Proresolving Lipid Mediators and Receptors in Stem Cell Biology: Concise Review

MARIO ROMANO a,b,c, SARA PATRUNO a,b,c, ANTONELLA POMILIO a,b,c, ANTONIO RECCHIUTI a,c

a Department of Medical, Oral, and Biotechnological Sciences, “G. D’Annunzio” University of Chieti-Pescara, Chieti, Italy; b StemTech Group, “G. D’Annunzio” University of Chieti-Pescara, Chieti, Italy; c Center on Aging Sciences and Translational Medicine (CeSI-MeT), “G. D’Annunzio” University of Chieti-Pescara, Chieti, Italy

SUMMARY

Accumulating evidence indicates that stem cells (SCs) possess immunomodulatory, anti-inflammatory, and pro-healing properties. The mechanisms underlying these functions are being investigated with the final goal to set a solid background for the clinical use of SCs and/or their derivatives. Specialized proresolving lipid mediators (SPMs) are small lipids formed by the enzymatic metabolism of polyunsaturated fatty acids. They represent a leading class of molecules that actively and timely regulate the resolution of inflammation and promote tissue/organ repair. SC formation of these mediators as well as expression of their receptors has been recently reported, suggesting that SPMs may be involved in the immunomodulatory, proresolving functions of SCs. In the present review, we summarize the current knowledge on SPMs in SCs, focusing on biosynthetic pathways, receptors, and bioactions, with the intent to provide an integrated view of SPM impact on SC biology. Stem Cells Translational Medicine 2019;8:992–998

SIGNIFICANCE STATEMENT

Harnessing stem cells (SCs) for immunoregulatory and regenerative purposes represents a pivotal goal in SC-related therapeutics. A proper knowledge of SC capability to release and/or respond to agents that promote the resolution of the inflammatory response as well as tissue/organ repair is key to develop innovative approaches, based on SCs, to treat diseases characterized by ongoing unresolved inflammation.

INTRODUCTION

In recent years, the involvement of stem cells (SCs) in inflammation resolution and tissue/organ protection programs has been established by numerous in vitro and in vivo studies (reviewed by Munir et al.) [1]. Such evidence has fueled great interest into the possibility to use SCs for the treatment of diseases characterized by ongoing chronic inflammation. To this end, a better knowledge of the mechanisms involved in SC modulation of the immune-inflammatory response is needed.

The resolution of inflammation is a well-organized process orchestrated by a variety of mediators released by bone marrow (BM), blood, and resident cells [2]. It is now established that the termination of an acute inflammatory event is an active process governed by the timely formation of proresolving mediators. Among these, the so-called specialized proresolving lipid mediators (SPMs), which originate from the enzymatic metabolism of polyunsaturated fatty acids, that is, arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA), represent a large class of small lipid molecules with well-documented potent proresolving bioactions in vitro and in vivo [3]. Differently from classical anti-inflammatory molecules, SPMs modulate, without completely suppressing, proinflammatory mechanisms while reprogramming the host immune response to promote tissue and organ repair and return to homeostasis [3].

We recently uncovered SPM biosynthesis by SCs from the human periodontal ligament (hPDLSC) as well as receptor-mediated modulation of hPDLSC functions by the SPM lipoxin (LXA4) (see below) [4]. These results suggest that SPMs and related receptors may play a role in SC biology. In this article, we will review the current literature on the impact that SPMs and related receptors may have on SC biology, focusing on two main questions:

1. Do SCs generate SPMs as part of their proresolving program?
2. Do SPMs exert proresolving actions by modulating SC recruitment and functions?

Correspondence: Mario Romano, M.D., Department of Medical, Oral, and Biotechnological Sciences, “G. D’Annunzio” University of Chieti-Pescara, CeSI-MeT, via Luigi Polacchi, 13, 66100 Chieti, Italy. Telephone: 39-0871-541475; e-mail: mromano@unich.it

Received March 14, 2019; accepted for publication May 19, 2019; first published June 12, 2019. © AlphaMed Press 1066-5099/2019/$30.00 http://dx.doi.org/10.1002/sctm.19-0078

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
SPMs Biosynthesis and Bioactions

SPMs Derived from AA

LXs and Aspirin-Triggered Lxs

LX (an acronym of “lipoxygenase interaction products”) A4 and B4 were the first SPMs identified by Serhan et al. as derived from the enzymatic conversion of AA by the cooperation of different lipoxygenases (LOs) during cell–cell interactions [5]. At least three enzymatic pathways lead to the formation of LX.

