

Proresolving Lipid Mediators and Mechanisms in the Resolution of Acute Inflammation

Christopher D. Buckley,¹ Derek W. Gilroy,² and Charles N. Serhan^{3,*}

¹Rheumatology Research Group, Center for Translational Inflammation Research, Queen Elizabeth Hospital, Birmingham B15 2WD, UK

²Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London WC1E 6JJ, UK

³Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Institutes of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

*Correspondence: cnserhan@zeus.bwh.harvard.edu

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Inflammatory responses, like all biological cascades, are shaped by a delicate balance between positive and negative feedback loops. It is now clear that in addition to positive and negative checkpoints, the inflammatory cascade rather unexpectedly boasts an additional checkpoint, a family of chemicals that actively promote resolution and tissue repair without compromising host defense. Indeed, the resolution phase of inflammation is just as actively orchestrated and carefully choreographed as its induction and inhibition. In this review, we explore the immunological consequences of omega-3-derived specialized proresolving mediators (SPMs) and discuss their place within what is currently understood of the role of the arachidonic acid-derived prostaglandins, lipoxins, and their natural C15-epimers. We propose that treatment of inflammation should not be restricted to the use of inhibitors of the acute cascade (antagonism) but broadened to take account of the enormous therapeutic potential of inducers (agonists) of the resolution phase of inflammation.

Introduction

Infection and tissue injury drive the acute inflammatory response, which, in its simplest form, is characterized by the sequential release of mediators (including histamine, bradykinin, and 5-hydroxytryptophan [5HT]), resulting in the immediate influx of polymorphonuclear leukocytes (PMNs) followed by phagocytosis via monocytes-macrophages, leading to leukocyte clearance and resolution. Indeed, for the past 40 years, research has focused on identifying factors that initiate and perpetuate inflammation with the objective of developing anti-inflammatory drugs to alleviate diseases driven by ongoing or dysregulated inflammation. More recently, emphasis has shifted to the other end of the inflammatory spectrum, i.e., resolution, in order to understand how immune-mediated inflammatory responses are terminated.

The concept that antagonists that limit the duration of a biological cascade are generated at the same time that a cascade is induced is very familiar in other self-limiting pathways of interest to immunologists such the complement and coagulation cascades. However, homeostasis takes an unexpected twist in the inflammation cascade. Events at the onset of acute inflammation establish biosynthetic circuits for a series of chemical mediators that later not only serve as antagonists but also serve as agonists; in other words, they don't just inhibit the inflammatory cascade, they actively dismantle it, leading to the restoration of tissue homeostasis and function. Anti-inflammation and proresolution are therefore not equivalent. The agonists that actively promote resolution (an emerging family of proresolving lipid mediators including lipoxins, resolvins, and protectins) are fundamentally different from the antagonists that limit the duration and magnitude of the inflammatory response at both the molecular and cellular levels (Ryan and Godson, 2010; Serhan, 2007). In this review we will explore the pathways,

cells and molecules involved in curbing inflammation and which begin the process of tissue repair. Advances in this area will help shed light on why inflammation persists and provide drug development opportunities based upon stimulating endogenous pro-resolution mediators and their pathways, which act as agonists along with the more traditional antagonists which are currently in clinical use.

What Is Resolution and Who Are the Main Players?

The mediators and cell types involved in the active resolution of acute inflammatory responses are emerging as important determinants of the immune system's status and function. Inflammation does not switch off in a passive manner but involves a program of unique pathways (Figure 1), mediators, and cell subtypes (Serhan, 2007). It is important to note that the cells can't move without specific instructions—marching orders—that in the acute inflammatory response come in the form of chemical gradients of mediators (*vide infra*). Hence, the focus on identification and decoding of the mediators of the terminating events in the resolution of inflammation are of considerable interest. At the tissue and cellular level, resolution of inflammation has been defined, in broad terms, by the rate of polymorphonuclear cell (PMN) clearance to the point when they are absent from the site of primary tissue injury. The key steps in this process include (1) clearance of the inciting stimuli, (2) catabolism of local survival signals and silencing of intracellular proinflammatory signaling pathways, (3) normalization of chemokine gradients, apoptosis of PMNs, (4) their efferocytosis by tissue and monocyte-derived macrophages, and (5) either incorporation of these myeloid cells into the local population or their recirculation via lymph or blood. Lipid mediators (LM) including eicosanoids and the more recently discovered omega-3 derived “specialized proresolution mediators” represent the key signaling molecules in this process (Figures 1

