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Discovery of Specialized Pro-Resolving Mediators Marks the Dawn of Resolution Physiology and Pharmacology

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Abstract

It is with great pleasure that I write this foreword and introduction to this Special Issue dedicated to the protective actions of the pro-resolving mediators and edited by my colleague Dr. Jesmond Dalli. Many of my collaborators and colleagues that helped to uncover the actions and clinical potential of the resolvins and other specialized proresolving mediators (SPM), namely, the superfamily of pro-resolving mediators that includes the resolvin (E-series, D-series and DPA-derived), protectin and maresin families, as well as the arachidonic acid-derived lipoxins, join me in this special issue. They have given contributions that present exciting new results on the remarkable actions and potency of these unique molecules, the SPM moving forward the importance of their mediators and pathways in human biology. Each contribution to this issue is presented by world authorities in their respective fields covering discoveries that demonstrate the importance and impact of resolution mediators in biology, medicine and surgery. While some of the authors were students and/or fellows with me and others, they are today the founding "resolutionists" of a new era of appreciation of autacoid biosynthesis and metabolomics in human health and disease with their rigorous attention to experimental detail and discovery. The chapters of this issue are filled with exciting new discoveries demonstrating the dynamics and potential of resolution mediators.

Keywords

resolvin; protectin; maresin; inflammation; omega-3; lipoxin

Introduction

Claude Bernard wrote "Physiology, pathology and therapeutics developed as distinct sciences. That was the wrong road. Only today can we begin to see the conception of an experimental, scientific medicine in the fusion of these three in a single point of view" in his

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Introduction to the Study of Experimental Medicine that appeared in France in 1865. These words remain profound today, as they teach us of the importance of a multidisciplinary approach, as we have taken, to study the molecules, mediators and mechanisms involved in the resolution phase of the acute inflammatory response. The resolution of inflammation is central to human health and its potential failure lies at the heart of many diseases where uncontrolled inflammation amplifies as well as creates illness.

Why study resolution of inflammation mechanisms and novel mediators?

In the post-genomic era, the forefront in medicine and health is controlling unwanted inflammation and infection. Hence, elucidating resolution mechanisms for inflammation can harness more effective treatments. Inflammation-associated diseases are a significant public health concern, placing considerable financial burden that impacts millions in the USA and worldwide (www.cdc.gov). It is well appreciated that human phagocytes (neutrophils & macrophages) play pivotal roles in host defense, the acute inflammatory response and its timely resolution (Colgan et al., 2013; Nathan and Ding, 2010; Serhan, 2010, 2014; Tabas and Glass, 2013). *Uncontrolled* inflammation is now widely appreciated as a unifying component in many chronic diseases including vascular diseases, metabolic syndrome, neurological diseases, and many others (Pomponi et al., 2010; Serhan et al., 2007; Tracey, 2002; Zhang and Spite, 2012). Since the acute inflammatory response is protective, evolved to permit repair of injured tissues and eliminate invading organisms (Cotran et al., 1999b), it is *ideally self-limited* and leads to complete resolution of leukocyte infiltrates and clearance of cellular debris enabling return to homeostasis (Figure 1). Although resolution of disease is appreciated by clinicians, resolution was considered a *passive* process (Cotran et al., 1999b), until our contributions (Serhan, 2004; Serhan et al., 2002) and now many others worldwide (Buckley et al., 2013; Chan and Moore, 2010; Miki et al., 2013; Rossi and Sawatzky, 2008; Wu et al., 2009) to obtain new evidence demonstrating *that resolution of self-limited inflammation is an active process*. With our strategy employing unbiased LM-lipidomics, genetically engineered animals (rabbits and mice), exudates and human cell systems, we obtained *the first evidence that resolution is* ***actively "turned on"*** *and* ***not simply*** *a passive process* (Serhan, 2007, 2009; Serhan et al., 2002; Serhan et al., 2003).

Local Mediators in Resolution

Key to our discoveries and resulting ***paradigm change*** was our identification of a novel genus of pro-resolving mediators that include *resolvins, protectins*, their aspirin-triggered forms (Buckley et al., 2013; Serhan et al., 2007) as well as the maresins (Serhan et al., 2009), which provided evidence that the resolution phase is orchestrated by local mediators and their biosynthesis from n-3 precursors EPA and DHA (Figures 2 and 3). From this, it's now become evident that ***resolution programs*** of acute inflammation hold promise and remain at the forefront of medicine and biology (Buckley et al., 2013; Haeggström and Hamberg, 2013). Challenges ahead are whether we can harness these novel mediators that *stimulate* resolution (i.e. we've coined agonists of resolution as pharmacologic agents ***immunoresolvents*** (Dalli et al., 2013b; Serhan, 2011; Serhan et al., 2012)), as disease treatments. Dietary n-3 supplements are widely used but <25% are directed by health care providers (Bailey et al., 2013). Clinical trials with n-3 fatty acids have shown mixed results

(De Caterina, 2011; Ramaswami et al., 2016; Ramsden, 2016; Roncaglioni et al., 2013). *It is clear that fatty acids themselves are not suitable drugs*. Hence, it was deemed critical for public health to establish the mechanisms that underlie their essential health requirements.

