2011)
Heart ischemia	RvE1	Protects heart against reperfusion injury (Keyes et al. 2010)
Bacterial pneumonia	RvE1	Protects mice from pneumonia (Seki et al. 2010)
Cigarette smoke-induced lung inflammation	RvD1	Promotes M2 macrophages and efferocytosis as well as accelerates resolution of lung inflammation (Hsiao et al. 2013)
Vascular inflammation (arterial angioplasty)	RvD1	Attenuates cell proliferation, leukocyte recruitment, and neointimal hyperplasia (Miyahara et al. 2013)
Fibromyalgia	AT-RvD1, RvD2	Reduces mechanical allodynia and thermal sensitization and prevent depressive behavior (Klein et al. 2014)
Vagotomy	RvD1	Rescues hyperinflammation (Mirakaj et al. 2014)

TMJ, temporomandibular joint.

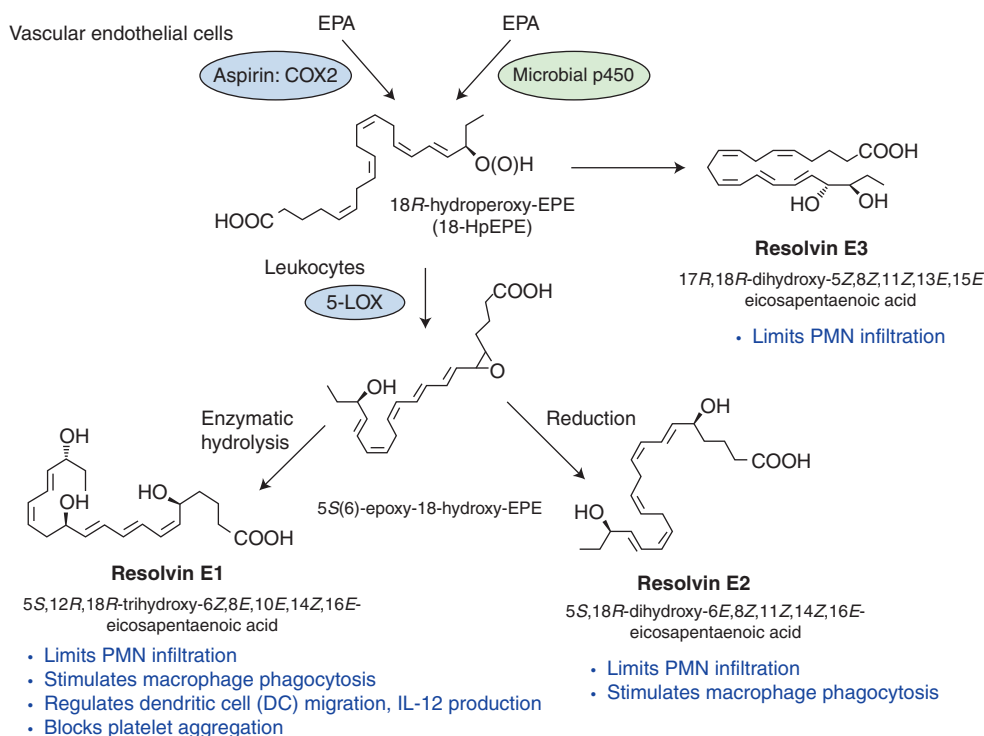


Figure 2. E-series resolvin biosynthesis and major function (see text for details).

hexaenoic acid) *natural* epimer (Dalli et al. 2013a). Using LC-MS-MS metabololipidomics, we matched the physical properties of RvD3 with those of synthetic materials possessing the stereochemistry that proved to be 4*S*,11*R*,17*S*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid (Fig. 3) and the AT-RvD3, or aspirin-triggered form, matched synthetic 4*S*,11*R*,17*R*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid (Dalli et al. 2013a). When administered *in vivo*, both of these synthetic epimers, at doses as low as 10 pg/mouse, gave potent reduction (40%–50%) of murine PMN recruitment to sites of inflammation. Both RvD3 and AT-RvD3 increased exudate IL-10 and reduced IL-6 and eicosanoids (Dalli et al. 2013a).