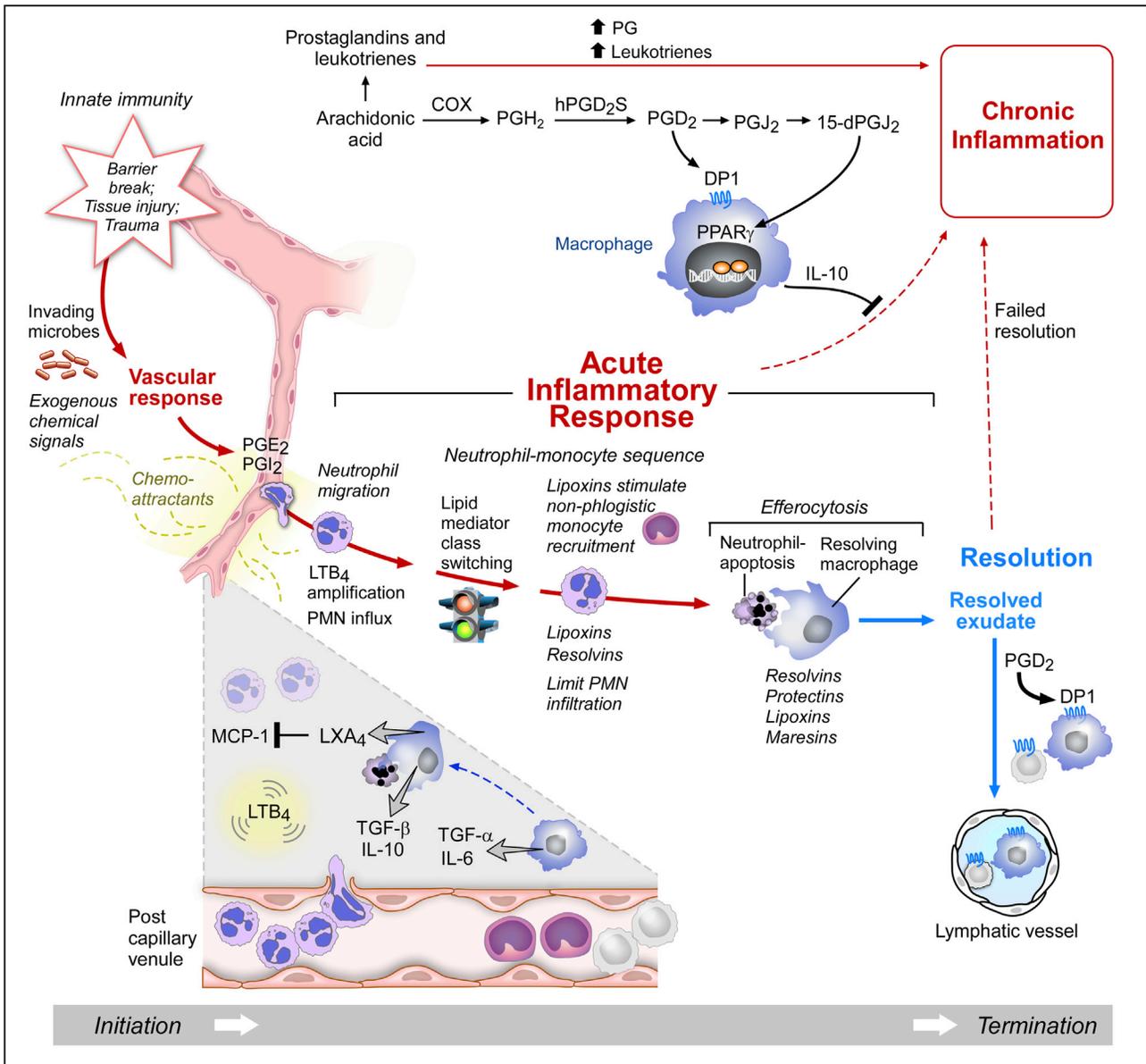


Figure 1. Acute Inflammatory Response and the Role of Lipid Mediators in Resolution or Its Failure

Initiation of the acute response starts with changes in blood flow stimulated by PGE₂ and PGI₂, and LTB₄, which are produced from arachidonic acid and stimulate PMN recruitment. Excess prostaglandins and leukotrienes contribute to chronic inflammation. Cyclooxygenase (COX) production of PGD₂ via human PGD₂ synthase (hPGD₂s) activates its receptor DP1, a GPCR that stimulates IL-10, an anti-inflammatory cytokine, which blocks the path to chronic inflammation. PGD₂ can be converted to PGJ₂ and 15-dPGJ₂ to products that activate PPAR-γ to activate resolution (see text for details).

Lipid mediator class switching is the temporal switch in inflammatory exudates that activates lipoxin production. LXA₄ regulates MCP-1 and nonphlogistic monocyte recruitment and stops LTB₄-stimulated PMN influx. Lipoxins and resolvins limit further PMN influx to the site and stimulate efferocytosis and the clearance of cellular debris by resolving macrophages. Resolvins, protectins, lipoxins, and maresins (SPM) stimulate and enhance efferocytosis and promote resolution. Loss of any of the cell-type receptors or chemical mediators can in theory lead to failed resolution that might underlie the persistent inflammation recognized as chronic inflammation associated with many diseases.

and 2), which regulate the inflammatory profile and promote the return of affected tissues to homeostasis (Serhan, 2010; Serhan et al., 2008).

The presence of specialized regulatory or proresolution cell subsets including phagocytosing monocyte-derived macrophages and myeloid-derived suppressor cells, T regulatory cells (Tregs), for instance, is also instrumental in helping switch off inflammation in a nonphlogistic manner (D'Alessio et al., 2009).

Resolution and clearance of cellular debris from mucosal surfaces involves the essential polyunsaturated fatty acids (PUFA)-derived mediators including SPM that accomplish this, as well as activate antimicrobial mechanisms in mucosal epithelial cells (Colgan et al., 2013). Functionally, proresolving mediators and cell subtypes serve to act not merely as inflammatory brakes but also facilitate the return of the site to homeostasis in the process of catabasis: the return from disease state

(Serhan, 2007; Serhan and Chiang, 2013). Failure of resolution has classically been discussed in terms of either an insufficiency or inadequacy leading to chronic inflammation, excess tissue damage, and dysregulation of tissue healing including fibrosis and has been implicated in multiple disease states (Serhan, 2007) including the development of autoimmunity (for reviews, see Tabas and Glass, 2013).

Resolvins, Protectins, and Maresins: Specialized Proresolving Mediators

Cells within multicellular responses require chemical gradients of signals that instruct each to move and/or stop as needed (Figure 1). In an acute inflammatory response, many chemical signals are produced. Some are from microbial origins, whereas others are biosynthesized by the host in response to tissue injury and invasion (Majno and Joris, 2004). Among the chemical signals at the site of an acute inflammatory response, those that originate from host essential fatty acids are of particular interest because of their nutritional regulation of the response (Zhang and Spite, 2012) and the potential to design small molecule mimetics of these molecules (Serhan, 2007).

Chemical mediators biosynthesized from arachidonic acid include prostaglandins and leukotriene B₄, which are involved in the initiating steps that permit white blood cells to leave the postcapillary venules, i.e., diapedesis (Samuelsson et al., 1987; Serhan, 2007). More recent research has focused on elucidating chemical mediators and mechanisms involved in endogenous anti-inflammation and its resolution (Levy et al., 2002; Serhan et al., 2000). A systems approach with liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based lipidomics, in vivo animal models, exudate cell trafficking, and functional assessment with isolated human cells has uncovered bioactive products identified within the resolution phase of acute sterile inflammation (illustrated in top panel of Figure 1) that activate proresolving mechanisms (Hong et al., 2003; Serhan et al., 2000, 2002).

Focusing on self-limited resolving exudates also has permitted a direct assessment of the host's responses that enable the return to homeostasis. Key bioassays that have proven critical in the initial studies focused on human neutrophil (PMN) transmigration across endothelial cells and epithelial cells (Colgan et al., 2013; Serhan et al., 2000) and the phagocytosis of cellular debris and dead PMN (Majno and Joris, 2004). Attention focused on these cellular responses because neutrophils are among the first responders to injury and microbial invasion. The hypothesis that endogenous chemical mediators are produced via cell-cell interactions within developing inflammatory exudates (i.e., pus) that control the size, magnitude, and duration of the exudate turned out to be the case in animal models (Schwab et al., 2007; Serhan et al., 2002). This approach has proven to be highly relevant to human disease in that anti-PMN therapy (Takano et al., 1998) has been shown to limit tissue damage and uncontrolled inflammation.

The historical milestones in resolution of inflammation from observation of the gross cardinal signs of inflammation (Figure 1) to active resolution to new therapeutics first in humans are an exciting new area of investigation. In ancient medical texts of the 11th and 12th century, the notion of treating inflammation with "resolvents" as "mollificants" to help resolve disease was already present. This concept of stimulating resolution of inflam-

mation was apparently lost until the chemical structures of endogenous mediators that stimulate resolution were finally elucidated (Serhan et al., 2002). From this line of investigation the resolvins, protectins, and maresins pathways were elucidated and their functions in activating resolution of inflammation uncovered. Within exudates resolving to homeostasis, the fundamental cellular processes proved predictive of the actions of SPM in more complex animal disease models because the cessation of PMN entry into tissue and removal of dead PMN, as well as cellular debris, are central to all organs of the body and many human disease pathologies. This is what makes proresolving different from simple anti-inflammation or blocking mediators and natural mechanisms in the host. It is now apparent that a broad range of endogenous and exogenous agents belong to the immunoresolvents (pharmacologic agents or local endogenous mediators) that stimulate resolution of inflammation in animal models and hopefully in human diseases (Dalli et al., 2013a).