Using a systems approach with resolving exudates, we elucidated novel n-3 essential fatty acid-derived SPM pathways (Serhan, 2009; Serhan and Savill, 2005) that carry specific antiphlogistic pro-resolving actions (see Table 1); each stimulated at pico-nanogram potencies. Their biosynthesis and complete stereochemistry of each major resolvin (RvE1, RvD1, RvD2, RvD3, RvD4, RvD5 and RvD6) conferring their potent biologic actions reviewed in (Serhan, 2017; Serhan and Petasis, 2011) are the focus of our investigations (Figures 2 and 3) first established from the C.N. Serhan laboratories and now independently confirmed by many worldwide. For example, following our publications, the structures and potent pico to nanogram actions of Rv are extended to many organs including vascular (Miyahara et al., 2013), airway (Seki et al., 2010), dermal (reviewed in (Lee, 2012; Serhan et al., 2008)), ocular (Li et al., 2010), pain (Feng et al., 2012; Huang et al., 2011; Lima-Garcia et al., 2011; Xu et al., 2010; Xu et al., 2013), fibrosis, wound healing (Campbell et al., 2010; de Paiva et al., 2012; El Kebir et al., 2012; Hisada et al., 2009; Ishida et al., 2010; Jin et al., 2009; Keyes et al., 2010; Kim et al., 2012; Lund et al., 2010; Qu et al., 2012; Rajasagi et al., 2011; Vassiliou et al., 2008; Wan et al., 2011). This is also the case for D series resolvins (RvD1 (Bang et al., 2010; Hellmann et al., 2011; Li et al., 2013; Liao et al., 2012; Liu et al., 2012; Palmer et al., 2011; Rogerio et al., 2012; Settimio et al., 2012; Tang et al., 2013; Terrando et al., 2013), RvD2 (Bohr et al., 2013; Pope et al., 2016)) and neuroprotectins/ protectins (Bazan et al., 2010; Isobe et al., 2012; Kenchegowda et al., 2013; Park et al., 2011; Schwab et al., 2007; Sheets et al., 2010); each has actions in organs throughout the body and experimental animal system. Protectin D1 also stops viral replication (Morita et al., 2013), and PDx, its isomer, is also bioactive (Serhan et al., 2006; White et al., 2014), demonstrating action of host-derived mediators directly on microbes of interest in host defense.

To pinpoint SPM *in vivo* actions, we also defined the first ***resolution indices*** that permit identification of SPM and drugs that shorten *resolution intervals* (Bannenberg et al., 2005; Chiang et al., 2008; Schwab et al., 2007). These indices are now used worldwide to monitor resolution in many systems (Hilberath et al., 2011; Morris et al., 2010; Navarro-Xavier et al., 2010; Pruss et al., 2011). Focusing on human phagocyte-directed actions (i.e. phagocytosis of apoptotic PMN and bacteria) as key characteristics for SPM structural elucidation proved that SPM impact many diverse preclinical disease models (Serhan, 2010), as well as pain (Xu and Ji, 2011), wound healing, cancer (Janakiram and Rao, 2009), and tissue regeneration (Serhan et al., 2012). Several other groups have reported on total organic syntheses that confirmed our original SPM structures and stereochemical assignments (reviewed in (Serhan, 2010; Serhan and Petasis, 2011)), including PD1 (Ogawa and Kobayashi, 2011), RvD1, RvD2 (Rodriguez and Spur, 2004), RvE1 (Ogawa and Kobayashi, 2009) and RvD5 (Rodriguez and Spur, 2012). Importantly, availability of commercial Rv has help to confirm and extend their many actions in controlling inflammation-resolution (Serhan and Chiang, 2013) and even viral influenza infection (Morita et al., 2013). SPM standards and protocols for targeted LC-MS-MS that originated from my NIH-supported

research permitted identification of Rv and SPM in human tissues of healthy individuals and in human diseases (Mas et al., 2012; Psychogios et al., 2011), human adipose (Claria et al., 2013) and reduced levels in those with multiple sclerosis (Pruss et al., 2013), trout (Hong et al., 2005), and even salmon (Raatz et al., 2011); see Figure 4 and references within, and for a recent review (Serhan, 2017). Hence, these structures are conserved in evolution from fish to humans and govern potent bioactions in all major organ systems. This is because phagocytes travel throughout the body to protect each organ from invaders or to clear debris from within, a programmed response (Schwab et al., 2007). The ability of SPM to control phagocyte function is at the heart of their versatile proresolving mechanism of action throughout the organs of the body. Each resolvin and SPM has its own receptors that are GPCR (Serhan et al., 2008), which evoke rapid intracellular signaling and long-term actions via regulating specific miR involved in resolution of inflammation (Krishnamoorthy et al., 2012; Recchiuti et al., 2011).

SPM Circuits: Alpha Signals Omega

Identification of SPM and their temporal biosynthesis in vivo taught us that a) resolution is active process, not passive, b) mediators of inflammation-resolution are temporally produced to control phagocyte functions and tissue numbers (Serhan, 2011; Serhan et al., 2008; Serhan and Savill, 2005), c) SPM also control pain (Ji et al., 2011), d) help clear infections (Chiang et al., 2012) and e) SPM regulate pro-inflammatory pathways and mediators (Chiang et al., 2012; Spite et al., 2009). Most important, f) SPM are not immunosuppressive, (Chiang et al., 2012; Spite et al., 2009; Spite and Serhan, 2010) unlike many current clinically used anti-inflammatories (Dinarello, 2010). SPM enhance the killing and clearance of bacteria (Chiang et al., 2012; Oh et al., 2011), an unexpected discovery that is confirmed in other laboratories and provided a new view on drugs that can function together with pro-resolving agonists to help lower unwanted side effects and/or emergence of bacterial resistance; see Table 2. Key to the cell-cell signaling actions of SPM is their ability to activate specific G-protein coupled receptors (GPCR)(Dalli et al., 2013a). RvE1 activates two separate receptors (Serhan et al., 2011), for example, to control PMN and macrophages (Arita et al., 2007; Ohira et al., 2010). RvD1 activates GPR32, a human orphan receptor (Krishnamoorthy et al., 2010; Recchiuti et al., 2011) that regulates PMN, MΦ phagocytosis as well as resolution phase miRNA that are each regulated in GPR32-dependent MΦ responses (Krishnamoorthy et al., 2010; Recchiuti et al., 2011). Hence, it is now clear that anti-inflammation and pro-resolving actions are not equivalent. The ability of SPM to clear dead cells, bacteria and infection is unique to resolvins and other SPM, and most importantly the beginning to the inflammatory challenge signals its termination in self-limited responses *(vide infra)*.

Neural Signals for Resolution and Novel Pro-Resolving Circuits?

