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Resolution of vascular injury: Specialized lipid mediators and their evolving therapeutic implications

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ABSTRACT

Acute vascular injury occurs in a number of important clinical contexts, including spontaneous disease-related events (e.g. plaque rupture, thrombosis) and therapeutic interventions such as angioplasty, stenting, or bypass surgery. Endothelial cell (EC) disruption exposes the underlying matrix, leading to a rapid deposition of platelets, coagulation proteins, and leukocytes. A thrombo-inflammatory response ensues characterized by leukocyte recruitment, vascular smooth muscle cell (VSMC) activation, and the elaboration of cytokines, reactive oxygen species and growth factors within the vessel wall. A resolution phase of vascular injury may be described in which leukocyte efflux, clearance of debris, and re-endothelialization occurs. VSMC migration and proliferation leads to the development of a thickened neointima that may lead to lumen compromise. Subsequent remodeling involves matrix protein deposition, and return of EC and VSMC to quiescence. Recent studies suggest that specialized pro-resolving lipid mediators (SPM) modulate key aspects of this response, and may constitute an endogenous homeostatic pathway in the vasculature. SPM exert direct effects on vascular cells that counteract inflammatory signals, reduce leukocyte adhesion, and inhibit VSMC migration and proliferation. These effects appear to be largely G-protein coupled receptor-dependent. Across a range of animal models of vascular injury, including balloon angioplasty, bypass grafting, and experimental aneurysm formation, SPM accelerate repair and reduce lesion formation. With bioactivity in the pM-nM range, a lack of discernible cytotoxicity, and a spectrum of vasculo-protective properties, SPM represent a novel class of vascular therapeutics. This review summarizes current research in this field, including a consideration of critical next steps and challenges in translation.

Vascular injury: clinical relevance and unmet need

Atherosclerosis is a chronic inflammatory disease with potentially devastating consequences in the coronary, cerebrovascular and peripheral vascular systems (e.g. myocardial infarction, stroke, critical limb ischemia). Diet, exercise, lipid lowering and other vasculo-protective medications can help slow progression of disease, however interventions are frequently required for treatment of advanced symptoms. These interventions, both endovascular (angioplasty, stenting) and surgical (endarterectomy, bypass), repair or replace damaged blood vessels and improve end organ perfusion. All of these commonly performed procedures are associated with injury and acute inflammation in the vessel wall. It is now well established that this post-intervention inflammatory response induces a series of events that are central to vascular repair and remodeling. When excessive this response leads to aggressive neointimal hyperplasia (NIH), lumen narrowing (re-stenosis), and recurrent ischemia (Tanaka et al., 1993; Kornowski et al., 1998; Shah, 2003; Muto et al., 2010). Additional interventions to treat re-stenosis in the coronary and peripheral circulation are common, costly, and incur significant risk to affected patients. Accordingly efforts to ameliorate this response remain of major importance in the field of cardiovascular medicine and surgery.

Currently, therapeutic approaches to prevent re-stenosis are

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focused on anti-proliferative and anti-inflammatory agents, and are limited in efficacy. Importantly, these approaches universally delay rather than accelerate healing of the vessel wall. The "off target" effects of these agents include toxicity to the endothelium with associated risk for thrombosis, and immune cell suppression with associated risk for impaired healing or infection (Joner et al., 2006; Garg and Mauri, 2007; Ostrovsky, 2008). Presently these approaches are applied in the form of drug-eluting stents (DES) and drug-coated balloons (DCB) that have made positive impact in the field of coronary intervention and, to a much less degree, in the peripheral circulation. Peripheral artery interventions provide a stringent test of vascular patency with a large burden of disease that frequently extends into small caliber distal vessels, especially in the growing diabetes population presenting with advanced stages of disease. Despite ongoing technical improvements in endovascular technologies, surgical bypass grafting remains an important and commonly employed intervention for those with advanced atherosclerosis. Bypass grafting and other vascular procedures, such as creation of hemodialysis grafts and fistulas, incur a similar process of vessel injury, repair and remodeling that can ultimately lead to re-narrowing and failure over time. Clinical trials testing anti-proliferative approaches to reduce NIH in these surgical scenarios have been uniformly disappointing (Alexander et al., 2005; Conte et al., 2006; Ostrovsky, 2008). Thus, there are no currently available therapies to reduce the incidence of re-stenosis following these common cardiovascular procedures. Risks of adverse effects in surgical patients, including wound complications or early thrombosis, highlight the importance of a safe, homeostatic approach that minimizes cytotoxicity while reducing vessel scarring.

The elucidation of biochemical pathways of resolution (Serhan, 2007; Spite and Serhan, 2010; Ortega-Gomez et al., 2013; Serhan, 2014) summarized in this compendium, suggest the hypothesis that excessive vessel scarring following intervention may represent an impairment of resolution. It follows that the local availability or activity of specialized pro-resolving mediators (SPM) may be an important modifier of vascular repair, representing a new potential therapeutic opportunity. This review provides a context for resolution pharmaco-biology in the setting of vascular injury, summarizes the mechanisms through which SPMs facilitate homeostasis within the vasculature, and evidence from animal studies supporting beneficial effects of SPM across a range of vascular injury models. Finally, we will comment on current gaps in knowledge and critical steps towards translation of "resolution pharmacology" in the arena of vascular intervention.

Vascular injury: from inflammation through resolution to repair

The clinical context of vascular injury takes many forms—e.g acute mechanical trauma from balloon angioplasty or surgery, ischemia-reperfusion of a harvested vein for bypass grafting, implantation of a metallic stent or prosthetic device, hemodynamic stress associated with venous arterialization. Endothelial (EC) injury, with variable damage to underlying vascular smooth muscle cells (VSMC), leads to a rapid and pronounced interaction with circulating blood elements and a thrombo-inflammatory response (Fig. 1). This bears resemblance to other scenarios of sterile inflammation, but is compounded by amplification from platelets and elements of the coagulation cascade (e.g. tissue factor, fibrinogen) that are immediately activated once the thrombo-resistance of intact endothelium is lost. Apoptosis of EC and VSMC is an early event. Recruitment of leukocytes, particularly neutrophils (PMNs) and monocytes, to areas of denuded endothelium brings an influx of pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α), chemokines (e.g. MCP-1), and reactive oxygen species into the vessel wall. Together with platelet-derived products (e.g. PDGF) and other growth factors (e.g. bFGF) locally available within the vascular matrix, these mediators rapidly activate VSMCs from a basal contractile state to a synthetic, de-differentiated, neointimal phenotype. Expression of leukocyte adhesion molecules by activated VSMC and EC augments the inflammatory response. The phenotypic switch of VSMC to a synthetic state is a critical event in the vessel repair process that leads to NIH. Activated VSMC demonstrate enhanced migration, proliferation, resistance to apoptosis, expression of pro-inflammatory signals, and elaboration of matrix proteins. Spatial and temporal regulation of this phenotypic switch, and the subsequent conversion of VSMC back to a quiescent contractile state, correlates with the magnitude and distribution of the NIH lesion that results (Tanaka et al., 1993; Kornowski et al., 1998; Shah, 2003; Muto et al., 2010). The exact process by which return to quiescence occurs remains incompletely understood. A resolution phase in the vascular injury setting is characterized by: cessation of PMN recruitment, decline in vessel wall macrophage numbers and conversion from M1 to M2 phenotype, reduction in pro-inflammatory cytokine and growth factor expression, decline in the VSMC proliferative index, regeneration of an intact endothelium, and the initiation of matrix remodeling. Accelerating the transition to the resolution phase following acute vascular injury offers the potential to hasten vessel repair and thereby reduce downstream NIH.