A main biosynthetic pathway involves the cooperation between leukocyte 5-LO and platelet (PLT) 12-LO. In peripheral blood polymorphonuclear (PMN) leukocytes, AA is metabolized by 5-LO to synthesize leukotriene (LT)A4, which is transferred to interacting PLT at sites of injury or thrombosis, where 12-LO converts LTBA4 into LX [6–8]. In vivo, this pathway accounts for LX generation during coronary angioplasty and strenuous exercise [9, 10].

In mucosal tissues, 15-LO, abundantly present in epithelia, converts AA into 15-hydro(peroxy)-eicosatetraenoic acid (15-H pETE). Following diapedesis and interactions of white blood cells with epithelial and endothelial cells, 15-H(p)ETE is taken up by leukocyte 5-LO to produce LXA4 and B4 [11]. Notably, human alveolar macrophages (MΦ) expressing 15-LO and 5-LO are singular cell sources of LX in the airways [12].

A third LX biosynthetic route is initiated by cyclooxygenase (COX)-2. In vascular endothelial and colonic epithelial cells, acetylation by aspirin makes COX-2 a “lipoxygenase-like” enzyme capable of introducing a single hydroxyl-group at C15 of AA with the R configuration. The resulting 15R-HETE is a substrate for 5-LO expressed by leukocytes interacting with endothelial and epithelial cells. As a result, epimeric LXA4 and B4 are produced and termed 15-epi-LX or “aspirin triggered” LX (ATL) [13]. ATL biosynthesis can be triggered by statins and pioglitazone [14–16] as well as by COX-2 acetylation by sphingosine-1-phosphate in neural tissues [17]. Evidence of ATL generation in humans following aspirin administration has been provided by independent studies [18, 19].

SPMs Derived from EPA

E-Series Resolvins

Studies by Serhan et al. first showed that in human endothelial cells exposed to hypoxia or inflammatory cytokines, aspirin-triggered (AT) COX-2 utilizes EPA to generate 18R-hydro(peroxy)-eicosapentaenoic acid (HEPE) [20]. This intermediate can be further modified by leukocyte 5-LO into Resolvin (Rv, from “resolution phase interaction product”) E1 [21].

Interestingly, 18R-HEPE is the dominant isomer in plasma from human volunteers taking EPA, whereas aspirin promotes 18S-HEPE as well as 18R-HEPE production following dietary supplementation of EPA [22]. Both 18R-HEPE and 18S-HEPE can be converted to the corresponding 18R-RvE1 or 18S-RvE1 by 5-LO and LTA4 hydrolase [21] and cytochrome P450 [20, 23]. Reduction of 18R-HEPE leads to the formation of RvE2 [24], whereas 12/15-LO in eosinophils converts this intermediate into 18R-RvE3 and epimeric 18S-RvE3 [25].

SPMs Derived from DHA

D-Series Resolvins

Metabololipidomic analyses of murine resolving exudates and human cells identified a novel set of dihydroxy- and trihydroxy-DHA derivatives that proved highly potent in dampening inflammation in vivo and in vitro and were named D-series Resolvins (RvD) [26].

Enzymatic pathways underlying their biosynthesis have been defined. For instance, RvD1 can be generated by transcellular exchanges between endothelial cells and PMN involving 15-LO that converts DHA into 17S-hydroperoxy-DHA and 5-LO that catalyzes conversion into RvD1 [26]. In the presence of aspirin-acetylated COX-2, DHA is converted into 17R-hydroperoxy-DHA giving rise to AT-RvD1 [27]. RvD1, AT-RvD1, and RvD2 [28] are the best characterized members of the RvD family, whereas the complete stereochemistry and some bioactions of other members of this family (i.e., RvD3-6 and corresponding AT-epimers) have been recently established (reviewed by Serhan) [29].

(NEURO)Protectins

In addition to RvD, DHA can be converted into a second family of dihydroxy-containing SPMs termed protectins (PD). PD generated in neural tissues are also called neuroprotectins in order to emphasize the site of their beneficial actions (e.g., protection of retina and brain from injuries). The founding member of this family was initially identified as a 10,17S-docosatriene [30] and termed PD1. A 17R epimer of PD1 is formed in the presence of acetylated aspirin and termed AT-PD1 [31].

Maresins

A fourth family of SPMs from DHA are maresins (from macrophage mediator in resolving inflammation). Two members of this family, MaR-1 and MaR-2, are produced by MΦ and PLT-PMN through the action of 12-LO [32].