During inflammation-resolution, human PMN and MΦ biosynthesize specific functionally distinct profiles (Dalli and Serhan, 2012) of lipid–derived mediators **(LM).** Those that are pro-inflammatory include classic prostaglandins (PG) and leukotrienes (LT) (Samuelsson, 2012), whereas the new SPM profiles (Figure 2) are generated by phagocytes during resolution from omega-3 essential fatty acids (EFA), e.g. EPA, n-3 DPA and DHA. During

natural resolution, apoptotic PMN are lost from inflammatory sites and tissues return to homeostasis (Serhan and Savill, 2005). In contained exudates, LM production is temporally dissociated. PG and LT appear first with PMN entry, followed by LX and Rv in resolution. Apoptotic PMN switch from producing LT to SPM, revealed with targeted LC-MS-MS-based metabolomics as a key source of SPM during resolution (Dalli and Serhan, 2012). Our results demonstrated for the first time that the type of LM produced during inflammation–resolution is both spatial and temporal in mice (Schwab et al., 2007; Serhan et al., 2002) and with isolated human PMN and MΦ (Dalli and Serhan, 2012). Also, LM in resolution of Lyme disease (Blaho et al., 2009), infections (Chiang et al., 2012) and the temporal role of leukocyte lipoxygenase in these are now being appreciated (Blaho et al., 2011). Hence, endogenous circuits that control resolution of acute inflammation are of general interest and operative throughout the whole organism and human body. Communications between brain and innate immune functions such as vagus nerve are of particular interest given its ability to signal anti-inflammatory pathways (Tracey, 2002). We found that vagus nerve controls resolution of acute inflammation via activating a novel resolvin circuit (Mirakaj et al., 2014).

Each of the SPM, given their unique structures and roles, opens new opportunity for treating human disease. For an example of this possibility, let's take the stereochemical assignment of SPM, i.e. RvD2 (7*S*,16*R*,17*S*-trihydroxy-4*Z*,8*E*,10*Z*,12*E*,14*E*,19*Z*-docosahexaenoic acid); this enabled us to uncover that RvD2 regulates both PMN and MΦ to limit tissue damage and enhance killing and clearance of bacteria (Spite et al., 2009). RvD2 controls murine survival in sepsis from cecal puncture (Spite et al., 2009), prolongs survival in severe burn and sepsis, (Jones et al., 2012; Kurihara et al., 2013) reduces colitis (Bento et al., 2011) and is temporally elevated during transition *from* initiation to resolution phase (Dalli et al., 2013b). These new findings point to specific functions of RvD2 and SPM (Table 2) in activating resolution (Chiang et al., 2015) and are responses activated by specific GPCR (Chiang et al., 2015; Chiang et al., 2017). We have approached the work up and elucidation of each SPM family member in a similar fashion, giving them more than factor status.

Neural Control of Resolution SPM: A New Link?—Vagus nerve exerts local anti-inflammatory effects (Tracey, 2002) that we found to directly govern resolution. Hence, it is important to establish the molecules and mechanism(s) involved. Vagotomy disrupts resolution and human MΦ incubated with acetylcholine (Ach) produce RvD1 and RvD2 (Mirakaj et al., 2014). Thus, we determined the impact of vagus control of resolution on LM/SPM biosynthesis with unbiased LM-lipidomic/metabolomic profiles, and establish the human RvD2 circuit and its human disease expression (Mirakaj et al., 2014), a new circuit that is also operative in PCTR production (Dalli et al., 2017).

Relationship of SPM in the World of Eicosanoids: Birth of the Resolvins & SPM

The history of the prostaglandins and their roles in physiologic processes date back to the 1930's, with relaxation of myometrium (Weissmann, 1980). While von Euler coined the name prostaglandins for these active substances, it soon became clear that they were not produced by the prostate gland. Bergström and colleagues at the Karolinska determined the

structures of the main prostaglandins in the late 1950's, and in the early 1960's Samuelsson established that arachidonic acid was the precursor, and biosynthesis of intermediates are rapidly converted from arachidonic acid to prostaglandins and other potent mediators.

Prostaglandins act on smooth muscle, gut, airway and blood vessels. Sir John Vane and his colleagues demonstrated that aspirin and other NSAIDs of the time blocked cyclooxygenase (Vane, 1982). Thromboxane A_2 and prostacyclin were identified next, and their roles in platelet aggregation and vasodilation elucidated (Samuelsson, 1983). Each of the cardinal signs of inflammation, known to physicians of ancient societies, *rubor, tumor, dolor* and *functio laesa*, are evoked by these potent mediators from arachidonic acid, thromboxanes, prostaglandins and prostacyclin (Vane, 1982; Weissmann, 1980). Next to arrive on the world map of autacoid biosynthesis and metabolomics from the arachidonic acid cascade was the structural elucidation of the leukotrienes, which are the slow-reacting substances of anaphylaxis (SRS-A). These leukocyte-derived conjugated trienes LTC_4, LTD_4 and LTE_4 are potent mediators in anaphylaxis, and leukotriene B_4 is a potent chemoattractant of human neutrophils (Samuelsson, 1983).

Confusion on Omega-3 PUFA in Human Health: Novel Role in Resolution of Inflammation

Numerous reports of the past ~40 years suggest that supplementation of dietary omega-3 polyunsaturated fatty acids (ω-3 PUFA) has beneficial effects in human diseases and laboratory animals (De Caterina et al., 1993; Lands, 1987). These include antithrombotic, immunoregulatory and anti-inflammatory responses relevant in arteriosclerosis, arthritis and asthma (De Caterina et al., 1993) as well as antitumor and antimetastatic effects (Iigo et al., 1997). Their potential for preventative actions in cardiovascular diseases was bolstered with the finding that major dietary ω-3 PUFAs, eicosapentaenoic acid (C20:5 ω-3; EPA) and docosahexaenoic acid (C22:6 ω-3; DHA) have a dramatic effect on ischemia-induced ventricular fibrillation and can protect against sudden cardiac death (Billman et al., 1999). Emergence of such preventative and/or therapeutic actions of ω-3 PUFA supplementation in infant nutrition, cardiovascular diseases and mental health called for recommended dietary intakes by an international workshop (Simopoulos et al., 1999). However, the molecular mechanisms(s) for dietary ω-3 protective actions remain unexplained at the cellular and molecular levels and still a subject of wide interest.