Clinical evidence linking the magnitude of the acute inflammatory response to the outcomes of vascular interventions comes from studies utilizing systemic biomarkers such as high sensitivity C-reactive protein (hsCRP), fibrinogen, serum amyloid A, interleukin (IL)-1, IL-6, and TNF-α (Buffon et al., 1999; Schillinger et al., 2002). Patients with advanced atherosclerosis represent a substrate of chronic low-grade inflammation as a baseline state (Ridker, 2003; Owens et al., 2007). Initial clinical evidence for a relative "resolution deficit" in atherosclerosis was provided by Ho and colleagues, who demonstrated that circulating levels of the SPM aspirin-triggered lipoxin A_4 (ATL; 15-*epi*-LXA_4) were significantly lower in symptomatic peripheral arterial disease patients than in healthy controls, and correlated inversely with clinical severity (Ho et al., 2010). Similar findings have been reported in patients with coronary artery disease as well as cerebrovascular disease (Elajami et al., 2016; Thul et al., 2017). In these settings of advanced atherosclerosis, acute superimposed vascular injury (e.g. angioplasty or surgery) triggers a robust systemic inflammatory response reflected in circulating biomarkers. In a prospective cohort study of patients undergoing lower extremity vein bypass grafting for advanced leg ischemia, pre-operative levels of hsCRP and other inflammatory markers were strongly associated with postoperative events, largely downstream re-interventions for bypass graft stenosis (Owens et al., 2007). Elevated plasma inflammatory markers were also associated with impaired early vein graft remodeling post-implantation, suggesting that hemodynamic adaptation of the vein graft to the arterial environment is influenced by the acute inflammatory response (Owens et al., 2012; Gasper et al., 2013). Biomarkers of resolution are currently in evolution, limited to date by the requirement of liquid chromatography-tandem mass spectrometry (LC-MS/MS) with validated standards to reliably identify and quantitate the bioactive lipid mediators (e.g. SPM) in blood and other tissues. Ongoing and future studies seek to identify a "resolution index" biomarker(s) that may potentially correlate with clinical disease progression or with responses to illness, injury, or intervention. Conceptually, the peri-procedural setting offers an opportunity for trials of resolution pharmacology to hasten recovery in the cardiovascular patient (Fig. 2).

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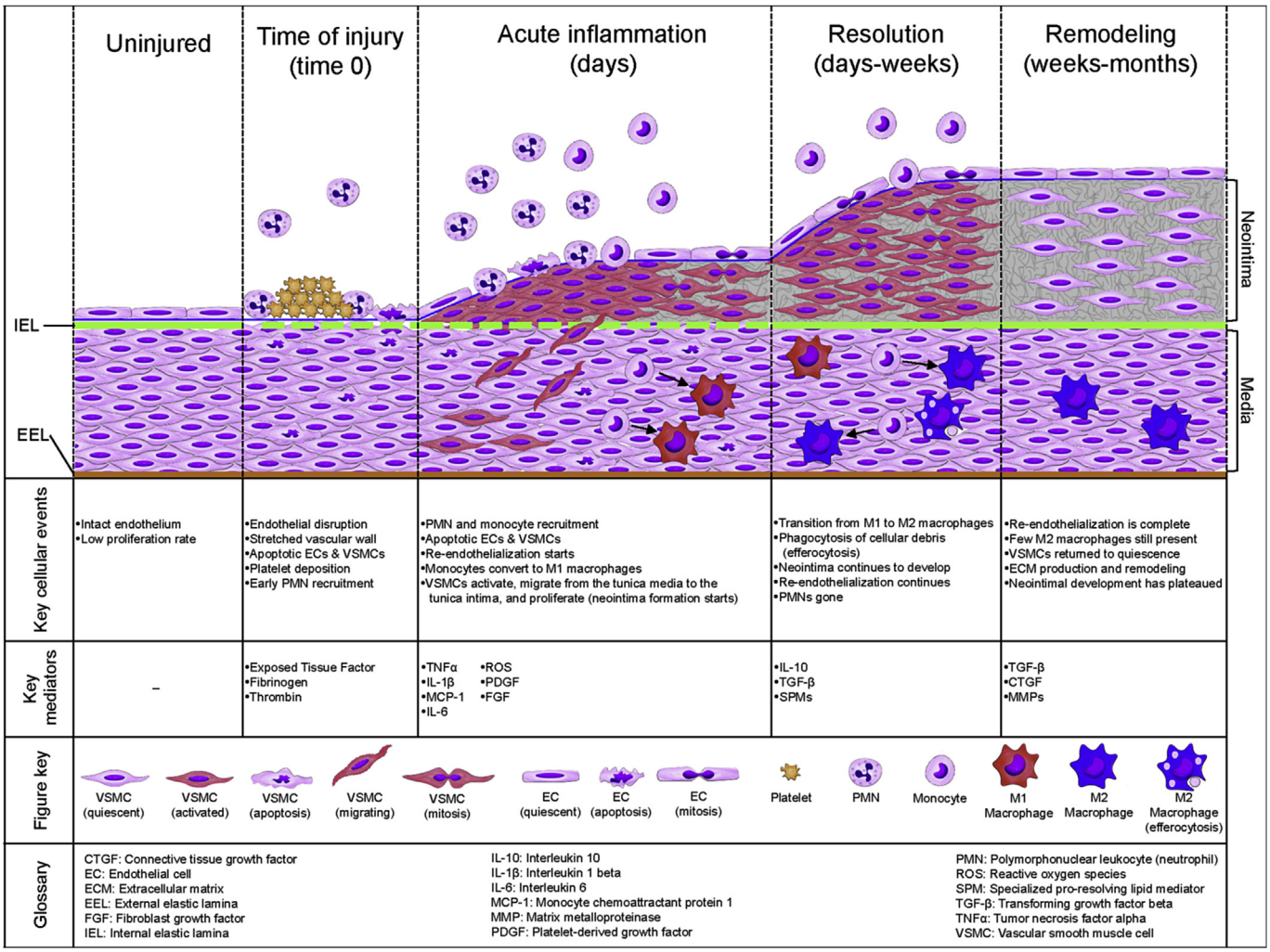

Fig. 1. Schematic illustrating the temporal sequence of cellular and molecular events in the vessel wall following acute injury, characterizing the phases of injury, inflammation, resolution, and remodeling.