With human leukocytes, RvD3 and AT-RvD3 each potently regulate leukocyte functions enhancing peritoneal macrophage phagocytosis and efferocytosis in a dose-dependent manner while reducing human neutrophil

transendothelial migration in response to tumor necrosis factor (TNF)- α (Dalli et al. 2013a). These results establish the complete stereochemistry and confirmed the potent anti-inflammatory and proresolving actions of RvD3 and its aspirin-triggered epimer denoted AT-RvD3 (see Fig. 3). Moreover, lipid-mediator metabololipidomic profiling of self-resolving exudates also placed RvD3 uniquely within the time course of inflammation resolution to vantage complete resolution, namely, in the later stages (Dalli et al. 2013a).

MARESINS: MACROPHAGE MEDIATORS IN RESOLVING INFLAMMATION

Recently, we also established the stereochemical assignments for both AT-PD1 (Serhan et al. 2011) and maresin 1 (MaR1) (Serhan et al. 2012). MaR1 produced by human macrophages (M Φ) from endogenous docosahexaenoic acid (DHA) matched the stereochemistry of syn-

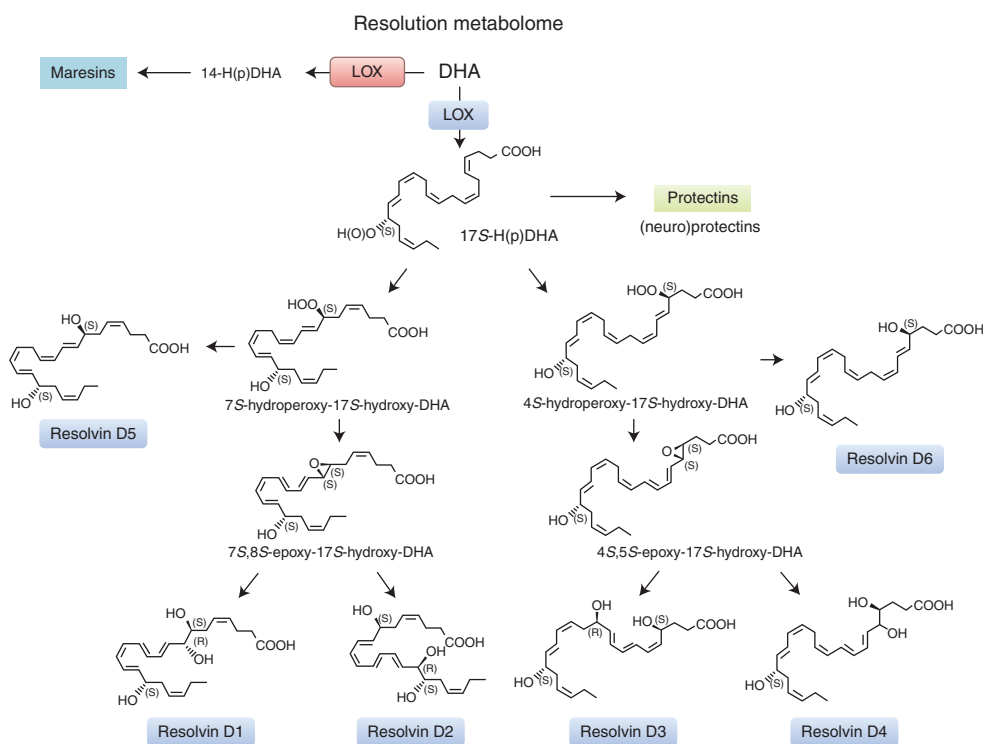


Figure 3. D-series resolvins biosynthesis. The complete stereochemistry of RvD1, RvD2, and RvD3 is established (see Dalli et al. 2013a and text for further details).

thetic 7*R*,14*S*-dihydroxydocosa-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid. MaR1 alcohol groups and *Z/E* geometry of conjugated double bonds were assigned using isomers prepared by total organic synthesis. MaR1's potent defining actions were confirmed with synthetic MaR1 (i.e., limiting neutrophil [PMN] infiltration in murine peritonitis (ng/mouse range) as well as enhancing human macrophage uptake of apoptotic PMNs).