At the time, it was widely believed that the actions of the major lipid of fish oil are caused by i) preventing conversion of arachidonic acid (C20:4 ω-6, AA) to proinflammatory eicosanoids (i.e., PG and leukotrienes (LT)); ii) serving as an alternate substrate producing 5-series LT that are less potent; and/or iii) conversion by cyclooxygenase (COX) to 3-series prostanoids (i.e., PGI_3) with potencies equivalent to their 4-series PG counterparts to maintain antithrombotic actions (Billman et al., 1999; De Caterina et al., 1993; Iigo et al., 1997). These and other explanations offered (Billman et al., 1999; De Caterina et al., 1993; Iigo et al., 1997; Simopoulos et al., 1999) are not embraced by us because of the lack of molecular evidence and the high concentrations of ω-3 PUFA required to evoke putative beneficial actions. Although the proinflammatory roles of LT and PG are well appreciated

(Marcus, 1999; Weissmann, 1991), new evidence emerged regarding other eicosanoids derived from arachidonate, namely lipoxins (LXs) and their endogenous analogs, the aspirin-triggered 15-epimer lipoxins (ATL), potent counterregulators of PMN-mediated injury and acute inflammation (Chiang et al., 1999; Clària and Serhan, 1995; Serhan et al., 1995). Acetylation of COX-2 by aspirin (ASA) prevents the formation of prostanoids (Herschman, 1998), but the acetylated enzyme remains active *in situ*, generating 15*R*-hydroeicosatetraenoic acid (15*R*-HETE) from C20:4 (Chiang et al., 1998; Xiao et al., 1997), which is converted by inflammatory cells to 15-epimeric lipoxins (ATL, a.k.a. aspirin-triggered lipoxins). Synthetic analogs of these natural local mediators with prolonged bio-half-life display potent anti-inflammatory properties (Chiang et al., 1999; Clish et al., 1999; Serhan, 1999), providing evidence that cell-cell “cross-talk” can convert arachidonic acid to mediators with anti-inflammatory properties (Serhan et al., 2000b), thus changing our view of the mechanism of action of this drug. Importantly, LX and ATL stimulate monocytes in a non-phlogistic fashion (Maddox et al., 1997; Maddox and Serhan, 1996), suggesting their role in monocyte/macrophage-mediating processes, i.e. tissue repair, healing and resolution. Hence, aspirin enables the endogenous resolution mechanisms and programs unlike other NSAIDs.

Since PMN-vessel interactions are pivotal to recruitment and PMN-dependent tissue injury (Cotran et al., 1999a), the local signals involved in their “cross-talk dialog” were our interest and starting point in this line of investigation. Our finding that aspirin-acetylated COX-2 remains active *in vivo* (Chiang et al., 1998) to generate specific ATL that can be effectors of well-established anti-inflammatory therapy offers a mechanism for ASA beneficial impact that cannot be attributed to prostanoids (Herschman, 1998; Marcus, 1999). Because new therapeutic uses for aspirin and related NSAIDs continue to be uncovered that require molecular definition, including prophylaxis against colorectal cancer and lower risk of myocardial infarction (Levy, 1997), and in view of overlapping beneficial profiles assigned to dietary ω-3 PUFA in human disease (Billman et al., 1999; De Caterina et al., 1993; Iigo et al., 1997; Simopoulos et al., 1999), we first sought evidence for novel mechanisms involved in the biosynthesis and production of lipid-derived signals that would provide a basis as well to explain some of the beneficial actions of ω-3 PUFA (Serhan et al., 2000a). Aspirin jump-starts resolution by triggering novel lipid mediators.

The resolution of inflammation has origins in the Canon of Medicine, which was brought to Europe in the 11th Century (Avicenna (Abu ^{c}Ali Sina) adapted by Laleh Bakhtiar, 1999; Serhan, 2011). The connection of omega-3 PUFA to novel mediators and resolution was elucidated with identification of novel structures of the SPM and new (Table 1) proresolving actions (Serhan and Savill, 2005). Earlier studies suggested that the omega-3 PUFA simply become prostaglandins, thromboxanes, or leukotriene-like structures that were without potent bioactivities. The discovery of novel structures that were previously unknown which stimulate resolution of inflammation and infection by evoking new biological functions has opened this area of investigation and the biology of resolution and resolution pharmacology. Thus, the SPM super-family members are each both tool compounds as well as physiologic mediators.

Temporal lipid mediator class (and family) switching (Figure 1) is central to this biosynthesis for active resolution (Levy et al., 2001). In addition to the resolvins, protectins and maresins (Hong et al., 2003; Serhan et al., 2002), conjugates of the epoxide intermediates in each of the SPM pathways were uncovered in recent studies; these novel SPM-peptido conjugates enhance tissue regeneration and bacterial killing and clearance; namely, these series are coined respectively MCTR, RCTR and PCTR, the maresin, resolvin and protectin **c**onjugates in **t**issue **r**egeneration CTR (Dalli et al., 2014; Dalli et al., 2015b). Their complex structures and potent actions underscore the critical role and importance of the specific epoxide-containing intermediates in SPM biosynthesis, stereochemistry and function (Aursnes et al., 2015; Serhan et al., 2015). Hence, resolution-phase mediators help control inflammation, infection and tissue regeneration, major essential processes that protect the host. Each member of the structurally distinct families evokes the cardinal signs of resolution of inflammation (Dalli et al., 2015a) to bring about resolution via counter regulation of pro-inflammatory mediators, giving them their unprecedented dual anti-inflammatory, proresolving status (Table 3).

The major hubs of PUFA-derived signaling families of molecules depicted in Figure 5 are involved in the initiation and resolution of inflammation. These molecules can also be used as biotemplates for designer drugs and new therapeutics that can control inflammation by stimulating resolution (Lee and Zeldin, 2015; Leslie, 2015; Serhan, 2014), namely resolution agonists. Now that the resolvin and lipoxin structures have opened the path to resolution of inflammation, many other resolution-phase mediators have been discovered including hydrogen sulfide gas, annexin peptides and carbon monoxide, to name a few (Perretti et al., 2015). There will likely be many more discoveries in the years ahead that will demonstrate the importance of resolution-phase mediators such as the resolvins, as well as their impact in human biology and potential in clinical development of novel therapeutics for a wide range of diseases. The contributions in this special issue can thus serve as a guide by experts to navigate the sea of resolution signals and the impact of the SPM pathways and superfamily of SPM mediators in human health, personalized medicine and nutrition as well as disease, hence marking the dawn of resolution physiology and pharmacology.