Of interest, the n-3 essential fatty acids EPA and DHA were found to be substrates for the biosynthesis of potent anti-inflammatory proresolving endogenous mediators within inflammatory resolving exudates (Hong et al., 2003; Serhan et al., 2002). Identification of omega-3 fatty acids as nutrients that activate proresolving mechanisms in inflammation has opened new areas of investigation, because uncontrolled inflammation is now widely appreciated to be a unifying theme and the fundamental basis for many widely occurring diseases (Figure 1). It is worth noting that there already exists a large body of literature addressing the anti-inflammatory potential of EPA and DHA (for a recent review, see Calder, 2013). Yet, the molecular basis by which these essential fatty acids exert anti-inflammatory responses has remained the subject of intense discussion. DHA and EPA have many known critical functions in mammalian biology, and neither EPA nor DHA is produced by humans to any great extent and therefore must be absorbed within the diet (Calder, 2013). One area where the function of DHA and its mechanism is clear is the role of DHA in the retina. It has been argued that DHA is an ancient molecule with functional roles in the brain and eye imposed via evolutionary pressure (Crawford et al., 2013). Thus, uncovering special chemical mediators biosynthesized from n-3 fatty acids EPA, DHA, and DPA during self-limited inflammatory responses in the resolution phase of mouse exudates with functions on individual human leukocytes has many implications. For further mechanistic details on the biosynthesis of the SPM (resolvins, protectins, and maresins), see recent reviews covering their biosynthesis (Serhan, 2007), actions, and total organic synthesis (Serhan and Petasis, 2011). In this review, we focus on the SPM production in resolution and activities on phagocytes and disease models relevant to acute inflammation and the innate response.

Resolvins and Protectins

Specialized proresolving mediators (SPMs, Figures 1 and 2), derived from different polyunsaturated fatty acid (omega-3 EPA and DHA) substrates, exert diverse biological effects on immune function including the ability to counterregulate mediators that trigger leukocyte trafficking (Figures 1 and 2). Of the essential polyunsaturated fatty acids, namely those that are not biosynthesized de novo to any great extent in humans, the omega-3 fatty acids such as DHA and EPA are supplied in the

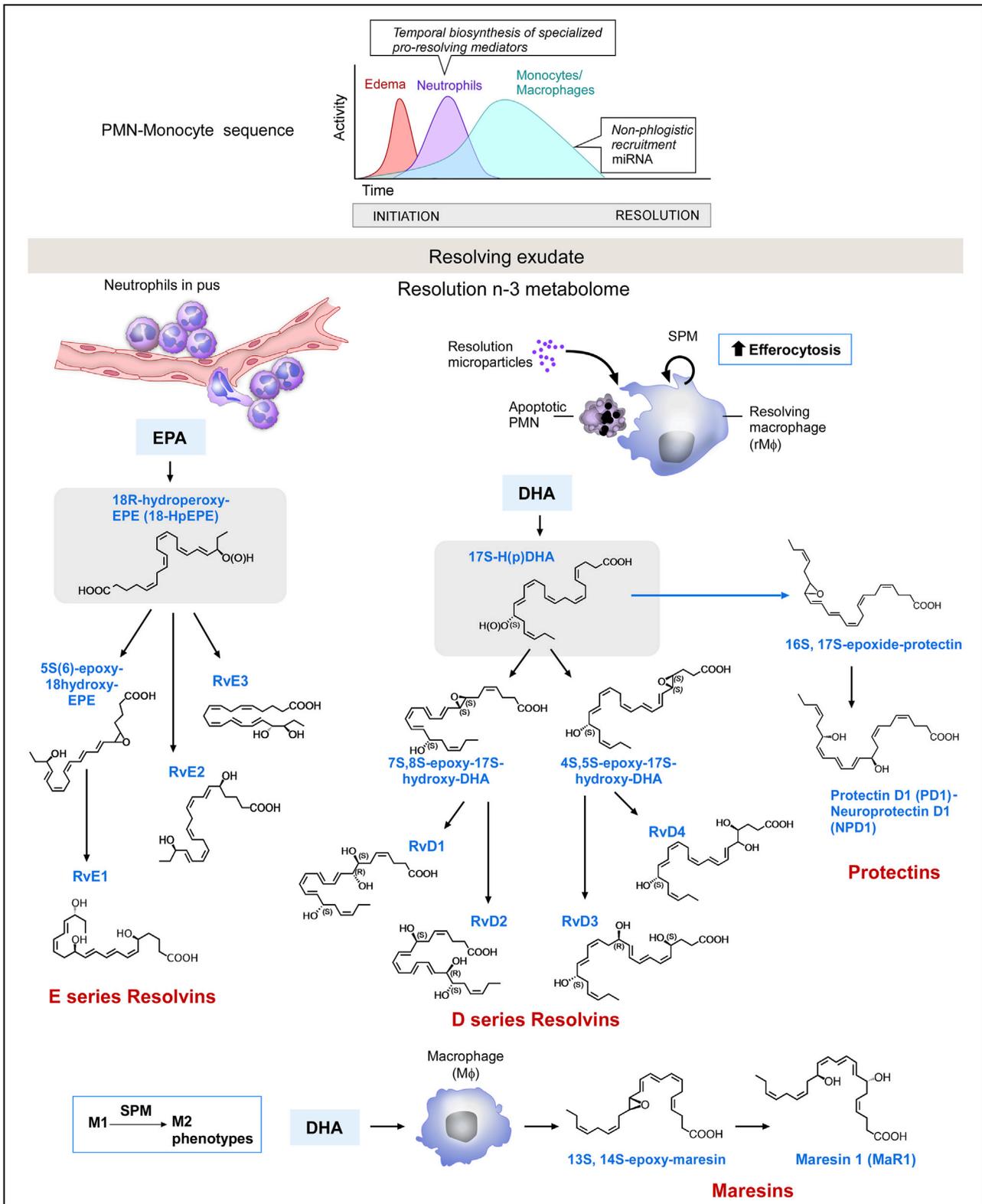


Figure 2. Time Course of Self-Limited Inflammatory Response and the Resolution n-3 Metabolome

Upper panel shows the ideal outcome for an acute challenge: edema, followed by PMN influx, then return to baseline and nonphlogistic recruitment of monocytes and macrophages for resolution. The temporal biosynthesis of SPM is initiated by leukocyte congregation within the exudate. In resolution phase, specific miRNA are regulated and some of these are controlled by resolvins in recent studies (see Li et al., 2013 and references within).