MaR1 is slightly more potent at 1 nM than Resolvin D1 (RvD1) in stimulating human M Φ efferocytosis, an action not shared by leukotriene B₄. Importantly, MaR1 also accelerates surgical regeneration in planaria, increasing the rate of head reappearance. On injury of the planaria (when cut in half), MaR1 is biosynthesized from deuterium-labeled (d₅)-DHA. MaR1 dose-dependently inhibited TRPV1 currents in neurons, blocked capsaicin-induced inward currents IC₅₀ ≈ 0.5 nM, and reduced

both inflammatory and chemotherapy-induced neuropathic pain in mice (Serhan et al. 2012). Hence, MaR1 has potent actions in regulating inflammation resolution, tissue regeneration, and resolving pain. These findings also suggest that chemical signals are shared in resolution cellular trafficking that is key in tissue regeneration across phyla from worms to humans.

Of special interest, the total organic synthesis of MaR1 was also achieved by Rodriguez and Spur using Sonogashira coupling (2012c), who also reported resolvins D6 (2012a) and organic synthesis of resolvins E2 (2012b) (Figs. 2 and 3). Kobayashi et al. also reported stereoselective total organic synthesis of protectin D1 (Ogawa and Kobayashi 2011), resolvins E2 (Ogawa et al. 2009), and resolvins E1 (Ogawa and Kobayashi 2009). The total organic synthesis of the 18-HEPE, a precursor of E-series resolvins, was also reported (see Fig. 2) (Krishnamurthy et al. 2011). Importantly, the stereoselective actions

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of each SPM proved highly effective in regulating human PMNs and monocytes in microfluidic chambers (Kasuga et al. 2008; Jones et al. 2012), clearly establishing the direct actions on human cells and hence their potential in translational medicine.

MICROPARTICLES IN RESOLUTION AND LEUKOCYTE SUBPOPULATIONS

With complete stereochemistry of many of the main SPMs established (Figs. 2 and 3), it was possible to carry out lipid-mediator (LM) metabololipidomics profiling via targeted LC-MS-MS-based analyses with distinct phagocyte populations, namely, neutrophils (PMNs), apoptotic PMNs, and macrophages (Dalli and Serhan 2012). Efferocytosis increased SPM biosynthesis, including RvD1, RvD2, and RvE2 (resolving E2, 5S,18R-trihydroxy-6E,8Z,11Z,14Z, 16E-eicosapentaenoic acid) (Figs. 2 and 3), which are further elevated by PMN microparticles (Norling et al. 2011). Apoptotic PMNs produced prostaglandin E₂, lipoxin B₄, and RvE2, whereas zymosan-stimulated PMNs showed predominantly leukotriene B₄ and 20-hydroxy-leukotriene B₄, as well as lipoxin biosynthesis pathway marker 5,15-diHETE. Using deuterium-labeled precursors (d₈-arachidonic acid, d₅-eicosapentaenoic acid, and d₅-docosahexaenoic acid), apoptotic PMNs and microparticles each contribute to SPM biosynthesis during the process of efferocytosis. Also, M2 macrophage phenotype (Lawrence and Natoli 2011) produces SPMs including MaR1 and LXA₄ (lipoxin A₄, 5S,6R,15S-trihydroxy-7E,9E,11Z,13E-eicosatetraenoic acid) with lower amounts of LTB₄ (leukotriene B₄, 5S,12R-dihydroxy-6Z,8E,10E,14Z-eicosatetraenoic acid) and prostaglandin (PG) than the macrophages of the M1 phenotype (Dalli and Serhan 2012). Of interest, the uptake of apoptotic PMNs by both macrophage subtypes led to modulation of their LM profiles and activation of transcellular SPM biosynthesis. These results establish LM signature profiles of human PMNs, apoptotic PMNs, and macrophage subpopulations (Dalli and Serhan 2012). Hence, microparticle regulation of spe-

cific endogenous LMs during defined stages of the acute inflammatory process and their dynamic changes in LM signatures are influenced by transcellular biosynthesis between apoptotic cells, microparticles, and macrophages.

RESOLUTION AND INFECTION: WHAT IS THEIR RELATIONSHIP?