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Abbreviations

DHA
docosahexaenoic acid

EPA
eicosapentaenoic acid

LC-MS-MS
liquid chromatography tandem mass spectrometry

LM
lipid-derived mediators

LOX
lipoxygenase

LT
leukotriene

LX
lipoxin

PG
prostaglandins

МΦ
macrophage

Maresins
macrophage mediators in ***res***olving ***in***flammation

PMN
polymorphonuclear leukocyte

PD protectin PD1/NPD1
protectin D1/neuroprotectin D1

SPM
specialized pro-resolving mediators

Rv, Resolvins
bioactive omega-3 derived ***resol***ution phase ***in***teraction products

E series Rv
resolvins from EPA

D series Rv
resolvins from DHA

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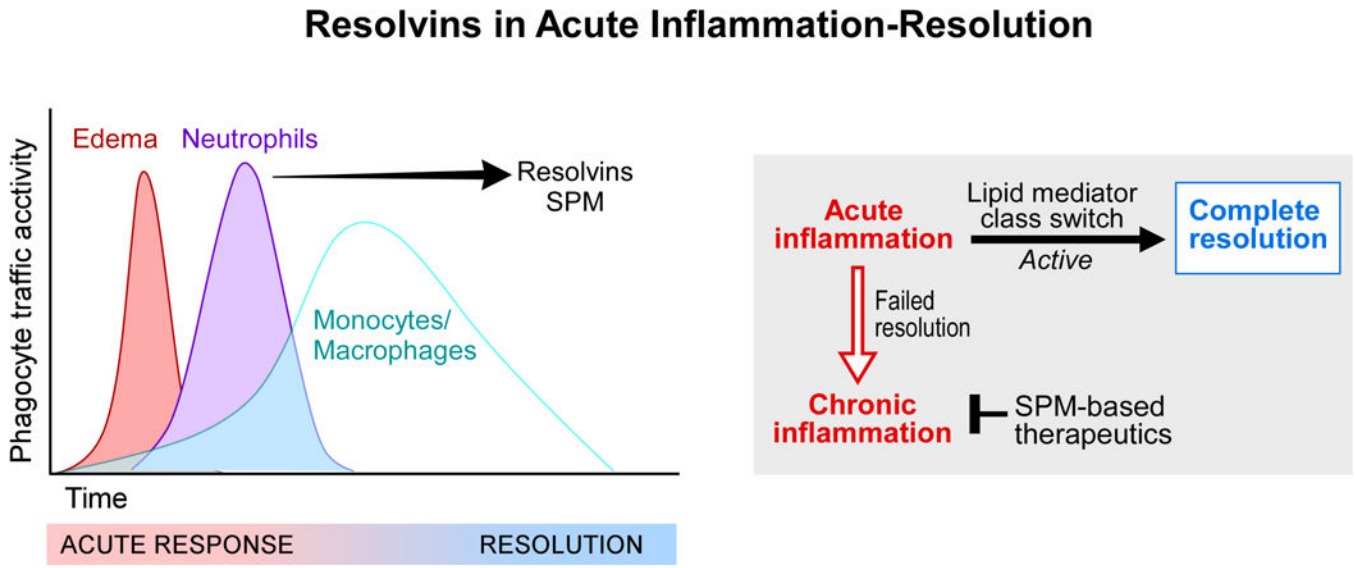

Figure 1. Function of Resolvins and Superfamily of SPM in acute inflammation resolution

(Left) In self-limited inflammation, acute vascular and leukocyte trafficking are rapid and protective to rid the host of invaders, resolving with time to return to homeostasis, namely the loss of pus and inflammatory exudate cells from the site to return to function of the tissue. Edema and neutrophil infiltration are governed by chemoattractants, both exogenous (microbial derived) and endogenous, such as leukotriene B_4 and chemokines. Resolvins and other SPM are temporally biosynthesized when neutrophils reach maximal numbers and begin to reduce in number from the inflamed site in tissues. Monocytes and resolution-phase macrophages (Stables et al., 2011) enter in a nonphlogistic fashion to help repair and remodel tissues as needed for complete resolution of the site.

(Right) Lipid mediator class switching is the process we introduced (Levy et al., 2001) to describe the temporal change in lipid mediators from initiation of inflammation to resolutionphase mediators as a biosynthetically active process, switching from PG and LT production to translational regulation of the leukocyte enzymes required to biosynthesize lipoxins, protectins and D-series resolvins. Failed resolution mechanisms may be responsible for persistent recurring bursts of acute infiltrates of leukocytes that can lead to chronic inflammation and the amplification of tissue injury. The potential of SPM-based therapeutics exemplifies a new approach, namely “one-to-many” counter-regulating pro-inflammatory targets to stop the progression (Business Wire, 2009) to chronic is depicted.