SPMs Conjugated in Tissue Regeneration

Recent studies by Serhan et al. have identified distinct families of SPMs arising from the conjugation of epoxy-DHA to gluta-thione (GSH) in exudates, tissues, and body fluids (including human blood and breast milk). In view of their tissue protective actions held in vivo, this set of cysteinyl-SPMs is referred as “SPM conjugated in tissue regeneration” (CTR).

Upon direct conjugation of GSH to 13,14-epoxy-maresin (an intermediate of MaR-1 and MaR-2 biosynthesis) by GSH transferase, also known as LTC4 synthase, and sequential cleavage of peptide bonds by peptidases, the following maresin conjugated in tissue regeneration (MCTR) are formed: MCTR1 (13-glutathionyl-14-hydroxy DHA), MCTR2 (13-cysteinylglycinyl-14-hydroxy DHA), and MCTR3 (13-cysteinyl-14-hydroxy DHA) [33–35]. In addition, attack of GSH at the 7,8-epoxide intermediate of RvD yields resolvin conjugate in tissue regeneration 1 (RCTR1) that is in turn cleaved into RCTR2 by γ-glutamyltranspeptidase and into RCTR3 via peptidases [3, 36]. Finally, conjugation of GSH at C16 of 16S,17S-epoxy-protectin methyl ester produces protectin conjugated in tissue regeneration 1 (PCTR1), which is converted into PCTR2 and PCTR3 [37].

SPMs Derived from DPA

In mammalian cells, ω-3 DPA is an ω-3 fatty acid precursor of DHA that serves as a biological substrate for the biosynthesis of SPM congeners of D-series Rv, MaR, and PD. Main members of the ω-3 DPA SPM family are RvDn−3 DPA, MaRn−3 DPA [38], and RvD5n−3 DPA [39]. Finally, bioactive molecules derived from DPA carrying an OH-group at carbon 13 and biosynthesized upon nitrosylation of COX-2 by statins have been identified.
and named 13-series resolvins (RvT) [40]. The SPM biosynthetic pathways are summarized in Figure 1.

**Bioactions**

SPMs share a wide array of target cells, including leukocytes, PLTs, lymphocytes, endothelial and vascular smooth muscle cells, epithelial and mesangial cells, osteoclasts, and microglial cells (reviewed by Recchiuti et al.) [41], thus modulating a large number of functions of these cells and their interactions. For instance, select SPMs limit the release of proinflammatory chemokines and cytokines as well as the expression of adhesion molecules, leukocyte trans-epithelial and transendothelial migration, reactive oxygen species (ROS) production, and PLT aggregation, while promoting the M2 phenotype of macrophages, efferocytosis and bacterial killing, nitric oxide, and prostacyclin release [41]. SPMs and their stable analogs have consistently demonstrated proresolving and tissue protecting activities in numerous experimental diseases including acute lung injury, peritonitis, colitis, sepsis, periodontitis, arthritis, cystic fibrosis, asthma, acute lung injury, eye diseases, obesity and diabetes, renal fibrosis, ischemia/reperfusion, and vascular injury [41].

**SPM Generation by SCs**

Direct evidence of SPM generation by human SCs isolated from the periodontal ligament (hPDLSC) has been recently provided by a collaborative study between our group and Dr. Serhan’s laboratory [4]. Using liquid chromatography–tandem mass spectrometry metabololipidomics, we detected hPDLSC production of resolvins (both D and E series), PD1, MaR, LX, and ATL. Interestingly, prostaglandin (PG)E2 was the most abundant lipid mediator formed by hPDLSC [4]. Although PGE2 is released in the early phases of inflammation and carries proinflammatory bioactions, it is also pivotal to start resolution [42] and to orchestrate immunosuppression in the postresolution phase of inflammation (reviewed by Feehan and Gilroy) [43]. Along these lines, PGE2 has been identified as a main determinant of the immunoregulatory functions of SCs from varying sources [44].

SPMs were also detected in mouse BM mesenchymal stromal cells (MSCs) ex vivo-preconditioned with carbon monoxide before administration to a mice model of polymicrobial sepsis induced by cecal ligation [45]. SPM production was associated with increased survival, alleviation of organ injury, improved bacterial clearance, and inflammation resolution. Notably, silencing of LO pathways (5-LO and 12/15-LO), which regulate SPM biosynthesis, resulted in loss of these therapeutic benefits.