How bacterial infections contribute to active resolution of inflammation is of wide interest. Hence, we focused on exudate leukocyte trafficking and mediator metabololipidomics with murine peritoneal *Escherichia coli* infections (Chiang et al. 2012) and documented the temporal identification of both proinflammatory (PG and LT) and SPMs. In self-resolving *E. coli* exudates (10⁵ CFU), the dominant SPMs were RvD5 (resolvin D5, 7S,17S-dihydroxy-4Z,8E,10Z,13Z,15E,19Z-docosahexaenoic acid) and PD1, which at 12 h were greater than levels in exudates from higher titer *E. coli* (10⁷ CFU)-infected mice. Of interest, germ-free mice produced endogenous RvD1 and PD1 levels higher than in conventional mice. RvD1 and RvD5 (ng/mouse) each reduced bacterial titers in blood and exudates, *E. coli*-induced hypothermia, and increased survival.

To translate these to humans, both human PMNs and macrophages were tested with RvD1, RvD5, and PD1, which each directly enhanced phagocytosis of *E. coli*, and both RvD1 and RvD5 counterregulate a panel of proinflammatory genes, including NF-κB and TNF-α. RvD5 activated the RvD1 receptor GPR32 to enhance phagocytosis. With self-limited *E. coli* infections, RvD1 and an antibiotic ciprofloxacin accelerated resolution, and each shortened resolution intervals (R_i). Host-directed RvD1 actions enhanced ciprofloxacin's therapeutic actions. In 10⁷ CFU *E. coli* infections, SPMs (RvD1, RvD5, PD1) together with ciprofloxacin also heightened host antimicrobial responses, enhancing clearance of *E. coli* in blood and exudates. In skin infections, SPMs stimulated vancomycin clearance of *Staphylococcus aureus*. Hence, specific SPM are temporally and differentially regulated during infections. They are antiphlogistic, enhance containment, and lower

antibiotic requirements for bacterial clearance. These endogenous resolution mechanisms are of interest in host defense because initiation of the host response is controlled in part by PG and LT (von Moltke et al. 2012), which when uncontrolled can lead to increased mortality from infection (Chiang et al. 2012), as also observed in zebrafish infections (Tobin et al. 2012). This goes beyond bacteria to viral and fungal infections. Of special interest, PD1 (Fig. 3) produced by the host was identified as a novel antiviral that directly blocks viral replication and increases host survival to influenza viral infection (Baillie and Digard 2013; Morita et al. 2013), which also suggests treating the host as with bacterial infections rather than treating the microbes alone with antibiotics (Chiang et al. 2012). The EPA-derived RvE1 (resolvin E1, 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid) (Fig. 2) also controls fungal infections as observed with *Candida albicans* (Haas-Stapleton et al. 2007).

GPC RECEPTORS IN RESOLUTION

We identified two GPCRs for RvD1 on human phagocytes, namely, ALX and GPR32. ALX/FPR2 is the lipoxin A₄ receptor, and GPR32 was an orphan receptor. RvD1 displays specific binding and reduces actin polymerization and CD11b on PMNs, as well as stimulates macrophage phagocytosis, an action dependent on ALX and GPR32 (Krishnamoorthy et al. 2010). In addition to RvD1, its AT epimer 17R-RvD1 and stable analog 17-R/S-methyl-RvD1 each dose-dependently activates ALX/FPR2 and GPR32 in GPCR-overexpressing β -arrestin systems and electric cell-substrate impedance sensing (Krishnamoorthy et al. 2012). Of interest, we showed that RvD5 also activates human GPR32 in the GPR32- β -arrestin systems, and stimulates macrophage phagocytosis of *E. coli* in a GPR32-dependent manner (Chiang et al. 2012). In addition, RvD3 and AT-RvD3 each activates GPR32, contributing to their proresolving actions in stimulating macrophage uptake of microbial particles (Dalli et al. 2013a).

A specific receptor for RvE1, *ChemR23*, is closely related to LX and LT receptors in deduced