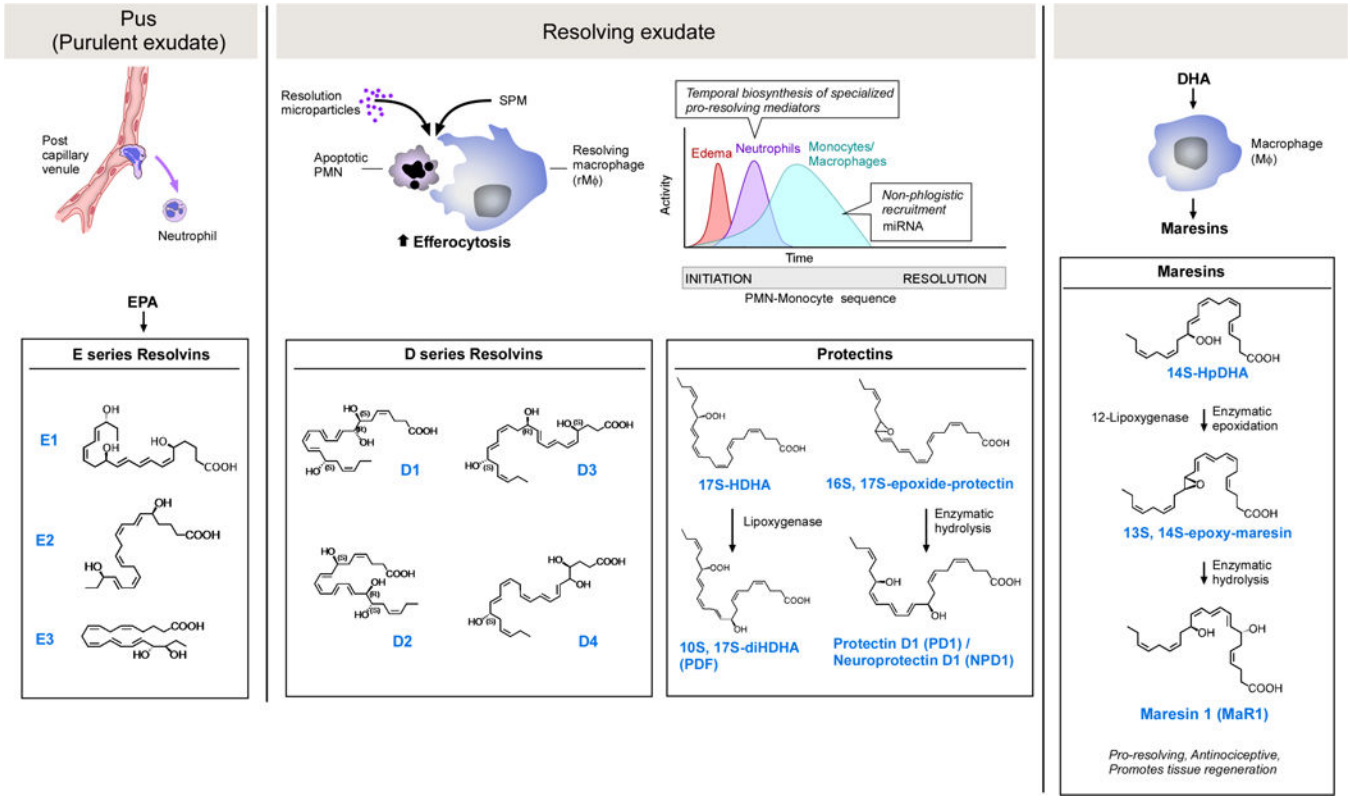

Figure 2. Resolvins, protectins and maresins in the frame of resolution of inflammation

(Left) Pus production from the first step of PMN-endothelial interactions is the nidus of E-series resolvin formation and actions, with three separate potent bioactive molecules produced. Microparticles, macrophages and apoptotic PMN produce resolvins and SPM (Dalli and Serhan, 2012), which enhance phagocytosis and limit further PMN infiltration. D-series resolvins are biosynthesized from DHA; four are depicted, six are currently elucidated and functionally defined. Maresins and protectins are also produced in inflammatory exudates from DHA. The potent PD1/neuroprotectin D1 is biosynthesized via an epoxide intermediate that is synthesized and confirmed via total organic synthesis, as is the eMaresin 13(14)-epoxide (see text for details). The 17S-hydroperoxy precursor to 10*S*,17*S*-diDHA, a.k.a. PDx, gives the trans-cis-trans conjugation (Serhan et al., 2015; Serhan et al., 2006). The complete stereochemistry of each resolvin, protectin and maresin is established, and their potent stereoselective actions are confirmed.