(legend continued on next page)

Table 1. Resolvins and SPM in Resolution of Infections and Increasing Survival in Murine Infections

Lipoxins, Resolvins, and Protectins	Increase Survival	Disease	Shorten Resolution	Reference
LXA ₄	√	Bacterial infections		Walker et al. (2011)
15-epi- LXA ₄	√	Lung injury		El Kebir et al. (2009)
RvE1	√	Colitis	+	Arita et al. (2005)
	√	<i>E. coli</i> peritonitis	+	Chiang et al. (2012)
	√	<i>Candida</i> yeast	+	Haas-Stapleton et al. (2007)
	√	Acid-induced lung injury	+	Levy and Serhan (2014)
RvD1, RvD5, PD1	√	<i>E. coli</i> peritonitis infection	+	Chiang et al. (2012)
RvD1	√	Acute lung injury	+	Wang et al. (2011)
RvD2	√	Cecal ligation and puncture sepsis	+	Spite et al. (2009)
	√	Burn wound sepsis	+	Bohr et al. (2013) Kurihara et al. (2013)
Protectins	√	H1N1 viral infections		Morita et al. (2013)

diet (De Caterina, 2011). Marine oils are rich in both DHA and EPA; in humans, DHA is concentrated in neural tissues including brain and retina and is enriched in human milk, plasma, and sperm, where their physical properties in the membrane bilayers govern membrane fluidity (Calder, 2013; Crawford et al., 2013). Within the immune system, PMN influx or chemotaxis occurs along chemical gradients that are either from exogenous sources (degradation products of microbial proteins and lipids [e.g., LPS] or endogenous chemoattractants from the host [chemokines, e.g., interleukin-8 (IL-8) and arachidonic acid-derived leukotriene B₄; see Figure 1, left side]). These endogenous and exogenous factors also stimulate the nonphlogistic recruitment of monocytes, which positively affect the efferocytosis of apoptotic granulocytes (Figures 1 and 2). Thus, SPMs have overlapping proresolving actions most likely arising from the ability to bind and act as agonists on alternate SPM receptors (e.g., RvD1 on the lipoxin A₄ [LXA₄] receptor [Wang et al., 2011]). However, despite common actions, the source of different families of specialized proresolution mediators in inflammation appears diverse. Recent evidence suggests that RvE1

and RvE2 are biosynthesized by PMNs via the 5-LOX pathway (Oh et al., 2011), whereas mouse eosinophils are responsible for generation of 12/15-LOX-derived mediators PD1 and the recently discovered RvE3 (Isobe et al., 2012; Yamada et al., 2011). Deficiency of these cell types in tissues during the resolution phase might lead to impaired biosynthesis with deleterious consequences (Yamada et al., 2011). The same might be the case for the essential PUFAs (n-3 polyunsaturated fatty acids, i.e., EPA and DHA) at the inflammatory site.

Functionally, SPMs enhance bacterial clearance by stimulating mucosal production of bactericidal peptides (Colgan et al., 2013), enhancing bacterial phagocytosis by PMNs and macrophages and working synergistically with antibiotics to enhance their therapeutic action and hence bacterial clearance (Chiang et al., 2012). Importantly, despite encouraging resolution, they do not compromise host immune competence (Serhan, 2007; Spite et al., 2009). Several of the proresolving mediators actually increase survival from infections in mouse models of disease (bacterial and viral infections) (Table 1). For instance, resolvin E1 (RvE1) administered prior to a murine model of aspiration pneumonia (hydrochloric acid with subsequent *Escherichia coli* challenge) is associated with a reduction in proinflammatory cytokines, decreased pulmonary PMN accumulation, enhanced bacterial clearance, and improved survival (Seki et al., 2010). Mechanistically, RvE1, at concentrations as low as 1 nM, enhances macrophage phagocytosis (Hong et al., 2008), as well as NADPH oxidase-mediated reactive oxygen species (ROS) generation. Resolvins of the D-series appear equally efficacious as RvE1 (Dalli et al., 2013a). Resolvin D1 (RvD1) treatment prior to LPS-induced acute lung injury improves pathological indices and survival rates (Wang et al., 2011) and might be equally effective in central nervous system inflammation (Xu et al., 2013). The common mechanism appears to be suppression of NF-κB activation in a partly PPAR-γ-dependent manner, with associated reduction in downstream signaling and alterations in transcriptomics (Arita et al., 2005; Liao et al., 2012).

Resolvin D2 (RvD2), but not its isomer *trans*-RvD2, improves survival in murine polymicrobial sepsis (cecal ligation and puncture [CLP]) (Table 1). Its actions are multifaceted, targeting the modulation of leukocyte-endothelial interactions directly (adhesion receptor expression) and via stimulation of endothelial nitric oxide (NO) production, altering the cytokine and eicosanoid profiles (reduced IL-17, IL-10, prostaglandin [PG]E₂, and LTB₄), enhancing bacterial phagocytosis and intraphagosomal vacuolar production of ROS (Spite et al., 2009). Recently, the ability of RvD2 to restore directionality to neutrophil migration and prevent sepsis-induced immune dysfunction and thus increase survival from a secondary septic challenge after burn injury has been demonstrated (Kurihara et al., 2013). Resolvin D3 appears later in the resolution phase of peritonitis, displaying potent

Lower panel shows resolving exudate. The E-series resolvins are biosynthesized from EPA, initiated by oxygen insertion at the 18th carbon position to produce RvE1 via an epoxide intermediate, RvE2 and RvE3. D-series resolvin biosynthesis is initiated with oxygen insertion at the 17th carbon position of n-3 DHA. The intermediate 17S-HpDHA is precursor to both protectin and D-series resolvins. Human and mouse macrophages also convert DHA to maresins via oxygen insertion initiated at the 14th carbon to biosynthesize maresin 1 (MaR1) via a recently identified 13S,14S-epoxy-intermediate that also is bioactive. The biosynthesis steps in human leukocytes and in mice are reviewed in Serhan (2007), and stereochemical assignments with confirmation of their potent proresolving actions are reviewed in Serhan and Petasis (2011). Apoptotic PMN resolution phase microparticles resolving macrophages produce SPM (Dalli and Serhan, 2012). By definition, each SPM enhances efferocytosis and resolution in vivo in animal models; see text for details. Also, some SPM stimulate the biosynthesis of other families of SPM. For example, RvE1 stimulates LXA₄ production in mouse lung (Levy and Serhan, 2014).

actions limiting PMN infiltration and stimulating macrophage uptake of apoptotic cells (Dalli et al., 2013a). Hence, despite being inherently anti-inflammatory and proresolution in nature, SPMs exert diverse actions in host defense and pathogen interactions (Table 1) in a manner that is, paradoxically, conducive to optimal bacterial clearance and not immunosuppressive.