amino acid sequences. ChemR23 displays specific RvE1 binding and RvE1-dependent signals to activate monocyte, and reduce dendritic cell migration and IL-12 production (Arita et al. 2005a). RvE1-ChemR23 interactions also stimulate macrophage phagocytosis via phosphorylation-signaling pathways including Ribosomal protein S6, a downstream target of the PI3K/Akt signaling pathway and the Raf/ERK pathway (Ohira et al. 2010). 18S-RvE1 also binds to ChemR23 with increased affinity and potency compared with the R-epimer, but was more rapidly inactivated than RvE1 (Oh et al. 2011). RvE2 is a partial agonist for ChemR23 (Oh et al. 2012). A leukotriene B₄ receptor, *BLT1*, also directly interacts with RvE1, which inhibits calcium mobilization, NF- κ B activation in vitro, and PMN infiltration in vivo (Arita et al. 2007). 18S-RvE1 and RvE2 also bind to BLT1 (Oh et al. 2011, 2012). Hence, RvE1 gives cell-type-specific actions: It functions as an agonist for ChemR23 on mononuclear and dendritic cells as well as an antagonist for BLT1 signals on PMNs. Recently, ChemR23-dependent actions of RvE1 were confirmed in mouse renal fibrosis (Qu et al. 2012).

Genetically Engineered Mice

To prepare transgenic (TG) mice for human ALX/FPR2, hALX transgene was placed under control of CD11b promoter that directed receptor expression in myeloid cells (Levy et al. 2002; Devchand et al. 2003). In non-TG littermates, RvD1 as low as 10 ng given together with zymosan, reduced leukocyte numbers by ~38% at 24 h. This action was further enhanced in ALX-TG mice giving 53% reduction of leukocytes. Also with RvD1 treatment, PMN numbers in TG mice was 50% lower than non-TG controls (Krishnamoorthy et al. 2012). We also prepared transgenic mice overexpressing human ChemR23, the RvE1 receptor, on myeloid cells. In these TG mice, RvE1 is 10-fold more potent in limiting PMN infiltration in zymosan-initiated peritonitis, compared with non-TG littermates. In addition, ligature-induced alveolar bone loss was diminished in ChemR23tg mice (Gao et al. 2013). Local RvE1 treatment of uni-

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form craniotomy in the parietal bone significantly accelerated regeneration of the bone defect, indicating that RvE1 modulates osteoclast differentiation and bone remodeling by direct actions on bone.

In mice deficient in ALX/*fpr2* (mouse ortholog of human ALX), the anti-inflammatory actions of RvD1 were dampened. Administration of RvD1 (1 ng/mouse) significantly reduces PMN infiltration in wild-type mice, but not in *fpr2*-deficient mice. Also in peritoneal exudates, RvD1 activates LX biosynthesis stimulating the production of the anti-inflammatory mediator LXB₄ (lipoxin B₄, 5S,14R,15S-trihydroxy-6E,8Z,10E,12E-icosatetraenoic acid) and stimulated the biosynthesis of the cyclooxygenase-derived PGE₂ (prostaglandin E₂, 9-oxo-11R,15S-dihydroxy-5Z,13E-prostadienoic acid) while down-regulating production of the proinflammatory LTB₄. This regulation of lipid mediator by RvD1 is lost in the *fpr2*-deficient mice (Norling et al. 2012). These results indicate that RvD1 dampens acute inflammation in part via ALX receptor. Also, 15-epi-LXA₄ interacts with ALX/FPR in vivo controlled by aspirin (Brancaleone et al. 2013). In BLT1 knockout mice, in vivo anti-inflammatory actions of RvE1 were sharply reduced when given at low doses (100 ng i.v.) in peritonitis. In contrast, RvE1 at higher doses (1.0 μg i.v.) significantly reduced PMN infiltration in a BLT1-independent manner (Arita et al. 2007). Hence, RvE1 binds to BLT1 as a partial agonist, serving as a local damper of BLT1 signals on leukocytes along with other receptors (e.g., ChemR23 receptor-mediated counterregulatory actions) to mediate the resolution of inflammation.

MICRO RNAs OF RESOLUTION: SPM-RECEPTOR-microRNA CIRCUITS

RvD1 controls specific miRNA expression in vivo and in vitro (Recchiuti et al. 2011). This panel of miRs, including miR-146b, 208a, and 219, was temporally regulated during self-limited inflammation and regulated by RvD1 in vivo as well as in a RvD1-GPCR- (ALX and GPR32) dependent manner in human macrophages (Recchiuti et al. 2011). Macrophages overex-

pressing miR-219 significantly down-regulate 5-LOX and reduce LTB₄. Hence, 5-LOX is a target of miR-219 (Recchiuti et al. 2011). In addition, RvD1 at low dose (10 ng) significantly increases miR-219 in ALX-TG mice, whereas this dose of RvD1 was not effective in non-TG controls (Krishnamoorthy et al. 2012). Additionally, delayed resolution initiated by high-dose zymosan challenges decreases miR-219-5p expression along with higher LTB₄ and lower SPMs (Fredman et al. 2012). Therefore, RvD1 initiated a resolution circuit that involves activation of ALX and miR-219.