Together with the evidence that stem cells (e.g., embryonic SCs, iPSC, hematopoietic SCs) express enzymes involved in SPM biosynthesis [46–48] and are abundant in SPM precursors (i.e., AA, EPA, and DHA) [49], these observations indicate that generation of SPMs may represent one of the mechanisms underlying the anti-inflammatory, immunoregulatory properties of SCs. Thus,
SPM profiling in SCs may provide valuable predictive information regarding their proresolving potential. On the other hand, more studies are needed to determine whether SPMs are generated during documented SC interactions with cells mainly involved in the immune-inflammatory response, such as B lymphocytes, dendritic cells, natural killer cells, neutrophils, and macrophages [2, 50–52]. Along these lines, Fang et al. demonstrated LXA4 formation during coculture of human BM-MSC with human alveolar epithelial cells, suggesting that LXA4 formation is involved in the resolution of acute lung injury promoted by BM-MSC [53].

Moreover, the intraperitoneal administration of amnion epithelial cells, a stem-like population isolated from the human placenta (hAECs), 24 hours after bleomycin challenge enhanced LXA4 formation as well as the expression of the LXA4 receptor (see below), which in turn stimulated macrophage phagocytic activity and induced T-cell suppression, thus promoting resolution of lung injury [54].

Thus, SCs can influence local SPM concentration either by individual biosynthesis, which can be modulated by agents present in the local milieu, including SPMs and their precursors [4, 45], or by interacting with other cell types. As a result, proresolving, tissue-repairing pathways are promoted.

### Impact of SPMs on SC Biology

Early work showed radioprotection by the LX precursor LTA4 as well as by LXBl of mouse hematopoietic SCs [55]. In another study, Stenke et al. demonstrated that LXs are formed in the human BM and suggested that LXs may participate in the regulation of human myelopoiesis [56]. More recently, LXA4 has been proposed as regulator of neural SC proliferation and differentiation [57]. Moreover, PD1 supplementation of mouse embryonic SC potently promotes neuronal and cardiac differentiation [49]. We observed stimulation of hPDLSC proliferation, migration, and wound healing capacity, while reducing chemokine and growth factor secretion.

### SPM Receptors and SCs

SPM intracellular signals are transduced by specific receptors, belonging to the G protein-coupled receptor type and termed ALX/FPR2, DRV1/GPR32, DRV2/GPR18, ERV1/ChemR23, and GPR37. ALX/FPR2, also termed FPR1, FPR2, and FPR2/ALX, was the first to be identified as a receptor for a SPM. Studies by Fiore et al. demonstrated LXA4-specific binding to this receptor in PMN [60]. Subsequent work determined that other proresolving

---

**Figure 2.** Specialized proresolving lipid mediator (SPM) biosynthesis and bioactions in stem cells (SCs). Direct evidence of SPM biosynthesis has been so far obtained in human periodontal ligament stem cells (hPDLSC) and in mouse bone marrow mesenchymal stromal cells (BM-MSC) preconditioned with carbon monoxide (CO) in the presence of arachidonic acid or docosahexaenoic acid, as well as coincubated with alveolar epithelial cells. In these last models, SPMs generated by SCs exerted protective actions on organ injury, thus promoting mice survival, bacterial clearance, and inflammation resolution. Direct SPM modulation of SCs functions was observed in mouse and human BM-MSC, mouse neural stem cells, mouse embryonic stem cells, hPDLSC, and SCs of the human dental apical papilla (SCAP) where LXA4 stimulated proliferation, migration, and wound healing capacity, while reducing chemokine and growth factor secretion.
mediators, namely Annexin A1 and RvD1, activate ALX/FPR2 [61, 62]. Although in vitro studies demonstrated that this receptor is also recognized by a variety of peptides, including SAA, antimicrobial (LL37) and viral peptides (reviewed by Romano et al.) [63] in vivo transgenic [64] and KO [65] mouse models consistently support the proresolving nature of ALX/FPR2. We recently characterized genetic and epigenetic regulatory mechanisms of ALX/FPR2 expression [66, 67], and showed that this receptor is present in hPDLSC, where it conveys proliferative and migration signals by LXA4 [4].

Consistent with our findings, Viswanathan et al. reported FPRL1 expression by human BM mesenchymal SCs [68]. The activation of this receptor by N-formyl methionyl leucyl phenylalanine enhanced cell adhesion and migration [68]. FPR2 expression was uncovered in rat neural SCs, where it promotes migration and neuronal differentiation by modulating the PI3K-AKT signaling and ROS generation [69, 70].