Biosynthesis of SPM in the vasculature and evidence for receptor expression and activity

SPM are synthesized from their polyunsaturated fatty acid (PUFA) precursors via sequential actions of lipoxygenases (LOX) and hydrolases. Lipoxins, the first identified SPM, are downstream products of arachidonic acid (AA); the E-series resolvins (RvE) are derived from eicosapentaenoic acid (EPA), whereas the D-series resolvins (RvD), protectins and maresins are derived from docosahexaenoic acid (DHA). Similar to other autocoids, SPM are rapidly inactivated locally by enzymes, such as 15- prostaglandin dehydrogenase (PGDH). SPM biosynthesis has been demonstrated in isolated leukocytes (esp. PMNs and macrophages) as well as via leukocyte-epithelial and leukocyte-endothelial interactions. Sources of SPM within the vasculature remain incompletely defined but their presence has been detected in a number of studies. The presence of endogenous LXA_4 after vascular intervention was initially described by Brazinski and colleagues, who identified intraluminal LXA_4 after percutaneous transcoronary angioplasty in humans (25 ng/mL) (Brezinski et al., 1992). Using LC-MS/MS analysis of whole vessel lysates, we identified various SPMs including RvD1, RvD5, Maresin-1 and LXB_4 in rabbit femoral arteries both at baseline and after balloon angioplasty, with a trend towards increased SPM production after injury (Miyahara et al., 2013). SPM have been identified in mouse atherosclerotic lesions (Fredman et al., 2016; Viola et al., 2016) where they correlate with histologic signs of plaque stability. More recently it was demonstrated that isolated human artery segments and primary cultured human vascular cells generate D-series resolvins in the presence of precursors (DHA,17-HDHA) (Chatterjee et al., 2017). Conditioned media from these DHA-supplemented vascular cells blunted leukocyte adhesion to activated EC, in a reaction that was attenuated by blocking the RvD1 receptors ALX and GPR32. These studies suggest that endogenous production of SPM within the vessel wall may represent a newly identified paracrine pathway to counter-regulate vascular inflammation and maintain homeostasis.

SPM exert their biologic actions on cells via G-protein coupled receptors (GPCR) such as ALX/FPR2, GPR32, ChemR23, BLT1, and GPR18 (Serhan, 2014; Chiang et al., 2017). Expression of ALX, GPR32, and ChemR23 has been demonstrated in vascular cells and tissues (Ho et al., 2010; Norling et al., 2012; Miyahara et al., 2013; Petri et al., 2015a, b). Studies employing a mouse knockout of the ALX/FPR2 homologue demonstrated its functional role in mediating LxA4-induced effects on VSMC migration, proliferation, and on NIH following carotid ligation in-vivo (Petri et al., 2015a, b). However further studies are needed to fully characterize the regulation of SPM receptor expression and activity in vascular cells, and the relationships between SPM synthesis, degradation and

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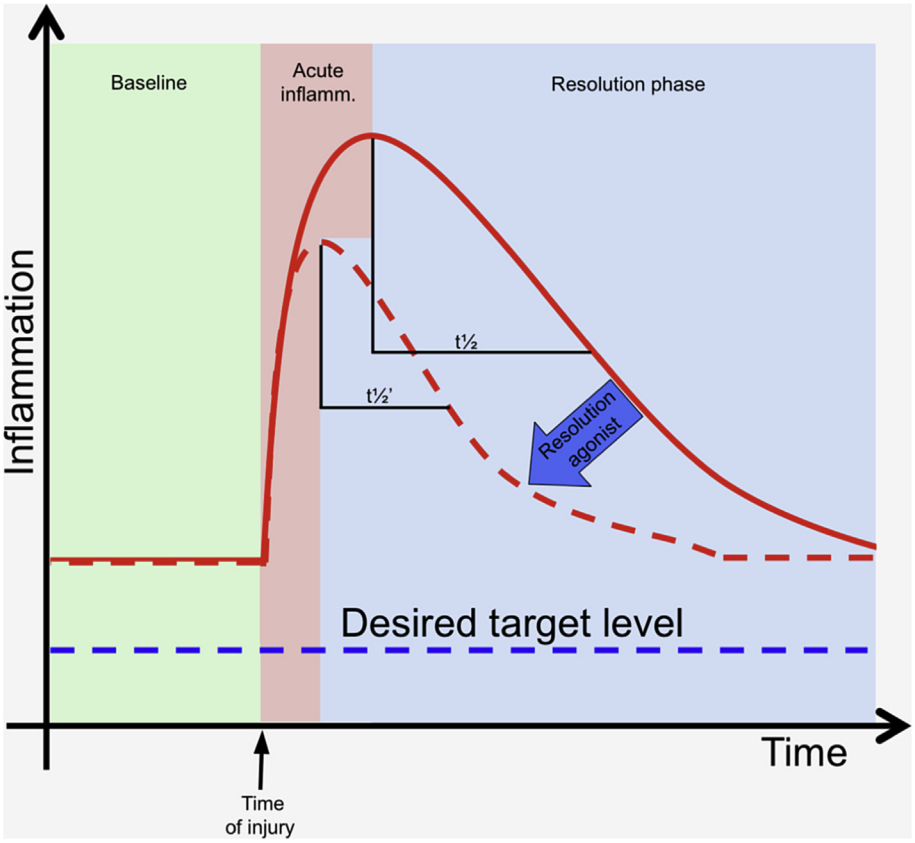

Fig. 2. Systemic inflammation in clinical cardiovascular disease and intervention, and the opportunity for resolution pharmacology in the peri-procedural setting. Patients with clinical atherosclerosis manifest chronic low grade inflammation that can me measured by biomarkers such as C-reactive protein (CRP) and others. Acute vascular injury (e.g. angioplasty) is superimposed and generates a prototypic injury response. A resolution index can be measured from the temporal decline in the acute inflammatory response, from peak to 50% of peak values. The dashed curve represents a hypothetical response to a pro-resolving therapeutic.

downstream signaling events in vascular tissues, in both health and disease.