CAN RESOLVINS AND SPMs REVERSE ONGOING INFLAMMATION IN HUMANS?

Clinical Development

An RvE1 analog significantly improved signs and symptoms in a phase 2 clinical trial in patients with dry eye syndrome. This is the first demonstration of clinical efficacy for the novel class of resolvins therapeutics. The phase III clinical trial is now in progress (Safety and Efficacy Study of RX-10045 on the Signs and Symptoms of Dry Eye, identifier NCT00799552; www.clinicaltrials.gov). The AT 15-epi-LXA₄ analog, 15-*R/S*-methyl-LXA₄, reduced infantile eczema, showing no apparent toxicity or side effects (Wu et al. 2013).

New Uses of SPMs in Animal Disease Models

For an early review and detailed descriptions of initial animal models defining SPM proresolution action, see Serhan 2007. Recently, with conjunctiva goblet cells, both RvD1 and RvE1 reduced LTD₄- and histamine-stimulated conjunctival goblet cell secretion (Dartt et al. 2011; Li et al. 2013). RvE1 delivered as its methyl ester in a murine model of dry eye improves the outcome measures of corneal staining and goblet cell density, indicating the potential of resolvins in the treatment of dry eye (de Paiva et al. 2012). In HSV-induced ocular inflammation, RvE1 significantly reduces cornea lesions and angiogenesis as well as T cells and PMNs. These results indicate that RvE1 represents a novel approach

to control virus-induced diseases (Rajasagi et al. 2011). A recent study showed a phenotype of delayed wound healing in cornea of female mice. Also in human corneal epithelial cells, estradiol reduced 15-LOX type-I and LXA₄. LXA₄ addition rescues the estradiol-abrogated wound healing, demonstrating gender-specific differences in the corneal repair mediated by the 15-LOX-LXA₄ circuit (Wang et al. 2012). In uveitis in rats, bolus intravenous injection of RvD1 (10–1000 ng/kg) significantly and dose-dependently reduced LPS-induced ocular derangement and PMNs, T-lymphocytes, as well as cytokines within the eye (Settimio et al. 2012).

In localized aggressive periodontitis (LAP) patients, macrophages show reduced phagocytosis. RvE1 rescues impaired phagocytic activity of LAP macrophages (Fredman et al. 2011). Humanized nanoparticles containing 17R-RvD1 or LXA₄ analog protect against inflammation in the temporomandibular joint, a model of temporomandibular joint disease (Norling et al. 2011). Exposure of salivary epithelium to TNF- α and/or interferon (IFN)- γ alters tight junction integrity, leading to secretory dysfunction. RvD1 (100 ng/mL) rescues TNF- α -induced tight junction and cytoskeletal disruption, and enhances cell migration and polarity in an ALX-dependent manner. Hence, RvD1 promotes tissue repair in salivary epithelium and restores salivary gland dysfunction associated with Sjögren's syndrome (Odusanwo et al. 2012). In rabbit arterial angioplasty, endogenous biosynthesis of proresolving lipid mediators, including RvD5 and LXB₄, was identified in the artery wall. Resolvins also reduce human smooth muscle cell proliferation and attenuate leukocyte recruitment and neointimal hyperplasia in rabbit balloon-injured arteries (Table 3) (Miyahara et al. 2013).