Recently, ALX/FPR2 expression has been detected in SCAP [58]. The activation of this receptor by LXA4 stimulated SCAP proliferation, migration, wound healing capacity, and immunomodulatory functions, while inhibiting cytokine, chemokine, and growth factor secretion [58].

In addition to SCs from different origin, the ALX/FPR2 receptor is expressed by progenitor cells. For instance, its activation by the WKYMVM peptide stimulated chemotactic migration, angiogenesis, and proliferation ability of human endothelial colony forming cells, thus promoting ischemic limb salvage [71]. Moreover, FPR2-dependent mobilization of circulating angiogenic cells contributed to myocardial protection and neovascularization in a murine model of myocardial infarction [72].

Notably, FPR2 KO in mice was associated with reduced number of Lin- c-Kit+Sca-1 myeloid precursors as well as with reduced expansion of this cell population following airways exposure to heat-inactivated bacteria [73]. Along these lines, emergency granulopoiesis was inhibited by FPR2 deficiency in mouse [74]. Altogether, these results indicate that the LXA4 receptor may play a role in stem and progenitor cell proliferation and homing and that signals conveyed by this receptor may influence immunomodulatory functions of SCs.

Little is currently known regarding the involvement of other SPM receptors in SC biology. Expression of DRV2/GPR18, which is recognized by RvD2 [75], has been reported in lymphoid progenitors and its requirement for the development and reconstitution of thymus-derived intestinal intraepithelial lymphocytes in the steady-state and after BM transplantation has been proposed [76]. On the other hand, BM-derived MSCs express the ChemR23 receptor, which is activated by RvE1 [20]. However, the impact of RvE1 on MSC pathobiology is unknown. Recently, binding and activation of second messengers by PD1 to the human GPR37 receptor has been uncovered [77]. GPR37 is broadly expressed in brain tissues and leukocytes and can be activated by the neurotrophic peptide prosaposin. Interestingly, GPR37 is highly expressed in mouse neural progenitor cells [78]. Moreover, prosaposin is secreted by marrow stromal-derived neural progenitor cells and protects neural cells by apoptosis [79]. Whether GPR37 as well as other SPM receptors are expressed on SCs where they can convey SPM-induced bioactions remains to be fully investigated.

**CONCLUSION**

As the stem cell era is rapidly approaching the phase of clinical application, the need for better characterization and definition of SC properties becomes urgent. It has been clearly demonstrated that SCs possess immunomodulatory, anti-inflammatory, pro-healing functions and that they exert these functions largely...
by paracrine mechanisms involving the release of mediators as well as extracellular vesicles [80]. It has been also suggested that preconditioning of SCs can enhance their beneficial effects. These are key points that need more extensive investigation. In this respect, the still limited evidence that SCs can generate SPMs and express SPM receptors, and that SPMs can modulate SC functions is relevant and opens new perspectives in SC biology and translational medicine.

REFERENCES

1 Munir H, Ward LSC, McGlynn RM. Mesenchymal stem cells as endogenous regulators of inflammation. Adv Exp Med Biol 2018;1060:73–98.

2 Sugimoto MA, Vago JP, Perretti M et al. Mediators of the resolution of the inflammatory response. Trends Immunol 2019;40:212–227.

3 Chiang N, Serhan CN. Structural elucidation of the physiologic functions of specialized pro-resolving mediators and their receptors. Mol Aspects Med 2017;58:114–129.

4 Cianci E, Recchiuti A, Trubiani O et al. Human periodontal stem cells release specialized proresolving mediators and carry immunomodulatory and prohealing properties regulated by lipoxins. Stem Cells Translational Medicine 2016;5:20–32.

5 Serhan CN, Hamberg M, Samuelsson B. Trihydroxyxetraenes: A novel series of compounds formed from arachidonic acid in human leukocytes. Biochem Biophys Res Comm 1988;157:801–809.

6 Edenius C, Haegstjorn J, Lindgren JA. Transcellular conversion of endogenous arachidonic acid to lipoxins in mixed human platelet-granulocyte suspensions. Biochem Biophys Res Comm 1988;157:801–809.

7 Serhan CN, Sheppard KA. Lipoxin formation during human neutrophil-platelet interactions. Evidence for the transformation of leukotriene A4 by platelet 12-lipoxygenase in vitro. J Clin Invest 1990;85:772–807.