Direct effects of SPM on vascular cells

Elucidation of the cellular actions of SPM has largely focused on leukocytes, particularly PMN and macrophages (Serhan, 2007, 2014). Effects on platelet aggregation, platelet-PMN interactions, and clot remodeling in-vivo have also demonstrated beneficial antithrombotic properties that are of clear relevance to vascular disease (Dona et al., 2008; Chen et al., 2009; Fredman and Serhan, 2011; Gong et al., 2015; Elajami et al., 2016; Lannan et al., 2017). Evidence for direct effects of SPM on EC and VSMC demonstrates an anti-inflammatory, homeostatic profile of actions that may constitute an important vasculo-protective biochemical pathway (Table 1). SPM are bioactive in the pM-nM range, consistent with levels that have been measured in circulating blood (Colas et al., 2014) as well as in a growing range of human biological samples (Brezinski et al., 1992; Ho et al., 2010; Colas et al., 2014; Elajami et al., 2016; Thul et al., 2017). Important for their consideration as candidate vascular therapeutics, we have observed no evidence of toxicity in EC or VSMC even when cells are exposed to micromolar ranges of resolvins and other SPM (Conte MS, unpublished data).

Endothelial cells (ECs) are located on the luminal surface and function to maintain the integrity of the vessel wall. Leukocyte-endothelial cell interactions are central in modulating vascular inflammation. Various reports have demonstrated that SPMs decrease leukocyte-endothelial cell interactions, potentially through up-regulation of endothelial cell nitric oxide (eNOS) and downregulation of adhesion molecules on both leukocytes and endothelial cells. For example, RvD1 and Mar1 were demonstrated to preserve endothelial cell function in various contexts through suppression of reactive oxygen species and regulation of adhesion molecules (Paul-Clark et al., 2004; Tian et al., 2009; Chattopadhyay et al., 2017). Merched and colleagues studied the actions of various SPMs (RvD1, PD1, LXA_4) *in vitro* on endothelial cells harvested from human aortas and observed down-regulation of adhesion molecules (VCAM-1 and P-selectin) and pro-inflammatory cytokines (MCP-1 and IL-8) (Merched et al., 2008). Similar results has been observed in examining the effects of RvD1 and MaR1 *in vitro* on endothelial cells harvested from human greater saphenous veins. In these studies MaR1 attenuated TNF-α induced monocyte adhesion to ECs with associated down-regulation of E-selectin and attenuation of TNF-α induced production of pro-inflammatory cytokines (PDGF-BB, MCP-1, IL-8, IL-16, ICAM, Eotaxin-2, GM-CSF, TIMP2, MIP1-β, RANTES, IP10) (Chatterjee et al., 2014). Endothelial regeneration is an important attribute in the setting of vascular injury, as EC migration and proliferation is required to re-establish a confluent monolayer. One study demonstrated enhancement of endothelial migration by RvD2 (Zhang et al., 2016). Studies from our laboratory have consistently demonstrated that SPM such as RvD1, RvD1, and MaR1 are non-toxic to endothelium and have no significant impact on human EC migration (Conte MS, unpublished data).

Mechanisms of SPM signaling in EC are under continued investigation, focused on modulation of prototypic inflammatory

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Table 1
Summary of effects of SPM on vascular cells.

Cell type	SPM[a]	Effects observed	Refs.[b]
EC	RvD1, MaR1, PD1, LXA_4, ATL	- Decrease leukocyte-endothelial cell interactions - Up-regulate nitric oxide synthesis (eNOS, iNOS) - Down-regulate adhesion molecules (ICAM, VCAM, E-Selectin, P-Selectin) - Down-regulate inflammatory cytokines (MCP-1, IL-8, PDGF-BB, RANTES) - Inhibit activation of NF-kB pathway - Inhibit formation of reactive oxygen species - Enhance endothelial cell migration	Nascimento-Silva et al. (2007), Paul-Clark et al. (2004), Merched et al. (2008), Tian et al. (2009), Zhang et al. (2013), Chatterjee et al. (2014), Zhang et al. (2016), Chattopadhyay et al. (2017), Sok et al. (2017)
VSMC	RvD1, RvD2, RvE1, MaR1, ALT	- Attenuate migration; cytoskeletal rearrangement - Decrease proliferation - Down-regulate adhesion molecules (ICAM-1, VCAM-1) - Down-regulate inflammatory cytokines (MCP-1, IL-1α, IL-1β, IL-6, IL-8, GM-CSF, TNF-α) - Inhibit activation of NF-kB pathway - Signaling through cAMP/PKA pathway	Ho et al. (2010), Miyahara et al. (2013), Chatterjee et al. (2014), Akagi et al. (2015), Hiram et al. (2015), Petri et al., (2015a, b), Mottola et al. (2017), Wu et al., (2017a, b),
Fibroblasts	RvE1, LXA_4, benzo-LXA_4, ATL	- Attenuate myofibroblast activation and proliferation	Martins et al. (2009), Borgeson et al. (2011), Qu et al. (2012), Roach et al. (2015)
Leukocytes	RvD1, RvD2, Mar1	- Decrease leukocyte infiltration in acute arterial injury, ischemia-reperfusion - Promote M1 to M2 macrophage polarization in vascular tissue - Enhanced clot phagocytosis	Duffield et al. (2006), Keyes et al. (2010), Serhan (2014), Miyahara et al. (2013), Akagi et al. (2015), Pope et al. (2016), Wu et al., (2017a, b)
Platelets	RvD1, RvE1, PD1	- Inhibit platelet aggregation	Dona et al. (2008), Chen et al. (2009), Fredman and Serhan (2011), Lannan et al. (2017)

EC = endothelial cell.
VSMC = vascular smooth muscle cell.
[a] List of SPMs provided, however not every mechanism has been studied for each mediator.
[b] Lists arenot comprehensive.

pathways. MaR1 attenuated TNF-α induced activation of the NF-kB pathway (IKK phosphorylation and nuclear translocation of the p65 subunit), as well as reactive oxygen species (ROS) production, with associated down-regulation of NADPH-oxidases (NOX1, NOX2, NOX4) (Chatterjee et al., 2014). These effects appear related to a time-dependent increase in intracellular cyclic AMP (cAMP), suggesting a role for the cAMP/PKA pathway. Other investigators have demonstrated similar effects of SPM on intracellular signaling in ECs (Nascimento-Silva et al., 2007; Zhang et al., 2013).