RvE1 promotes resolution in part via reducing IL-23 and IL-6 in allergic airways of mice as well as increasing IFN- γ (Haworth et al. 2008). Also, RvE1 regulates natural killer (NK) cell migration and cytotoxicity (Haworth et al. 2011), and LXA₄ regulates NK cells and type 2 innate lymphoid cell activation in asthma (Barnig et al. 2013). AT-RvD1 and RvD1 each markedly shorten resolution intervals for lung eosino-

philia and reduce select inflammatory peptides and lipid mediators (Rogerio et al. 2012). In acute lung injury, AT-RvD1 improves epithelial and endothelial barrier integrity, decreases airway resistance, and increases epinephrine levels in bronchoalveolar lavage fluid (BALF) (Eickmeier et al. 2013). Of interest, Fat-1 transgenic mice that have increased endogenous lung n-3 PUFA (Hudert et al. 2006) also show higher PD1 and RvE1 levels after bronchoprovocative challenge (Bilal et al. 2011). These transgenic mice, which do not require dietary EPA and DHA to maintain high tissue levels, suggest a protective role for endogenous SPMs in allergic airway responses.

Human eosinophils biosynthesize PD1 as one of their main proresolving mediators, and PD1 production by eosinophils is impaired in patients with severe asthma. PD1, in nanomolar concentrations, reduces eosinophil chemotaxis and adhesion molecules (Miyata et al. 2013). In cigarette smoke-induced lung inflammation in the airways of mice, RvD1 protects and reduces PMN infiltration. RvD1 also promotes differentiation of M2 macrophages and efferocytosis in vivo, one of the cardinal signs of resolution. RvD1 also accelerated resolution of lung inflammation, demonstrating potential of SPMs to resolve lung injuries caused by toxicants such as cigarette smoke (Hsiao et al. 2013).

Resolvin D1 and Resolvin E1 potentially regulate inflammatory pain (Xu et al. 2010), and intrathecal injections of RvD1 in rats reduces postoperative surgical pain (Huang et al. 2011). Along these lines, RvD1 (100 ng/kg) decreases TNBS-induced mechanical allodynia and blocked cytokine production in spinal dorsal horn (Quan-Xin et al. 2012), and RvD2 (0.01–1 ng) prevents formalin-induced pain. As part of the molecular mechanisms, RvD2, RvE1, and RvD1 differentially regulated transient receptor potential (TRP) channels (Park et al. 2011). AT-RvD1 significantly reverses the thermal hypersensitivity, and knockdown of epidermal TRPV3 blunts these antinociceptive actions (Bang et al. 2012). In arthritis, AT-RvD1 shows marked antihyperalgesia, decreases production of TNF- α and IL-1 β in rat hind paw (Lima-Garcia et al. 2011), and RvD1 reduc-

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es neuroinflammation, stimulating phagocytosis of amyloid- β ($A\beta$) by Alzheimer's disease macrophages and inhibits fibrillar $A\beta$ -induced apoptosis. These actions are dependent on GPR32 (Mizwicki et al. 2013).

In the original structure elucidation of resolvin E1, PMN infiltration to mouse skin (dorsal air pouch) was used as one of the bioassay outcomes (Serhan et al. 2000). In burn models, RvD2 at 25 pg/g/animal given systemically post burn prevents thrombosis of the deep dermal vasculature, dermal necrosis, and PMN-mediated damage (Bohr et al. 2013). RvD2 restored PMN directionality in this system and increased survival after a second septic challenge (Kurihara et al. 2013). In DNFB-stimulated atopic dermatitis, RvE1 reduces skin lesions, lowers both IL-4 and IFN- γ , stimulates recruitment of CD4⁺ T cells, and decreases serum IgE levels (Kim et al. 2012).

In murine models of colitis, systemic RvE1, AT-RvD1, RvD2, or 17R-HDHA (17R-hydroxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid) in nanogram ranges improve disease severity, prevent body weight loss, colonic damage, and PMN infiltration as well as lower select colonic cytokines. The results suggest that some of the SPMs have potential in treating inflammatory bowel diseases (Arita et al. 2005b; Bento et al. 2011).

In adipose macrophages, RvD1 stimulates nonphagocytic phagocytosis and reduces macrophage reactive oxygen species production (Titos et al. 2011). In leptin receptor-deficient (db/db) mice, RvD1 (2 μ g/kg) improves glucose tolerance, decreases fasting blood glucose, and increases adiponectin production and markers of alternatively activated M2 macrophages (Hellmann et al. 2011). Here, LXA₄ (1 nM) attenuates adipose inflammation and improves insulin sensitivity in a model of age-associated adipose inflammation (Borgeson et al. 2012). In diabetic wounds, local application of RvD1 accelerates wound closure and reduces accumulation of apoptotic cells in the wounds (Tang et al. 2013). It is noteworthy that in streptozotocin (STZ)-induced diabetes, fat-1 transgenic mice do not develop hyperglycemia and β -cell destruction compared with wild-type mice.