8 Romano M, Chen XS, Takahashi Y et al. Lipoxin synthase activity of human platelet 12-lipoxygenase. Biochem J 1993;296:127–133.

9 Brezinski DA, Nesto RW, Serhan CN. Angioplasty triggers intracellular leukotrienes and lipoxin A4, Impact of aspirin therapy. Circulation 1992;86:65–63.

10 Gangemi S, Luciotti G, D’Urbano E et al. Physical exercise increases urinary excretion of lipoxin A4 and related compounds. J Appl Physiol 2003;94:2240.

11 Edenius C, Kumlin M, Bjork T et al. Lipoxin formation in human nasal polymy and bronchial tissue. FEBS Lett 1990;272:25–28.

12 Levy BD, Romano M, Chapman HA et al. Human alveolar macrophages have 15-lipoxygenase and generate 15(S)-hydroxy-5,8,11-cis-13-trans-eicosatetraenoic acid and lipoxin A. J Clin Invest 1993;92:1572–1579.

13 Claria J, Serhan CN. Aspirin triggers previously undescribed bioactive eicosanoids by human endothelial cell-leukocyte interactions. Proc Natl Acad Sci USA 1995;92:9475–9479.

14 Birnbaum Y, Ye Y, Lin Y et al. Augmentation of myocardial production of 15-epi-lipoxin-a4 by pioglitazone and atorvastatin in the rat. Circulation 2006;114:929–935.

15 Planagumà A, Pfeffer MA, Rubín G et al. Lovastatin decreases acute mucosal inflammation via 15-epi-lipoxin A4. Mucosal Immunol 2010;3:270–279.

16 Gutierrez AD, Sathyarayanan P, Konduru S et al. The effect of pioglitazone treatment on 15-epi-lipoxin A4 levels in patients with type 2 diabetes. Atherosclerosis 2012;223:204–208.

17 Lee JY, Han SH, Park MH et al. Neuronal SpHK1 acetylates CDX2 and contributes to pathogenesis in a model of Alzheimer’s Disease. Nat Commun 2018;9:1479.

18 Sardina M, Romano M, Santucci L et al. Interaction of a selective cyclooxygenase-2 inhibitor with aspirin and NO-releasing aspirin in the human gastric mucosa. Proc Natl Acad Sci USA 2003;100:10937–10941.

19 Ridker PM, Huvunts S, Chiang N et al. Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. Proc Natl Acad Sci USA 2004;101:15178–15183.

20 Serhan CN, Clish CB, Brannon J et al. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med 2000;192:1197–1204.

21 Arta M, Bianchini F, Alberti J et al. Stereoechemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. J Exp Med 2005;201:713–722.

22 Oh SF, Pillai PS, Recchiuti A et al. Proresolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. J Clin Invest 2011;121:569–581.

23 Haas- Stapleton EI, Lu Y, Hong S et al. Candida albicans modulates host defense by biosynthesizing the pro-resolving mediator resolvin E1. PLoS One 2007;2:e13136.

24 Tjonahen E, Oh SF, Siegelman E et al. Resolvin E2: Identification and anti-inflammatory actions: Pivotal role of human 5-lipoxygenase in resolvin E series biosynthesis. Chem Biol 2006;13:1193–1202.

25 Isobe Y, Arita M, Matsueda S et al. Identification and structure determination of novel anti-inflammatory mediator resolvin E3, 17,18-dihydrocycopenstaenoic acid. J Biol Chem 2012;287:10525–10534.

26 Serhan CN, Hong S, Gronert K et al. Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med 2002;196:1025–1037.

27 Sun Y-P, Oh SF, Uddin J et al. Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. J Biol Chem 2007;282:9323–9334.

28 Spite M, Norling LV, Summers L et al. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. Nature 2009;461:1287–1291.

29 Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. FASEB J 2017;31:1273–1288.

30 Hong S, Gronert K, Devchand PR et al. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. J Biol Chem 2003;278:14677–14687.

31 Serhan CN, Fredman G, Yang R et al. Novel proresolving aspirin-triggered DHA pathway. Chem Biol 2011;18:976–987.

32 Serhan CN, Yang R, Martinod K et al. Marisens: Novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med 2009;206:15–23.

33 Dalli J, Ramon S, Norris PC et al. Novel proresolving and tissue-regenerativ resolvin and protectin sulfido-conjugated pathways. FASEB J 2015;29:2120–2136.