It is well established that VSMC activation, migration and proliferation are central to the pathobiology of NIH (Tanaka et al., 1993; Kornowski et al., 1998; Shah, 2003; Muto et al., 2010). Attenuation of VSMC migration by SPMs (ATL, RvD1, RvD2, RvE1, MaR1) has been a consistent finding *in vitro*, both with VSMC harvested from human saphenous veins (Ho et al., 2010; Miyahara et al., 2013) and with arterial VSMC harvested from rodent aortas (Akagi et al., 2015; Petri et al., 2015a, b; Wu et al., 2017a, b) as well as human pulmonary arteries (Hiram et al., 2015). This effect has been demonstrated across several prototypic VSMC motogens including PDGF, thrombin, angiotensin II, TNF-α and IL-6 (Hiram et al., 2015; Mottola et al., 2017; Wu et al., 2017a, b). Associated with this effect, resolvins induce rapid and reversible changes in VSMC cell-shape with a decreased length:width ratio corresponding to an anti-migratory phenotype (Ho et al., 2010; Miyahara et al., 2013; Mottola et al., 2017; Wu et al., 2017a, b). The anti-migratory effects of AT-RvD1 in human saphenous vein VSMC appear dependent on the cAMP/PKA pathway, with downstream involvement of Rac1, VASP, and paxillin ((Mottola et al., 2017)).

Several SPMs (RvD1, RvD2, MaR1) have demonstrated modest anti-proliferative effects on VSMC *in vitro* (Miyahara et al., 2013; Akagi et al., 2015; Petri et al., 2015a, b; Wu et al., 2017a, b). Unlike migration, proliferation can be easily observed *in vivo* and intravascular, perivascular and systemic delivery of SPMs (RvD2, RvD1 and RvD1/MaR1, respectively) attenuated VSMC proliferation in various models of vascular injury (Miyahara et al., 2013; Akagi et al., 2015; Wu et al., 2017a, b). Importantly, there has been no evidence of VSMC cytotoxicity related to SPMs within their therapeutic range either *in vitro* (Ho et al., 2010; Miyahara et al., 2013; Chatterjee et al., 2014; Wu et al., 2017a, b) or *in vivo* (Wu et al., 2017a, b).

For vascular interventions that denude the endothelium (i.e. angioplasty and stenting), leukocyte-VSMC interactions are particularly important for early leukocyte recruitment. SPMs (RvD, RvD2, MaR1) decrease monocyte-VSMC adhesion with associated down-regulation of adhesion molecule expression (ICAM-1, VCAM-1) (Miyahara et al., 2013; Chatterjee et al., 2014). SPMs (RvD1, RvD2, MaR1) modulate inflammatory cytokine expression from TNF-α stimulated VSMC *in vitro* (decreased secretion of MCP-1, IL-1α, IL-1β, IL-6, IL-8 and GM-CSF) (Ho et al., 2010; Miyahara et al., 2013; Chatterjee et al., 2014; Akagi et al., 2015). *In vivo*, RvD2 (10 nM, intra-arterial for 20 min after injury) treatment decreased the expression of inflammatory cytokines (TNF-α, MCP-1, and IL-1α) in rabbit femoral arteries after angioplasty, which injures the vessel wall via stretch as well as endothelial denudation (Miyahara et al., 2013).

Many SPM-mediated intracellular signaling mechanisms demonstrated in leukocytes and endothelial cells appear relevant within VSMCs. Attenuation of the NF-kB signaling pathway has been observed *in vitro* after stimulation with TNF-α (RvD1, RvD2, MaR1) (Miyahara et al., 2013; Chatterjee et al., 2014; Akagi et al., 2015; Wu et al., 2017a, b) and *in vivo* in rat carotid arteries after angioplasty (RvD1, 200 ng perivascular) (Wu et al., 2017a, b). Attenuation of VSMC-derived ROS by SPMs has been observed *in vitro* after stimulation with TNF-α (RvD1, RvD2, MaR1) (Miyahara

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Table 2
Summary of effects of SPM in animal models of vascular injury.

Study	Animal Model	SPM and Delivery	Findings[a]
Akagi et al. (2015)	Carotid ligation (mouse)	Systemic RvD2 or MaR1 (100 ng IP day 0, 1, 3, 5, 7)	62-67% decrease in neointimal formation vs controls (14 days post-injury)
Petri et al., (2015a, b)	Carotid ligation (mouse)	Systemic ATL (250 ng, cont SQ pump)	50% decrease in neointimal formation by ATL in wild type mice, with no effect in ALX knockout mice (4 weeks post-injury)
Wu et al., (2017a, b)	Carotid angioplasty (rat)	Perivascular RvD1 (200 ng, via wrap or gel)	45-59% decrease in neointimal formation vs controls (14 days post-injury)
Miyahara et al. (2013)	Femoral angioplasty (rabbit)	Intraluminal RvD2 (10 nM × 20 min after angio)	29% decrease in neointimal formation vs control (28 days post-injury)
Wu et al., (2017a, b)	Vein bypass (rabbit)	Perivascular RvD1 (1 mg, via wrap or gel)	38-63% decrease in neointimal formation vs controls (28 days post-injury)
Duffield et al. (2006)	Renal I/R (mouse)	Systemic RvD (1-3) or PD1 (3.5–35 μg prior to ischemia)	Decrease leukocyte infiltration, preserve renal function and inhibit renal fibrosis
Brancaleone et al. (2013)	Mesenteric I/R (mouse)	Systemic LXA_4 (1–100 ng prior to reperfuse)	Decrease platelet-neutrophil aggregates
Smith et al. (2015)	Cerebral I/R (mouse)	Systemic ATL (0.5–4 μg prior to reperfuse)	Decrease leukocyte-endothelial cell interactions and decrease mortality
Keyes et al. (2010)	Cardiac I/R (rat)	Systemic RvE1 (9–90 μg prior to reperfuse)	Decrease leukocyte infiltration, decrease cardiomyocyte death and limit infarction size
Gilbert et al. (2014)	Coronary ligation (rat)	Systemic RvD1 (1 μg, at time of ischemia)	Decrease infarct size and improve functional recovery
Kain et al. (2015)	Coronary ligation (mouse)	Systemic RvD1 (3 μg/kg/day SQ)	Decrease left ventricular scarring and improves left ventricular function
Zhang et al. (2016)	Hindlimb ischemia (mouse)	Systemic RvD2	Increased skeletal muscle regeneration
Pope et al. (2016)	AAA formation (murine)	Systemic RvD1 or RvD2 (100 ng/kg IP every 3 days)	25-41% decrease in aortic diameter vs controls

AAA = abdominal aortic aneurysm.
I/R = ischemia reperfusion.
*List of SPMs provided, however not every mechanism has been studied for each mediator.
[a] (Primary outcomes listed only).

et al., 2013; Chatterjee et al., 2014; Akagi et al., 2015) and *in vivo* in rabbit femoral arteries and rat carotid arteries after angioplasty (Miyahara et al., 2013; Wu et al., 2017a, b). SPM (RvD1, MaR1) signaling in VSMC appears to involve the cAMP/PKA pathway (Chatterjee et al., 2014; Mottola et al., 2017; Wu et al., 2017a, b).