Maresins: Macrophage Mediators In Resolving Inflammation and Organ Regeneration

From the study of resolution phase macrophages, a new pathway able to produce potent mediators from DHA has been uncovered and coined “maresins.” The stereochemical assignments of maresin 1 (MaR1) and its related isomers have been established (Serhan et al., 2012), as well as the key epoxide intermediate (Figure 2, lower panel) in the maresin biosynthetic pathway (Dalli et al., 2013b). MaR1 is produced by human macrophages from endogenous DHA and is the newest pathway and family of mediators identified. In these recent studies, MaR1 was obtained and matched to synthetic 7*R*,14*S*-dihydroxydocosa-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid prepared by total organic synthesis. MaR1 alcohol groups and *Z/E* geometry of conjugated double bonds were assigned with isomers also prepared by total organic synthesis and confirmed using NMR. MaR1's potent defining actions were confirmed with synthetic MaR1, namely limiting neutrophil (PMN) infiltration in murine peritonitis (ng/mouse range), as well as enhancing human macrophage uptake of apoptotic PMNs. Leukocyte-derived microparticles contribute to the production of MaR1 and SPM in that they stimulate efferocytosis (Figure 2), as well as provide substrates and pathway intermediates in SPM biosynthesis to recipient cell types (Dalli and Serhan, 2012).

The appearance of MaR1 in the inflammatory response can be in the later stages with the entry of resolution phase macrophages that release maresins. MaR1 appears slightly more potent than Resolvin D1 (RvD1) in stimulating human macrophage efferocytosis, an action not shared by prostaglandins or leukotriene B₄. MaR1 and RvE1 each accelerate tissue regeneration in planaria, increasing the rate of head reappearance. With surgery or injury of planaria (when cut in half), MaR1 is biosynthesized from deuterium-labeled (d₅)-DHA indicating that this pathway is conserved in evolution from flatworm to humans (Serhan et al., 2012). Blocking this pathway delays organ regeneration, and MaR1 rescues this primordial response of the organism. 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. MaR1's potent anti-inflammatory and proresolving actions were recently confirmed in murine colitis, where it is protective in both DSS and TNBS models of colitis (Marcon et al., 2013). Hence, MaR1 has multiple potent actions in regulating inflammation resolution, tissue regeneration, and resolving pain. These findings also suggest that shared chemical signals occur in biological processes as diverse as cellular trafficking in the resolution of inflammation to tissue regeneration in worms.

In addition to the assignments of SPM stereochemistry of the endogenous bioactive products (i.e., RvE1, RvD1, RvD2, RvD3, etc.) and structure function with materials prepared by organic synthesis (Serhan and Petasis, 2011), other groups have focused on the synthesis of these molecules that are now commercially

available and expanded their roles and mechanisms in a range of systems relevant to human biology. Recently, the total organic synthesis of resolvins and MaR1 has also been achieved by Rodriguez and Spur (2012). Kobayashi et al. also reported on the total organic synthesis of protectin D1 and E-series resolvins (Ogawa and Kobayashi, 2011). Total organic synthesis of 18-HEPE, a precursor from 18-HpEPE of E-series resolvins (see Figure 2), has also been reported (Krishnamurthy et al., 2011), confirming the earlier biogenic synthesis of this previously undescribed structure and precursor (Serhan et al., 2000). Importantly, the stereoselective actions of each SPM have proven highly effective in regulating human PMN and monocytes in microfluidic chambers (Jones et al., 2012; Kasuga et al., 2008; Oh et al., 2012). Together, these clearly establish the direct actions of these compounds on human cells, where they can activate specific G protein-coupled receptors and hence their potential for therapeutic use in man.

Resolvins and lipoxin A₄ are present in human breast milk in high amounts (Weiss et al., 2013), in fish such as salmon (Raatz et al., 2011), and are produced in humans following supplementation with omega-3 (EPA, DHA) in peripheral blood at amounts where they are found to be bioactive in experimental systems (Mas et al., 2012). Also, they are produced in humans following strenuous exercise (Markworth et al., 2013) and in human adipose tissue (Clària et al., 2013).

Leukotrienes and Lipoxins: Arachidonic Acid-Derived Mediators

Alongside omega-3-derived SPMs, arachidonic acid-derived lipoxins and their carbon 15 position epimers (Figures 1 and 3) also exert beneficial actions on inflammation and resolution (Chiang et al., 2005). Although the LXs were first identified and biosynthesized from isolated human leukocytes and eosinophils (Samuelsson et al., 1987), their functions in inflammation *in vivo* remained to be established. For instance, in a rabbit model of periodontal disease, transgenic overexpression of the 15-LOX type I is protective of inflammation-induced bone loss and dermal inflammation via increased production of LXA₄ monitored with LC-MS/MS-based identification (Serhan et al., 2003). Also, treatment with LXA₄ following inhaled LPS-induced lung injury has been demonstrated to limit inflammation (Jin et al., 2007) and to reduce pro- and anti-inflammatory cytokine production, enhance macrophage recruitment, reduce blood bacterial load, and improve mortality in a rat CLP model (Walker et al., 2011). In the latter study, macrophage recruitment was increased without impairing phagocytic function, and systemic inflammation reduced without increasing bacterial spread, mirroring the actions of resolvins, namely RvE1 and RvD2 (Seki et al., 2010; Spite et al., 2009; and see references in Table 1).

A similar paradoxical relationship between an attenuated innate immune response (PMN trafficking to the infected site) versus increased host-pathogen interaction (as determined by survival) has been demonstrated in both wild-type mice treated with MK 886 (a 5-lipoxygenase [5-LOX] inhibitor) and in 5-LOX-deficient mice (Benjamim et al., 2005). This effect could be partially replicated if antagonists of cysteinyl-leukotrienes (cysteinyl-LTs, a family including LTC₄ – E₄) were given, but crucially not on antagonism of the classically proinflammatory leukotriene B₄ (LTB₄). This elegantly demonstrates the hierarchical, multifaceted, and often opposing effects of eicosanoids