34 Dalli J, Sanger JM, Rodriguez AR et al. Identification and actions of a novel third marisin conjugate in tissue regeneration: MCTR3. PLoS One 2016;11:e0149319.

35 Dalli J, Vlasakov I, Riley IR et al. Marisens conjugates in tissue regeneration biosynthesis enzymes in human macrophages. Proc Natl Acad Sci USA 2016;113:12232–12237.

36 de la Rosa X, Norris PC, Chiang N et al. Identification and complete stereochmemical assignments of the new resolvins conjugates in tissue regeneration in human tissues that stimulate proresolving phagocyte functions and tissue regeneration. Am J Pathol 2018;188:950–966.

37 Ramon S, Dalli J, Sanger JM et al. The protectin PCTR1 is produced by human M2 macrophages and enhances resolution of infectious inflammation. Am J Pathol 2016;188:962–973.

38 Dalli J, Colas RA, Serhan CN. Novel n-3 immunoresolvents: Structures and actions. Sci Rep 2013;3:1940.

39 Gobbetti T, Dalli J, Colas RA et al. Protectin D1(n-3 DPA) and resolvin D5(n-3 DPA) are effectors of intestinal protection. Proc Natl Acad Sci USA 2017;114:3963–3968.

40 Dalli J, Chiang N, Serhan CN. Eludication of novel 13-series resolvins that increase with atorvastatin and clear infections. Nat Med 2015;21:1071–1075.

41 Recchiuti A, Gianci A, Simiele F et al. Lipoxins, resolvins and the resolution of inflammation. In: Steinhalber D, ed. Lipoxigenase in inflammation. Switzerland: Springer International Publishing, 2016:211–239.

AUTHOR CONTRIBUTIONS

M.R., S.P., A.P., A.R.: wrote and reviewed the manuscript, prepared the figures, critical reading of the literature.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.
998 Stem Cells in Inflammation Resolution

42 Levy BD, De Sanctis GT, Devchand PR et al. Multi-pronged inhibition of airway hyper-responsiveness and inflammation by lipoxin A4. Nat Med 2002;8:1018–1023.

43 Feehan KT, Gilroy DW. Is resolution the end of inflammation? Trends Mol Med 2019;25:198–214.

44 Najar M, Raievic G, Boukfer Hl et al. Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: Combined comparison of adipose tissue, Wharton’s Jelly and bone marrow sources. Cell Immunol 2010;264:171–179.

45 Tsouy K, Hall SRR, Dalli J et al. Carbon monoxide improves efficacy of mesenchymal stromal cells during sepsis by production of specialized proresolving lipid mediators. Crit Care Med 2016;44:e1236–e1245.

46 Finkensieper A, Kieser S, Bekhite MM et al. The 5-lipoxygenase pathway regulates vasculogenesis in differentiating mouse embryonic stem cells. Cardiovasc Res 2010;86:37–44.

47 Wu Y, Sun H, Song F et al. Deletion of Alox5 gene decreases osteogenic differentiation but increases adipogenic differentiation of mouse induced pluripotent stem cells. Cell Tissue Res 2014;358:135–147.

48 Kinder M, Wei C, Shelat SG et al. Hematopoietic stem cell function requires 12/15-lipoxygenase-dependent fatty acid metabolism. Blood 2010;115:5012–5022.

49 Yanes O, Clark J, Wong DM et al. Metabolic oxidation regulates embryonic stem cell differentiation. Nat Chem Biol 2010;6:411–417.

50 Prokop DJ, Youn OJ. Mesenchymal stem/stromal cells (MSCs): Role as guardians of inflammation. Mol Ther 2012;20:14–20.

51 Wang Y, Chen X, Cao W et al. Plasticity of mesenchymal stem cells in immuno-modulation: Pathological and therapeutic implications. Nat Immunol 2014;15:1009–1016.

52 Di NM, Carlo-Stella C, Magni M et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99:3838–3843.

53 Fang X, Abbott J, Cheng L et al. Human mesenchymal stem (stromal) cells promote the resolution of acute lung injury in part through lipoxin A4. J Immunol 2015;195:875–881.

54 Tan JI, Tan YZ, Muljadi R et al. Amnion epithelial cells promote lung repair via lipoxin A4. Stem Cells Translational Medicine 2017;6:1085–1095.

55 Walde JRTL. Radioprotection of mouse hematopoietic stem cells by leukotriene A4 and lipoxin B4. J Radiat Res 1988;29:255–260.