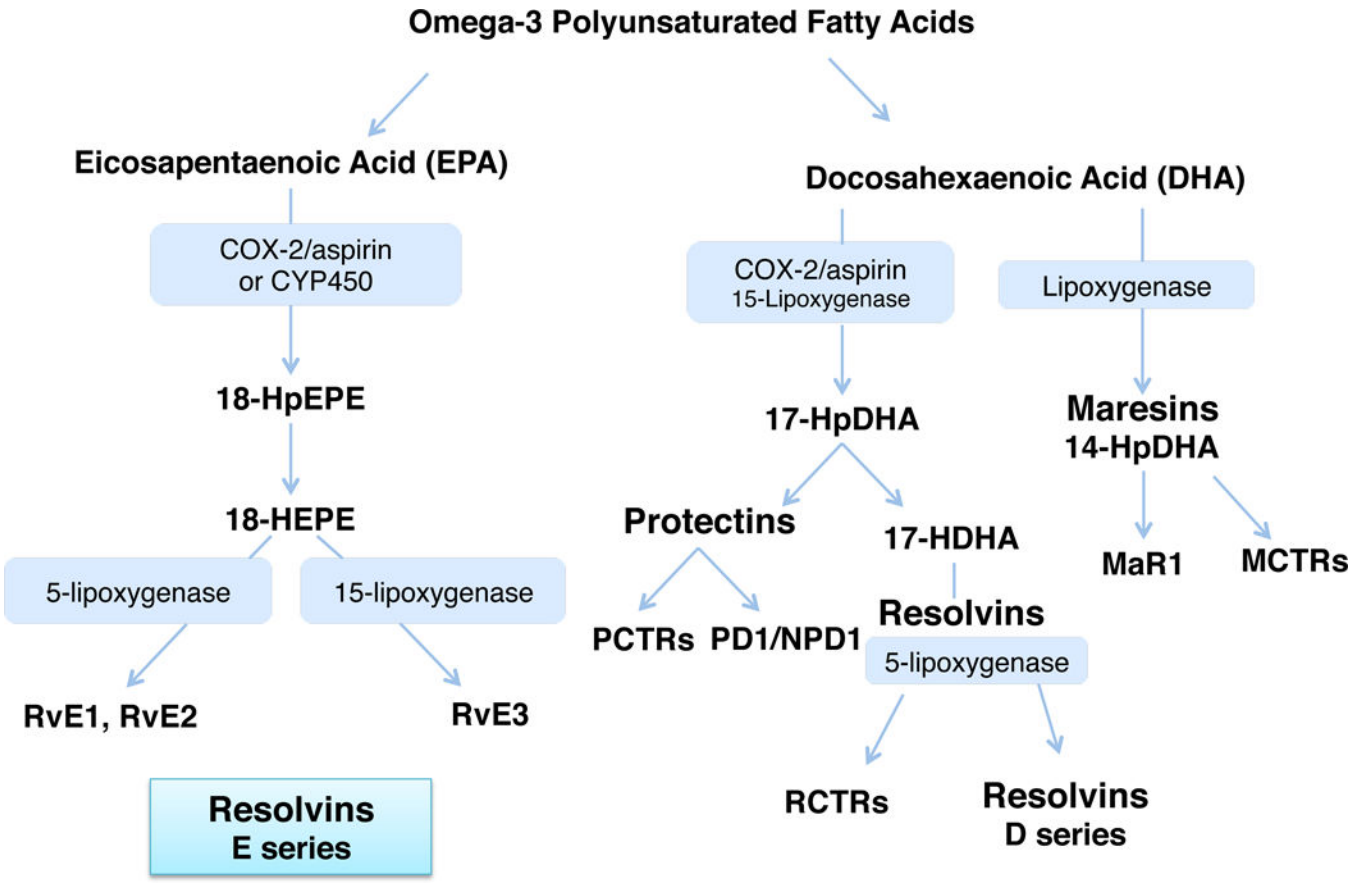

Figure 3. Biosynthesis routes for resolvins and SPM

The main biosynthesis routes are depicted. Each was confirmed via label tracking of precursors and intermediates as well as trapping of proposed intermediates. In addition to lipoxygenase-initiated pathways that produce mediators with alcohols, for example in PD1 or D-series resolvins in predominantly the 17*S* configuration, aspirin acetylation of cyclooxygenase-2 (COX-2) produces intermediates predominantly in the R configuration at the 17-carbon position producing the 17*R* epimers of 17*R*-PD1 and D-series resolvins coined the aspirin-triggered resolvin and protectin mediators. Statins can also lead to S-nitrosylation of COX-2 that, like aspirin acetylation, changes the enzyme's catalytic site or produce R epimer-containing intermediates (see text for details).

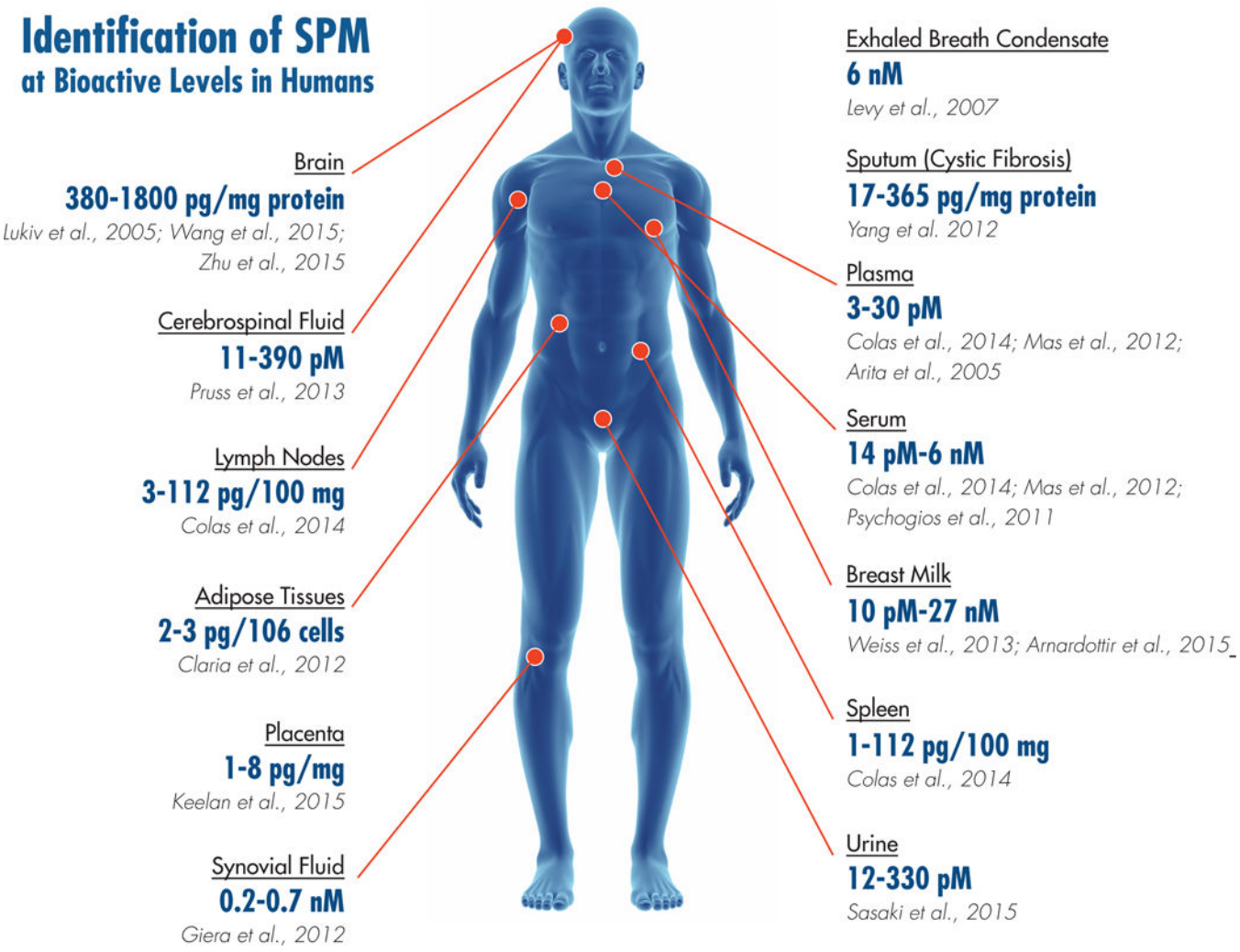

Figure 4. Identification of resolvins and SPM in vivo

Illustration depicts the location of SPM identified by rigorous LC-MS-MS-based methods that are present in concentrations that are bioactive in experimental model systems in vivo. See accompanying references in Figure 4.