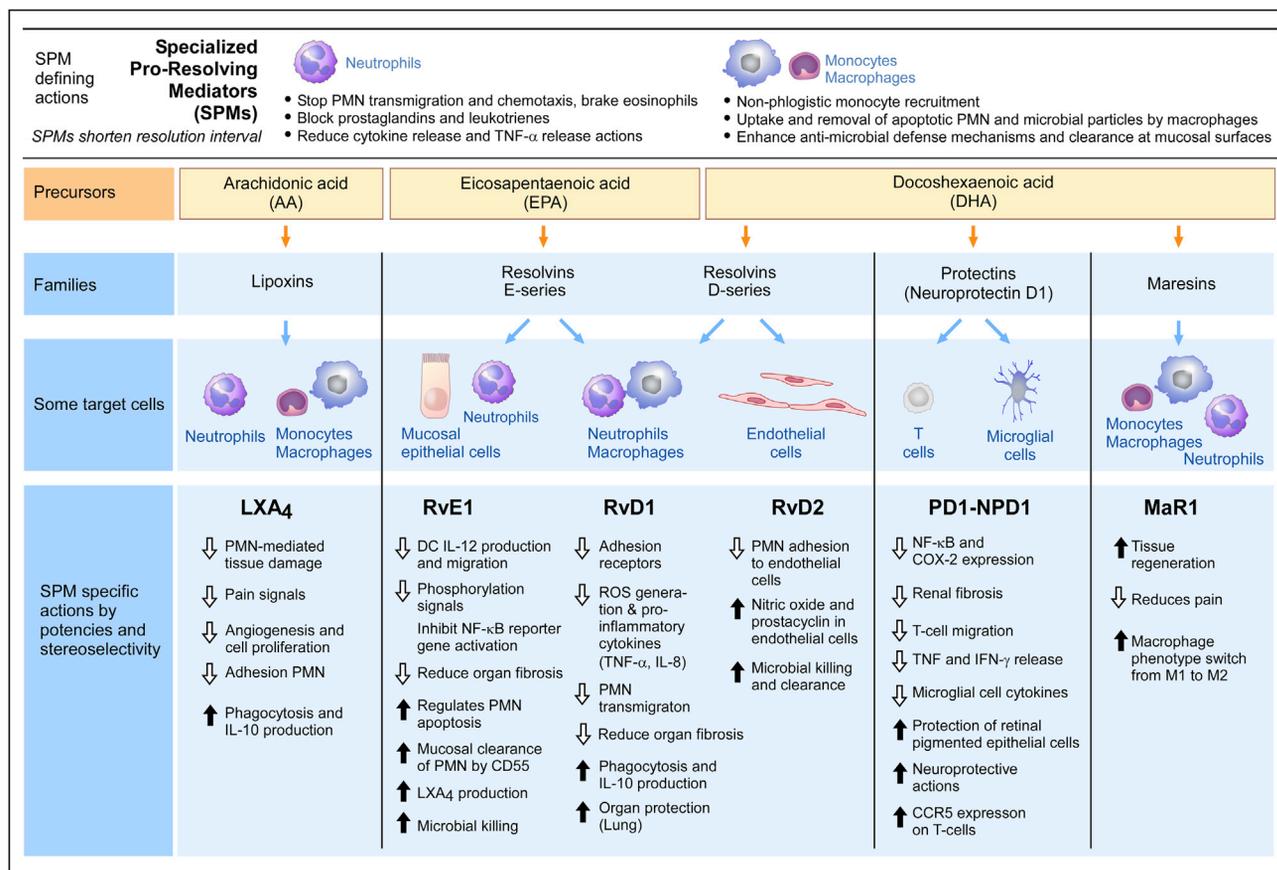


Figure 3. SPM Actions and Target Cell Type

Shown are the defining actions of SPM in the innate response of interest in immunology and the actions to stimulate termination and resolution. The precursor essential polyunsaturated fatty acids (AA, EPA, DHA) are converted by leukocytes to separate chemically distinct families of mediators that stimulate active resolution responses of isolated cell types and tissues *in vivo* in animal models. Some of the specific target cell types and representative potent actions of the SPM members from each family of related structures are listed. All of these actions of SPMs are stereoselective and in the picogram-nanogram range potency. See Serhan and Chiang (2013) and text for further details.

within infection and sepsis. In this setting, it appears that the prevention of the cysteinyl-LT's deleterious effects on the vasculature (and hence host haemodynamics) assumes primacy as the main cause of benefit in 5-LOX antagonism (or deletion). In contrast, selective LTB₄ inhibition prior to and post cecal ligation and puncture (CLP) in a model of sepsis appears to have little effect on vascular tone and permeability, but might have blunted the innate immune response (specifically neutrophil trafficking), exacerbating the infective insult (Lämmermann et al., 2013; Rios-Santos et al., 2003). Hence the 5-LOX-derived mediators play critical roles in the physiologic response of the host to infection.

The complex interplay between AA-derived LM in systemic inflammation has also been highlighted in recent results showing that flavocoxid, a dual cyclooxygenase (COX)-2 and 5-LOX inhibitor, reduces the expression of NF- κ B, COX-2, and 5-LOX with improved survival in a murine-CLP model (Bitto et al., 2012). Plasma IL-10 and counterintuitively LXA₄ concentrations were increased while TNF- α , IL-6, LTB₄, and PGE₂ were decreased. The authors suggest that LXA₄ is biosynthesized in mice via another biosynthetic route, for example, initiation via the combined mouse lipoxygenase that carries both 12-LOX

and 15-LOX activities in murine systems (a type of 15-LOX found in humans) when both COX and 5-LOX are inhibited. Whether the improvement in outcome is due to enhanced proresolution effects driven by increased LXA₄, decreased cytokine storm (TNF- α and IL-6), augmentation of the immune response via reducing PGE₂ and 5-LOX-derived LTs (discussed below), selective shunting of AA down the COX or LOX pathways (Chen et al., 1994), or a combination of all the above is unclear.

Both biologically active ATL and aspirin-triggered resolvins (Serhan, 2007) trigger resolution (Figures 1 and 3) by inhibiting leukocyte trafficking in a NO-dependent manner in both murine (Paul-Clark et al., 2004) and human inflammation (Morris et al., 2009) and by downregulating extracellular release of superoxide in neutrophils along with macrophage inflammatory peptide 2 and IL-1 β production (Serhan, 2007). The importance of ATL and LXA₄ has previously been demonstrated in severe inflammation: the absence of LXA₄ leading to unbridled inflammation and elevated mortality in animal models of infection due to DC hypersensitivity. Along these lines, certain parasites can stimulate supraphysiologic amounts of LXA₄ as part of their highly evolved mechanism to evade the host response (Bannenberg et al., 2004; Serhan, 2007). Indeed, administration of

15-lipoxygenase to mice stimulates endogenous LXA₄ and is anti-inflammatory, and certain parasites carry their own 15-lipoxygenase to presumably act on host substrates. Moreover, during *Mycobacterium tuberculosis* infection, 5-lipoxygenase-derived LXA₄ is elevated, dampening T helper 1 (Th1) cell cytokine responses essential for bacterial clearance. Thus, not only are lipoxins used by infectious agents to parry host-defense responses, but also inhibitors of their biosynthesis could prove useful in clearing such recalcitrant infections as tuberculosis (Bafica et al., 2005).

Prostaglandins and Resolution: It's Time and Place that Counts!