56 Stenke L, Mahmoud M, Edenius C et al. Formation and proliferative effects of lipoxins in human bone marrow. Biochem Biophys Res Commun 1991;180:255–261.

57 Wada K, Arita M, Nakajima A et al. Leukotriene B4 and lipoxin A4 are regulatory signals for neural stem cell proliferation and differentiation. FASEB J 2006;20:1785–1792.

58 Gaudin A, Tolar M, Peters OA. Lipoxin A4 attenuates the inflammatory response in stem cells of the apical papilla via ALX/FPR2. Sci Rep 2018;8:8921.

59 Van Dyke TE. Pro-resolving mediators in the regulation of periodontal disease. Mol Aspects Med 2017;58:21–36.

60 Fiore S, Ryeom SW, Weller PF et al. Lipoxin recognition sites. Specific binding of labeled lipoxin A4 with human neutrophils. J Biol Chem 1992;267:16168–16176.

61 Perretti M, Chiang N, La M et al. Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor. Nat Med 2002;8:1296–1302.

62 Recchiuti A, Lee C-H, Petasis NA et al. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci USA 2010;107:1660–1665.

63 Romano M, Recchia I, Recchiuti A. Lipoxin receptors. ScientificWorldJournal 2007;7:1393–1412.

64 Sethan CN, Devchand PR, Hong S et al. Human ALX receptor regulates neutrophil recruitment in transgenic mice: Roles in inflammation and host defense. FASEB J 2003;17:652–659.

65 Dufston N, Hannon R, Brancaleone V et al. Anti-inflammatory role of the murine formyl-peptide receptor 2: Ligand-specific effects on leukocyte responses and experimental. J Immunol 2010;184:2611–2619.

66 Simiele F, Recchiuti A, Mattosco D et al. Transcriptional regulation of the human FPR2/ALX gene: Evidence of a heritable variant that impairs promoter activity. FASEB J 2012;26:1323–1333.

67 Simiele F, Recchiuti A, Patruno S et al. Epigenetic regulation of the formyl pepti receptor 2 gene. Biochim Biophys Acta Gene Regul Mech 2016;1859:1252–1258.

68 Viswanathan A, Painter RG, Lanson NA et al. Functional expression of N-formyl peptide receptors in human bone marrow-derived mesenchymal stem cells. Stem Cells 2012;25:1263–1269.

69 Wang G, Zhang L, Chen X et al. Formylpeptide receptors promote the migration and differentiation of rat neural stem cells. Sci Rep 2016;6:25946.

70 Zhang L, Wang G, Chen X et al. Formylpeptide receptors promote neural differentiation in mouse neural stem cells by ROS generation and regulation of PI3AKT signaling. Sci Rep 2017;7:1–16.

71 Heo SC, Kwon YW, Jang IH et al. Formyl peptide receptor 2 is involved in cardiac repair after myocardial infarction through mobilization of circulating angiogenic cells. Stem Cells 2017;35:654–665.

72 Chen K, Singh VK, Tang P et al. Deficiency in Fpr2 results in reduced numbers of LinKitSca1 myeloid progenitor cells. J Biol Chem 2018;293:13452–13463.

73 Lee HY, Kim HS, Bae Y-S et al. Activation of formyl peptide receptor 2 by WKYVMv enhances emergency granulopoiesis through phospholipase C activity. BMB Rep 2018;51:418–423.

74 Chiang N, Dalii J, Colas RA et al. Identification of resolvin D2 receptor mediating resolution of infections and organ protection. J Exp Med 2015;212:1203–1217.

75 Becker AM, Callahan DJ, Richner JM et al. GPR18 controls reconstitution of mouse small intestine intraepithelial lymphocytes following bone marrow transplantation. PLoS One 2015;10:e0133854.

76 Bang S, Xie YK, Zhang Z et al. GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. J Clin Invest 2018;128:3568–3582.

77 Berger BS, Acebron SP, Herbst J et al. Parkinson’s disease-associated receptor GPR37 is an ER chaperone for LRPS. EMBO Rep 2017;18:712–725.

78 Li N, Sarojini H, An J et al. Prosaposin in the secretome of marrow stroma-derived neural progenitor cells protects neural cells from apoptotic death. J Neurochem 2010;112:1527–1538.

79 Bruno S, Deregibus MC, Camussi G. The secretome of mesenchymal stromal cells: Role of extracellular vesicles in immunomodulation. Immunol Lett 2015;168:154–158.