To date, there is limited data relating to the effect of SPMs on vascular fibroblasts. Extrapolating from studies on vascular fibroblasts using precursors fatty acids, we find suggestions that SPMs may inhibit macrophage-mediated pro-inflammatory activation within vascular fibroblasts (Endo et al., 2014) and that SPMs may attenuate proliferation as well as conversion to pro-fibrotic myofibroblasts (Faggin et al., 2000). The myofibroblast is particularly important in the context of vein bypass grafting, as these cells not only can migrate to contribute to neointimal formation but can cause negative (inward) remodeling of the vessel wall (Garbey and Berceli, 2013; Owens et al., 2015). Direct evidence for anti-fibrotic effects of SPMs (RvE1, LXA_4 and its synthetic analog benzo-LXA_4) has been provided in a rodent model of renal fibrosis (unilateral ureteric obstruction), where these SPM attenuated myofibroblast activation and proliferation (Borgeson et al., 2011; Qu et al., 2012). Similarly, treatment with SPMs (ALX_4, ATL) in models of pulmonary fibrosis attenuates myofibroblast activation and proliferation both *in vitro* and *in vivo* (Martins et al., 2009; Roach et al., 2015). These studies of renal and pulmonary myofibroblasts can be extrapolated to vascular fibroblasts in general and suggest that SPMs may provide homeostatic actions on all three layers of the vessel wall.

In-vivo effects of SPM in animal models of vascular injury

Neointimal hyperplasia (NIH)

There are various “proof-of-concept” animal models through which restenosis can be studied, with a common theme of inducing inflammation within the vessel wall (Table 2). Ligation of the distal common carotid artery in mice produces profound alterations in flow dynamics proximally, leading to an extensive neointimal hyperplasia in the presence of an intact endothelium (Kumar and Lindner, 1997; Holt and Tulis, 2013). Petri and colleagues used this model to study the effects of aspirin-triggered lipoxin (ATL), with a focus on its signaling mechanism through the ALX receptor. Their investigations involved administration of ATL (250 ng) systemically through a continuous subcutaneous pump placed after carotid ligation and demonstrated a 50% decrease in neointimal formation by ATL in wild type mice, with no effect in ALX knockout mice (Petri et al., 2015a, b). This murine model has also been used to study the effect of RvD2 and MaR1 on neointimal hyperplasia (Akagi et al., 2015). Serial intra-peritoneal injections of either RvD2 or MaR1 (100 ng injection at 0, 1, 3, 5, and 7 days after ligation) were found to result in a 62% decrease in neointimal formation by RvD2 and a 67% decrease in neointimal formation by MaR1. Of note, treatment with either SPM decreased neutrophil and macrophage recruitment to the vessel wall, with increased polarization of M2 macrophages, and reduced VSMC proliferation in this model (Akagi et al., 2015).

Although low flow-induced remodeling models provide useful information in the context of restenosis, models involving balloon angioplasty provide more fidelity to clinical vascular interventions. Balloon angioplasty of the rat carotid artery is a well-established model of stretch and endothelial denudation-induced injury and utilizes a similar catheter to that used for coronary and peripheral vascular interventions. Angioplasty produces a prototypic response to injury, involving VSMC migration to the intima, proliferation within the intima and subsequent formation of neointimal hyperplasia (Clowes et al., 1983a, b). Perivascular application of RvD1 (200 ng, delivered via either a biodegradable film or via a pluronic gel) significantly inhibited neointimal hyperplasia in this model.

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RvD1-loaded "wraps" reduced neointimal formation by 59% versus no-wrap controls and 45% versus vehicle-wrap controls, while RvD1-loaded gels reduced neointimal formation by 49% versus no-gel controls and 52% vehicle-gel controls. Of note, neither perivascular treatment was associated with infection, thrombosis or negative vessel remodeling. Proliferation, NF-kB activation and oxidative stress in the wall were all significantly lower in arteries treated with RvD1 (Wu et al., 2017a, b).

Balloon angioplasty of rabbit femoral arteries creates stretch and endothelial denudation-induced injury with ensuing neointimal hyperplasia similar to clinical restenosis (Simosa et al., 2005). Intraluminal incubation with RvD2 (10 nM) decreased neointimal hyperplasia in this model by 29% at 28 days post-injury, with associated reductions in leukocyte recruitment (41%), proliferation (51%), ROS and expression of inflammatory genes (TNF-α, MCP-1, and IL-1α) at 3 days post-injury. Of note, endogenous production of various SPMs was detected in both uninjured and injured rabbit arteries, with a trend towards increased SPM production after injury (Miyahara et al., 2013).

Vein bypass grafting offers the most durable long-term outcomes for peripheral and coronary occlusive disease, however injury related to vein harvest and hemodynamic stresses during arterialization cause inflammatory changes and subsequent restenosis. Many of the mechanisms of failure after vein bypass appear to be similar to those after arterial injury, as previously described (Muto et al., 2010; Owens et al., 2015; de Vries et al., 2016). A rabbit vein graft model can be used to investigate the neointimal response after vein bypass (Jiang et al., 2004; Wang et al., 2005; Owens et al., 2015). We recently demonstrated that perivascular delivery of RvD1 (1 mg, via either a biodegradable film or gel) attenuated vein graft neointimal hyperplasia in this model. Specifically, RvD1-loaded gels reduced neointimal formation by ~60% while RvD1-loaded perivascular "wraps" reduced neointimal formation by 50% versus bypass-only controls. Perivascular RvD1 treatments did not influence rates of graft thrombosis, wound infection or death. Total leukocyte infiltration, macrophage infiltration as well as cellular proliferation were significantly lower in vein grafts treated with perivascular RvD1 (Wu et al., 2017a, b).