Prostaglandins (PGs) derived from COX metabolism of arachidonic acid regulate the changes in blood flow required for leukocytes to exit the postcapillary venules (Figure 1) in the initiation phase, as well as mediate the class switching of lipid mediators (Levy et al., 2001) required for termination of the acute response (Figure 2, upper panel), and can exert immunosuppressive effects through upregulation of intracellular cAMP (Aronoff et al., 2006; Luo et al., 2004). PGE₂ and PGI₂, for example, reduce the ability of inflammatory leukocytes to phagocytose and kill microorganisms (Aronoff et al., 2004; Rossi et al., 1998; Weinberg et al., 1985), as well as inhibit the production of downstream proinflammatory mediators (Aronoff et al., 2007; Takayama et al., 2002; Xu et al., 2008). In contrast, these PGs enhance the production of IL-10 (Harizi et al., 2002). Indeed, overexpression of PGE₂ has been reported in a number of conditions associated with increased susceptibility to infection, including cancer (Starczewski et al., 1984), aging (Hayek et al., 1997), and cystic fibrosis (Medjane et al., 2005; Strandvik et al., 1996). Interestingly, PGE₂, generated during the onset phase of inflammation, also indirectly elicits proresolution actions by switching on the transcription of enzymes required for the biosynthesis of other classes of bioactive lipids that are potent proresolution mediators, such as LXs (Levy et al., 2001), resolvins (Rvs), and protectins (PDs) (Hong et al., 2003; Marcheselli et al., 2003; Serhan et al., 2000; Serhan et al., 2002).

While PGD₂ can elicit immunomodulatory and anti-inflammatory effects in the same manner as described for PGE₂ and PGI₂ via ligation to DP1 (Figure 1, upper panel), it can also act independently of DP1 and DP2 receptor activation when nonenzymatically dehydrated into biologically active PGs of the J₂ series (e.g., PGJ₂, Δ12,14-PGJ₂ and 15-deoxy-Δ12,14-PGJ₂ [15d-PGJ₂]) (Diab et al., 2002). These cyclopentenone PGs, as they are so called, form covalent attachments with reactive sulphhydryl groups on intracellular regulatory proteins, enabling them to modulate their function (Kim et al., 2006; Oliva et al., 2003; Renedo et al., 2007). 15d-PGJ₂ for example, via ligation to the nuclear receptor PPAR-γ (Khan, 1995), decreases proinflammatory cytokine release and modifies gene expression (Ricote et al., 1998), as well as directly inhibits the actions of IκB kinase (IKK), the kinase responsible for the activation of NF-κB (Cernuda-Morollón et al., 2001; Straus et al., 2000). Independent of PPAR-γ, 15d-PGJ₂ can preferentially inhibit monocyte rather than neutrophil trafficking through differential regulation of cell-adhesion molecule and chemokine expression (Gilroy et al., 2003; Pasceri et al., 2000), regulate macrophage activation and proinflammatory gene expression (Lawrence, 2002), and induce leukocyte apoptosis through a caspase-dependent

mechanism (Bishop-Bailey and Hla, 1999; Gilroy et al., 2003; Lawrence et al., 2001). Moreover, it has been illustrated that PGD₂-derived compounds act as endogenous braking signals for lymphocytes to stimulate resolution (Trivedi et al., 2006).

It is now clear that the inflammatory program contains key checkpoints and temporal and spatial switches that regulate its onset, maintenance, and resolution. It turns out that the resolution phase of inflammation is just as actively orchestrated and carefully choreographed as its induction and maintenance. A key finding in recent years is that the biosynthetic pathways required for inflammation to resolve often require the prior production of lipid mediators that are produced locally during the initiation of acute inflammatory response. In particular, PGE₂ and PGD₂, which are responsible for inflammation induction, subsequently stimulate anti-inflammatory circuits by inducing 15-LOX in neutrophils. This class switch in eicosanoid production, from LTs and PGs to lipoxins (Levy et al., 2001), provides temporal and spatial check points during the inflammatory cascade (the lipid mediator class switch is illustrated in Figure 1).

Whereas the anti-inflammatory prostanoids (e.g., PGD₂ and PGE₂) can limit the extent of inflammation, they and their metabolites can also stimulate active tissue remodeling and repair; in other words, class switching might not always be required for resolution to be initiated. Within a single pathway of the eicosanoid family initiated by COX-2 and subsequently regulated by the enzyme hematopoietic PGD₂ synthase (hPGD₂S), proresolving mediators PGD₂ and 15d-PGJ₂ are produced at sufficient amounts in vivo (Figure 1, upper panel) to drive the resolution of acute inflammation (Rajakariar et al., 2007).

Abandoned for over 15 years primarily due to one null randomized-controlled trial (Bernard et al., 1997), the concept of COX inhibition, and hence lipid mediator manipulation in severe inflammatory states, is regaining traction (Aronoff, 2012; Eisen, 2012). A key factor in this has been the recent publication of multiple observational data sets relating predominantly aspirin and statin administration, but also nonsteroidal anti-inflammatory agents (NSAIDs), to clinical benefit. This information, coupled with a more advanced appreciation of how inflammatory resolution pathways, and local-acting lipid mediators in particular, might impact immune competence, necessitates a careful clinical reappraisal of validity of these drugs.

Cells of the Resolution Cascade

Inflammation does not occur in isolation, but in distinct organs with quite different anatomical locations and physiological functions. The architecture of organs is very closely adapted to their function. Tissue-resident stromal cells such as fibroblasts, endothelial, and epithelial cells define the microanatomy and architecture of organs and provide the appropriate microenvironment in which specialized immune functions can occur. In addition to their landscaping properties, these stromal cells are not just passive players in immune-mediated inflammatory responses but play an active role in governing the persistence of inflammatory disease, as well as enabling immunological memory to become established in a site-specific manner (Hammerschmidt et al., 2008). The response of the immune system to tissue damage involves a carefully choreographed series of cellular interactions between immune and nonimmune cells (Figure 1). Immune cells require stromal cells in order to home to and survive within the site of inflammation. Given that all inflammatory reactions take

place within a defined background of specialized stromal cells, understanding the biology of both hematopoietic and nonhematopoietic cells is important in understanding how inflammatory cell infiltrates become established and persistent in chronic immune-mediated inflammatory diseases.

Several specialized cell phenotypes have been implicated in the resolution of inflammation (Figure 1). Monocyte-derived macrophages in particular exhibit a wide-range of phenotypic plasticity, the origins of which lie in specific tissue- and hematopoietic cell-derived stimuli (Sica and Mantovani, 2012). These lineage subtypes might exert a wide range of effects both pro- and anti-inflammatory, beneficial and detrimental, in diverse disease states (Mantovani et al., 2004) and in response to different pathogens (Mège et al., 2011). Our group has recently described a previously unknown resolution-phase macrophage denoted rM that possesses a hybrid phenotype of alternative activation, mannose receptor expression, and synthesis of IL-10 and arginase 1 (classically M2, anti-inflammatory [Gordon, 2003]) with high COX2 and iNOS expression (classically M1, proinflammatory) (Bystrom et al., 2008). This rM phenotype, inducible by elevating intracellular cAMP, is vital in encouraging innate-type lymphocyte repopulation of inflamed cavities (Bystrom et al., 2008), a key step in restoring tissue homeostasis and controlling responses to secondary infective challenge (Rajakariar et al., 2008). Transcriptomic analysis of rM has suggested a potential role in antigen processing and presentation, T and B lymphocyte recruitment, termination of inflammatory cell trafficking, and clearance, but also highlighted the naivety of attempting to rigidly define and categorize such plastic cells in a dynamic environment (Stables et al., 2011).