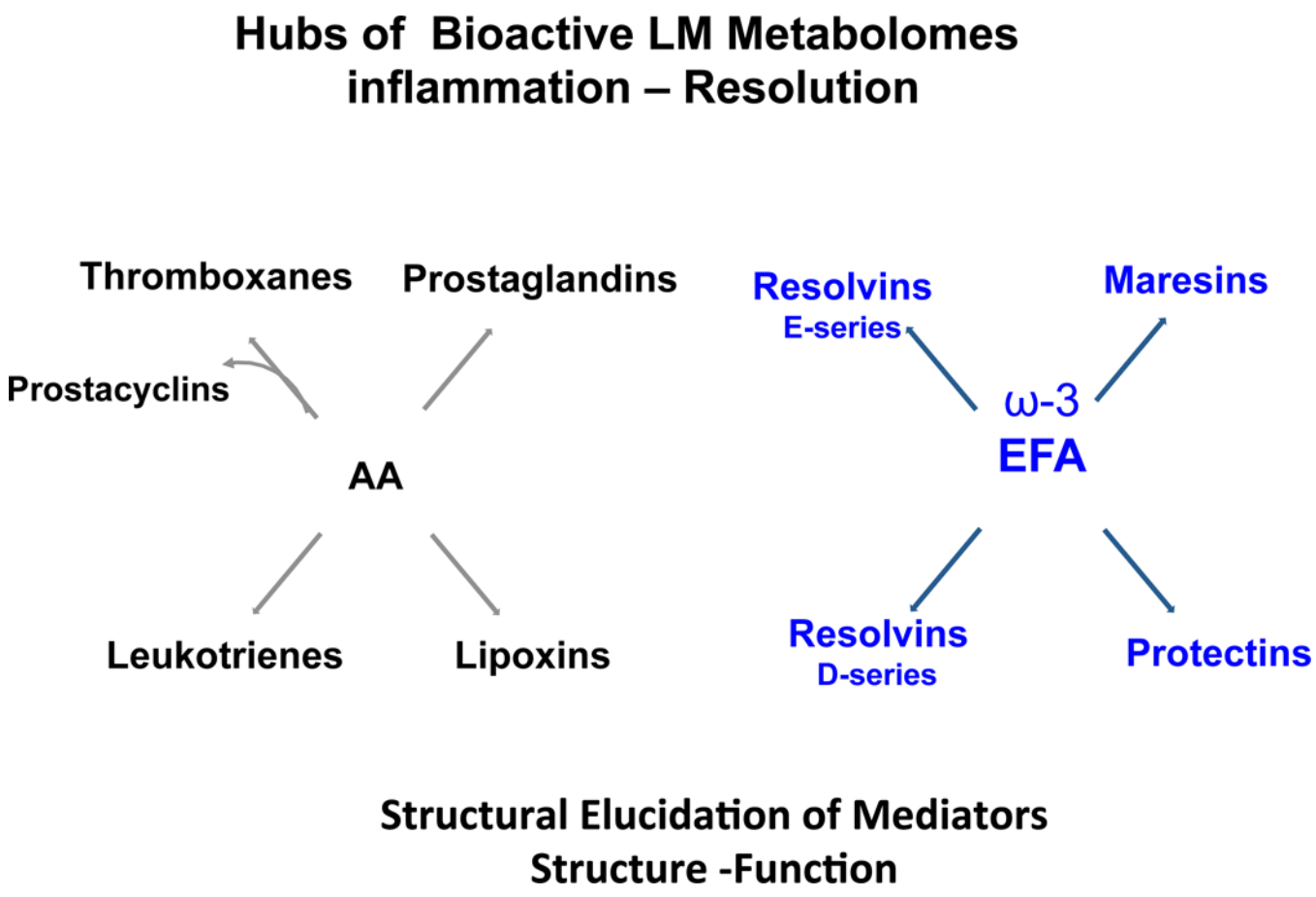

Figure 5. Hubs of conserved bioactive lipid mediator metabolomes

(Left) The arachidonic acid-derived mediators.

(Right) The ω-3 essential fatty acid-derived mediators.

These families and their function illustrate the importance of structural elucidation in metabolomics based on structure-function in biologic and human systems.

Table 1

Specialized Pro-resolving Mediators (SPM): Anti-Phlogistic Pro-Resolving Actions

SPM defining bioactions
• Temporal stereospecific biosynthesis with leukocyte exudate traffic
• Cessation of PMN infiltration; stop signals to limit further PMN recruitment and stop PMN-mediated tissue damage
• Enhance macrophage phagocytosis of apoptotic PMN, cellular debris and bacteria killing
• SPM have broad anti-inflammatory and pro-resolving actions
• Actions at both transcriptional and translational level, miR
• SPM act via specific receptors in pico to nanomolar range in stereoselective fashion
• Shorten time to resolution and activate endogenous resolution programs

Table 2

SPM Shorten Resolution of Infections, Increase Survival and Outcomes in Murine Infection & Disease Models

SPM	Increase Survival	Disease	Shorten resolution intervals R_i	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)
	+	Candida yeast	+	(Haas-Stapleton et al., 2007)
	+	Acid-induced lung injury	+	(Levy and Serhan, 2014)
RvD5, PD1	+	*E. coli* infection	+	(Chiang et al., 2012)
RvD1, RvD5, PD1	+	Acute lung injury	+	(Wang et al., 2011)
RvD2	+	Cecal ligation and puncture sepsis	+	(Chiang et al., 2017; Spite et al., 2009)
RvD2	+	Burn wound sepsis	+	(Bohr et al., 2013)
RvD2 **RvD3** **RvD4** **MCTRs**	+ +	Burn wound sepsis Aging mice, peritonitis Skin Inflammation peritonitis, organ protection	+ + + +	(Bohr et al., 2013) (Arnardottir et al., 2014) (Winkler et al., 2016) (Dalli et al., 2014)

Table 3

Counter-Regulate & Reduce Cardinal Signs of Inflammation

- Prostaglandins (COX-2 expression) and leukotrienes (LTB_4, LTC_4, LTD_4)
- PAF formation and actions
- Chemokines and cytokines (TNFa, IL-1, IL-6, IL-8, IL-12, etc.)
- $NF\text{-}_kB$ associated gene products
- Growth factors (VEGF)
- Extracellular ROS
- Edema
- Reduce Pain