Ischemia and ischemia-reperfusion

Resolution biology is relevant for other acute vascular events, such as renal, mesenteric, cerebral and myocardial ischemia. Ischemia-reperfusion models involve end organ ischemia followed by a massive inflammatory insult during reperfusion, during which specific temporal spatial relationships are essential to prevent or minimize permanent damage. SPM administration in several of these models has suggested therapeutic potential. Duffield and colleagues demonstrated that systemic administration of either an RvD cocktail (3.5–35 μg total of a RvD1/RvD2/RvD3 cocktail prior to ischemia) or PD1 (3.5–35 μg prior to ischemia) decreased leukocyte infiltration, preserved renal function and inhibited renal fibrosis in a murine model of renal ischemia-reperfusion (Duffield et al., 2006). Brancaleone and colleagues demonstrated that intravenous administration of LXA_4 (1–100 ng prior to reperfusion) decreased platelet-neutrophil aggregates in a murine model of mesenteric ischemia-reperfusion (Brancaleone et al., 2013). Smith and colleagues reported that intravenous administration of ATL (0.5–4 μg prior to reperfusion) decreased leukocyte-endothelial cell interactions and provided a survival benefit in a murine model of cerebral ischemia-reperfusion (Smith et al., 2015). Keyes and colleagues employed intravenous administration of RvE1 (9–90 μg prior to reperfusion) in a rodent model of cardiac ischemia-reperfusion to decrease leukocyte infiltration as well as cardiomyocyte death and limit infarction size (Keyes et al., 2010).

Gilbert and colleagues demonstrated intraventricular injection of RvD1 (1 μg, at the time of coronary ligation) reduces infarct size and improves functional recovery in a rat model of myocardial infarction (Gilbert et al., 2014). Similarly, subcutaneous delivery of RvD1 (3 μg/kg/day) decreases left ventricular scarring and improves left ventricular function in a mouse model of myocardial infarction (Kain et al., 2015). Zhang and colleagues recently demonstrated improved skeletal muscle regeneration with administration of exogenous RvD2 in a mouse model of hindlimb ischemia (Zhang et al., 2016). All of these studies suggest deficient resolution may play a role in the downstream end organ pathogenesis after acute ischemia.

Aneurysm disease

Inflammation within arterial walls can lead to formation of life-threatening aneurysms, such as abdominal aortic aneurysms (AAA) (Shimizu et al., 2006). Various murine models of AAA formation have been developed to investigate therapeutics for treatment of AAA with most inhibitory strategies aimed at early inflammatory events. Treatment with n-3 PUFA has previously been implicated as a potential therapeutic strategy in this context (Wales et al., 2014). Pope and colleagues demonstrated that systemic administration of either RvD1 or RvD2 (100 ng/kg IP every 3 days) significantly decreased AAA formation in a surgical elastase-perfusion model, associated with preservation of elastin, reduced macrophage (but not T-cell) infiltration, a broad reduction in local inflammatory cytokine signals (TNF-α, IL-1α, IL-1β, MCP-1, CXCL-1, RANTES), increase anti-inflammatory cytokines (IL-10), and reduction in MMP activity by gelatin zymography (Pope et al., 2016). When specifically examined, RvD2 treatment resulted in a shift in aortic wall macrophage phenotype favoring M2 polarization. They also examined the effects of RvD2 in a non-surgical model of angiotensin II infusion in the $ApoE^{(-/-)}$ mouse, with similar overall findings. Importantly, these investigators also tested the effects of RvD2 in a treatment model three days after aneurysms had been initiated, observing a 25% reduction in subsequent aortic dilation. Clinical relevance of inflammation-resolution has been demonstrated after surgical repair of AAA, with a distinct subset of patients having measurable early increases in SPM pathways postoperatively (Pillai et al., 2012). These studies suggest that SPM may have important effects in both aneurysm pathogenesis and in postoperative repair.

Translation: resolution pharmacology in vascular injury

Although the optimal pharmacokinetics for therapeutic application of SPM after vascular injury remains unknown, local delivery at the time of injury might be ideal in surgical settings. Local approaches are also advantageous because enzymes that rapidly degrade SPM such as 15-PGDH are ubiquitous. Local vascular delivery can be achieved through direct injection into the vessel wall, drug coated balloons or drug eluting stents after endovascular interventions (angioplasty, stenting) or through perivascular approaches (gels, films) after open surgical procedures (endarterectomy, bypass). Recent studies have demonstrated efficacy in reducing NIH in animal models with both intraluminal and perivascular delivery of D-series resolvins (Miyahara et al., 2013; Wu et al., 2017a, b). For local vascular delivery, the small size and lipophilic nature of SPM as a class provide favorable tissue transfer properties similar to those of currently available therapies (Kotani et al., 2006; Tepe et al., 2008; Hawkins and Hennebry, 2011).

Perivascular delivery of SPM after open surgical procedures is facilitated as the target vessel is exposed. To maintain controlled and sustained delivery, biodegradable carrier gels or films can be

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utilized (Miyahara et al., 2013; Lance et al., 2017; Wu et al., 2017a, b). We recently described a thin film poly(lactic-*co*-glycolic acid) [PLGA] device that allows for sustained and directed release of RvD1 that can be oriented towards the vessel wall as a "wrap" (Lance et al., 2017). The device eluted biologically active RvD1 for more than 3 weeks *in vitro*. A similar approach was taken by Sok et al. in loading AT-RvD1 into PLGA scaffolds implanted under mouse skin (Sok et al., 2017). Sustained release of SPM (e.g. weeks) is likely important for clinical vascular applications as the healing phase in human arteries is prolonged compared to the small animal models. Of note, stable synthetic benzo-analogs for various SPMs have recently been developed which resist degradation, but have not yet been investigated in the vascular arena (Petasis et al., 2008; Orr et al., 2015).

Systemic administration of SPM or augmentation of their biosynthetic pathways may also provide an approach to improve outcomes of clinical vascular interventions. The specific actions of SPMs could explain some of the cardio-protective benefit derived from dietary intake of their precursor omega-3 fatty acids (DHA and EPA) (Bang et al., 1976; Dyerberg et al., 1978; Kagawa et al., 1982; Investigators, 1999, 2002; Yates et al., 2014). However, aggregate results of clinical trials involving omega-3 fatty acids in the cardiovascular setting are conflicting (Kris-Etherton, 2002; Filion et al., 2010; Mozaffarian and Wu, 2011). These differences are likely related to the heterogeneity of these cohorts in addition to relatively low doses of omega-3 fatty acids that were administered (Rizos et al., 2012). Additionally, a fundamental challenge to these nutritional trials is the importance of the balance that exists between oral intake and metabolism of omega-3 and omega-6 fatty acids. This delicate balance may be dysregulated in aging and obesity, leading to impaired resolution (Lopez et al., 2015; Halade et al., 2016). In both transgenic mice and rabbits overexpressing 15-LOX, one of the key enzymes involved in the biosynthesis of SPMs, atherogenesis is significantly reduced compared to wild type controls when these animals are fed a standard chow diet (Serhan et al., 2003; Merched et al., 2008). However, the same transgenic mice fed a high-cholesterol diet developed more significant atherosclerosis compared to wild type controls (Merched et al., 2011). The reason for this is rooted in the fact that 15-LOX can also contribute to oxidation of low-density lipoprotein (Fredman and Spite, 2017). In this scenario, diet composition determined the preferred pathway through which fatty acids were metabolized, leading to either SPM production or the alternative formation of pro-atherogenic lipids.