Medeiros and colleagues (Medeiros et al., 2009) have shown that the efferocytosis of apoptotic cells by activated macrophages causes suppression of Fc γ receptor-mediated phagocytosis and bacterial killing by an autocrine and/or paracrine PGE₂ mechanism in the lung. E-prostanoid 2 (EP2) receptor-mediated elevation of intracellular cAMP appeared to be the primary pathway with apoptotic cell-induced functional impairment, being reversed with aspirin or indomethacin pretreatment and direct EP2-receptor antagonists (Medeiros et al., 2009). Other authors have implicated transforming growth factor β (TGF- β) (Freire-de-Lima et al., 2006), potentially via PGE₂ again (directly or indirectly (Diaz et al., 1989)) or 15-LOX-derived LXA₄ (Freire-de-Lima et al., 2006), and an interferon- γ (IFN- γ) activated NO mechanism (Ren et al., 2008) as the soluble immunosuppressive mediators involved in the effect of apoptotic cells on phagocytes and their resultant function. This heterogeneity indicates that the exact pathway of apoptotic cell immune regulation is pleiotropic and might depend on the type and activation state of the efferocytosing phagocyte (Dalli and Serhan, 2012; Medeiros et al., 2009; Ryan and Godson, 2010).

More recent, as-yet-unpublished results have highlighted that these cells are phenotypically similar to myeloid-derived suppressor cells (MDSCs). In mice, MDSCs represent a heterogeneous group of GR-1⁺CD11b⁺ cells, composed of both granulocytic and monocytic subsets—the precursors of neutrophils, macrophages, and dendritic cells (DCs) (Gabrilovich and Nagaraj, 2009). They are notable for their potent ability to suppress T cell proliferation and responses, in particular Th1 cells, through production of nitric oxide and reactive oxygen species

(especially peroxynitrite), and for their expression upon activation of immune suppressive inducible nitric oxide synthase, arginase, and a range of both pro and anti-inflammatory cytokines (Gabrilovich and Nagaraj, 2009). They might also induce the de novo development of T regulatory (Treg) cells (Huang et al., 2006).

Like MDSCs, Treg cells have an increasingly appreciated role in inflammatory resolution (Venet et al., 2008). These CD4⁺ T cells are characterized by high surface expression of CD25 (IL-2R α chain), the T cell inhibitory receptor CTLA-4, the glucocorticoid-induced TNF receptor (GITR), and the transcriptional regulator forkhead box p3 (Foxp3⁺), the latter correlating with Treg cell suppressive activity (Campbell and Ziegler, 2007). Treg cells might be subdivided into natural and induced (or adaptive) Treg cells. The former arises during the normal process of maturation in the thymus, the latter developing from conventional CD4⁺CD25⁻ T cells in the periphery under specific stimulatory conditions elicited by infection and collateral tissue damage (Bluestone and Abbas, 2003). At the site of inflammation, Treg cells exert three major immunomodulatory effects: direct killing of cytotoxic cells, inhibition of proinflammatory cytokine secretion by cytotoxic cells (especially IL-2 and TNF- α), and secretion of anti-inflammatory cytokines (notably TGF- β and IL-10) (Kessel et al., 2009). Classically studied in the setting of chronic infection, the potential for Treg cell numbers, activation, and functional capacity to influence the outcome of pathogen-host interactions is well established (Belkaid and Rouse, 2005). Their role in the resolution of organ-specific autoimmune inflammation and ability to attenuate subsequent reactions has recently been described (Rosenblum et al., 2011), whereas in LPS-induced acute lung injury, depletion of Treg cells has been associated with worse outcomes (D'Alessio et al., 2009) as was abolition of their chemotactic gradient (Wang et al., 2012).

Implications for Treatment: Resolution of Inflammation without Immune Suppression?

It is now increasingly clear that the inflammatory cascade has a number of tactically placed controllers and checkpoints that limit the magnitude and duration of its response. However, the identification, isolation and molecular dissection of the new families of specialized proresolving mediators described in this review (Figure 3) will encourage a move away from focusing on the development of yet more anti-inflammatory, potentially “resolution toxic” drugs toward those that are “resolution friendly” replacement therapies (Chiang et al., 2008; Gilroy et al., 2004; Schwab et al., 2007). While the total organic synthesis of the natural SPM is challenging and costly, requiring many steps, the syntheses as well as those of biologically and chemically stable mimetics have been achieved (O'Sullivan et al., 2007; Serhan and Petasis, 2011). Along these lines, a resolvin E1 mimetic that has performed well in Phase I and II clinical trials in patients with ocular inflammation is currently in Phase III clinical trial (<http://www.anidapharma.com/science.html>; <http://www.auventx.com/auven/products/RX10045.php>; <http://www.resolve.com/news-pubs/releases/050108.asp>; <http://www.resolve.com>). Other SPMs, including PD1 and MaR1, are also in clinical development programs with the goal of stimulating the endogenous resolution programs of inflammation.

Although the SPMs and proresolving prostaglandins are attractive new therapeutic targets, they have some inherent pharmacological limitations that will need to be overcome before they can be easily adopted for clinical use. For example, time of administration in the inflammatory cascade might turn out to be critical, particularly because the tight spatial and temporal regulation of prostaglandins might be difficult to recapitulate in humans, where timing the start of an inflammatory insult can be challenging. It remains unclear whether the SPMs and proresolving prostaglandins will have any therapeutic efficacy in chronic persistent inflammation as opposed to acute, potentially resolving inflammatory conditions such as sepsis. Equally, although the differential role of lipid mediators in host defense is becoming increasingly appreciated, it must be emphasized that certain families including lipoxins and resolvins can each prime leukocytes for bacterial killing, while others, namely prostaglandins, impair this process. Considering results from research on tuberculosis infections (Bafica et al., 2005), it might be possible to tailor lipid mediators, their mimetics, and/or inhibitors of lipid mediator biosynthetic pathways in specific cell types to tackle certain classes of bacterial infections.

Developing new proresolving agents will mean producing stable, cost-effective pharmacological agents that limit leukocyte (e.g., PMN) traffic, encourage PMN apoptosis at sites of inflammation and tissue injury, as well as clearance, and help restore the stromal microenvironment to its preinflammatory state. This is likely to benefit patients with defects in the resolution of a range of diseases not only including inflammation but also infection and possibly cancer. But such an approach will require a change in philosophy away from inhibition and depletion strategies toward activation and replacement. It will also require a search for defects in the resolution of inflammation in clinical settings: leaky resolution as the cause of persistent disease rather than the lack of sufficient anti-inflammatory therapy. Perhaps only then will the next generation of compounds, namely immunoresolvents, with the potency and proresolving mechanisms of aspirin and steroids, but without the crippling side effects of bleeding and immune suppression, emerge.

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