RvE1 levels are highly increased in these fat-1 mice, emphasizing endogenous roles for RvE1 in diabetes (Bellenger et al. 2011). Thus, select SPMs and their mimetics may be novel approaches to reduce adipose inflammation and insulin resistance, key in type 2 diabetes.

Fibrosis

In a unilateral ureteric obstruction (UUO)-driven murine fibrosis, RvE1 at only 300 ng/day/mouse reduces accumulation of myofibroblasts, deposition of collagen IV, and myofibroblast proliferation. RvE1 (\sim 1–30 nM) directly inhibits PDGF-BB-induced proliferation of fibroblasts, an action dependent on ChemR23 receptor expression (Qu et al. 2012).

CONCLUDING REMARKS

It is now clear from our efforts that pus, specifically contained resolving inflammatory exudates, produced from nutrient essential fatty acids, contains potent molecules that stimulate resolution and the return of tissues to homeostasis. The main families of molecules reviewed herein are the resolvins, protectins, and maresins, which together with the lipoxins and their ATepimeric versions (Serhan 2005) form a larger genus of molecules we denote as SPMs. Each SPM shows temporal and spatial formation dependent functions within contained inflammatory exudates. The key molecules from each of the families, structures, and actions have been confirmed via total organic synthesis, and their complete stereochemistries assigned. Availability of commercial resolvins and lipoxins has led to a recent surge in reports documenting their novel proresolving and anti-inflammatory actions in many disease models, some of which are reviewed here.

Although the resolvins and SPMs are locally produced and act as autacoids to terminate acute inflammatory responses, recent evidence indicates that these molecules can also reach circulating levels, for example, in human peripheral blood (Oh et al. 2011; Mas et al. 2012). These results demonstrating circulating levels of SPMs that are in the concentration

ranges found for their anti-inflammatory and proresolving actions suggest that the SPMs, in addition to their local production and action, can also influence other organs. In this context, they might be able to signal anti-inflammation in second organs in addition to their target tissue exudates of origin. Hence, it is particularly relevant that resolvins and protectins can reduce neutrophilic infiltration and protect organs in the response to acute second organ ischemia reperfusion injury (Kasuga et al. 2008) and serve as immunoresolvents (Dalli et al. 2013a). Also, high levels of lipoxins and resolvins were recently identified in human breast milk (Weiss et al. 2013) as well as in animal placenta (Jones et al. 2013). These findings raise important new far-reaching implications for whether SPMs can play roles in cell traffic associated with organ development as well as regulate acute inflammatory responses around surgical events and tissue regeneration (Pillai et al. 2012; Dalli et al. 2013b). The presence of these proresolving lipid mediators can impact, for example, child development, and could impact diseases such as allergic asthma encountered later in life (Peebles 2013), as they are encountered during development and serve as determinants in later disease pathologies.

With the availability of commercial resolvins, we have also learned that they are effective in reducing inflammation in a wide range of inflammation-associated diseases (Tables 2 and 3), which taken together support the concept that the return of acute inflammatory responses to tissue homeostasis involves the active biosynthesis of proresolving mediators that function as local autacoids. Because the cell types that are responsible for the biosynthesis of SPMs travel within blood within vasculature that interact with the vascular endothelium and mucosal surfaces, their production is ubiquitous throughout the body as is the flow and traffic of leukocytes. Hence, in addition to their temporal and targeted actions within contained inflammatory exudates and their resolution, additional new biological functions of these mediators are likely to unfold in the years ahead, because they are also produced in vital nutrients in mammals such as in human milk, and, thus, SPMs may

also impact both physiologic as well as resolving pathophysiological processes in humans.

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CONFLICT OF INTEREST DISCLOSURE

Disclosure: C.N.S. and B.D.L. are inventors on patents [resolvins] assigned to BWH and licensed to Resolvix Pharmaceuticals. C.N.S. was scientific founder of Resolvix Pharmaceuticals and owns equity in the company. The interests of C.N.S. and B.D.L. were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies.

J.D. and N.C. have no financial conflicts of interest to disclose.

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