It has been well established that oral supplementation with omega-3 fatty acids or diets rich in their marine sources increase both plasma and cell-membrane levels of EPA and DHA (Grenon et al., 2015; Wang et al., 2015). Unfortunately, the relationship between blood levels of these n-3 fatty acids and the downstream biochemical pathways producing SPM is poorly understood. The physiological impact of oral supplementation of n-3 PUFA for each individual is variable depending on baseline characteristics such as prior dietary intake and hereditary metabolic factors (von Schacky, 2014). Recently, the OMEGA-PAD-I Trial demonstrated the effects of short-term n-3 fatty acid supplementation on altering biochemical SPM pathways in PAD patients (Grenon et al., 2015). In this study, eighty subjects were randomized to either 4.4 g of fish oil, corresponding to 2.6 g of EPA and 1.8 g of DHA daily, or placebo for one month. In the fish oil group there was a significant increase in the plasma levels of several downstream SPM pathway markers. Unfortunately not all lipid mediators that were investigated in the study were detected in subject plasma, so changes in most of the bioactive SPMs could not be assessed. This study provides a basis for continued investigation of oral supplementation of n-3 fatty acids in the context of vascular disease. Future efforts in this regard would benefit from greater consistency in formulations and dosing, and potential development of oral SPM cocktails.

In murine models of acute inflammation, such as peritonitis, periodontitis, and sepsis, various studies have demonstrated that oral administration of SPMs is effective (Spite et al., 2009; Recchiuti et al., 2014; Hasturk et al., 2015; Chacon et al., 2016). The effect of omega-3 fatty acids in acute illness in humans has been studied frequently in the context of the intensive care unit. The most comprehensive meta-analysis on this topic has concluded that parenteral treatment with omega-3 containing lipid emulsions significantly reduces infections and trended towards a reduction in the number of days of mechanical ventilation as well as overall hospital length of stay (Manzanares et al., 2015). Additionally, in subgroup analysis there was a trend toward decreased mortality in patients who received n-3 fatty acids via enteral nutrition. In a cohort of subjects undergoing major hepatobiliary operations, it was found that preoperative treatment with EPA for 5 days lead to significantly increased plasma RvE1 levels and fewer infectious complications, as well as overall lesser severity of complications, compared to a control group (Uno et al., 2016). Collectively, these studies begin to set the stage for future investigation of the effects of oral SPM or their precursors in the setting of an acute vascular intervention.

These studies also highlight a number of relevant issues and obstacles to systemic resolution therapies. First, there is a complex relationship between omega-3 and omega-6 fatty acids (Lands, 1992; Yaqoob et al., 2000; Kris-Etherton, 2002; Yates et al., 2014). Second, downstream bioactive mediators (SPMs) may be more potent and biologically relevant than their nutritional precursor fatty acids (Ho et al., 2010; Fredman and Serhan, 2011; Duffield et al., 2006). Third, biosynthesis pathways for both omega-3 and omega-6 fatty acids are complex and involve competition for enzymes to production various bioactive mediators (Levy et al., 2001; Serhan, 2007; Spite and Serhan, 2010; Merched et al., 2011; Colas et al., 2014; Serhan, 2014; Poorani et al., 2016) and this competition can produce isomers without proresolving actions (Dona et al., 2008; Spite et al., 2009). Furthermore, similar pathways might play antagonistic roles in different cell types and/or different species (Wittwer and Hersberger, 2007; Chatterjee et al., 2017) and additional factors such as aging (common in the atherosclerosis population) may alter the biosynthetic pathways (Halade et al., 2016). An additional consideration is that oral administration of precursors might not produce adequate systemic or local amounts of specific bioactive mediators (Endo et al., 2014), especially in the setting of a high cholesterol diet (Faggin et al., 2000). Finally, and perhaps most importantly, tissue distribution and metabolism of orally administered SPM are not well understood and improved formulations will likely be needed to achieve consistent therapeutic levels in target tissues. A more complete understanding of cellular mechanisms of resolution within the vasculature (including SPM biosynthesis, degradation and receptor specificity and expression) is needed to accelerate the translation of resolution biology to vascular therapies.

Conclusions and next steps

In summary, the pharmaco-biology of resolution is a young and rapidly expanding field, with potential benefits across a wide range of disease states. The need for improved adjuvant therapies after cardiovascular interventions is clear, and restenosis remains one of the greatest challenges for cardiovascular biologists, interventionalists and surgeons alike (Hedman et al., 2003; Conte et al., 2006). SPM exert homeostatic effects on vascular cells and their interactions with blood elements, reducing inflammation and improving healing in several preclinical models of vascular injury.

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Recent work highlights their potential as *anti*-restenosis agents. Current scientific challenges in the field include more readily available analytics, as well as optimal therapeutic formulations for early stage clinical studies. This review provides cautious optimism for the future therapeutic use of SPMs or their analogues in vascular injury, and highlights the need for ongoing basic and translational research.

Disclosures

MSC is an inventor on a patent assigned to Regents of the University of California and Brigham and Women's Hospital.

List of acronyms used

AA	arachidonic acid
AAA	abdominal aortic aneurysm
ApoE	apolipoprotein-E
ATL	aspirin-triggered lipoxin
AT-RvD1	aspirin-triggered resolvin D1
cAMP	cyclic adenosine monophosphate
CRP	C-reactive protein
DCB	drug coated balloon
DES	drug eluting stent
DHA	docosaheaenoic acid
EC	endothelial cell
EPA	eicosapentaenoic acid
FGF	fibroblast growth factor
GPCR	G-protein couple receptor
17-HDHA	17-hydroxy-docosahexaenoic acid
hsCRP	high sensitivity C-reactive protein
IL-1, 6, 8	interleukins (-1,6,8)
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOX	lipoxygenase
LXA4, LXB4	lipoxin-A4, B4
M1/M2	macrophage phenotypes
MaR1	maresin-1
MCP-1	monocyte chemoattractant protein-1
MMP	matrix metalloprotease
NIH	neointimal hyperplasia
PD1	protectin D1
PDGF	platelet derived growth factor
PGDH	prostaglandin dehydrogenase
PKA	protein kinase A
PLGA	poly (lactic-*co*-glycolic acid)
PMN	polymorphonuclear leukocyte
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
Rv(D, E)	resolvin (D,E)
SPM	specialized pro-resolving mediator
TNF-α	tumor necrosis factor-α
VSMC	vascular smooth muscle cell

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