

## Concise Review: Pro-Resolving Lipid Mediators and Receptors in Stem Cell Biology

MARIO ROMANO <sup>a,b,c</sup> SARA PATRUNO,<sup>a,b,c</sup> ANTONELLA POMILIO,<sup>a,b,c</sup> ANTONIO RECCHIUTI<sup>a,c</sup>

<sup>a</sup>Department of Medical, Oral, and Biotechnological Sciences, “G. D’Annunzio” University of Chieti-Pescara, Chieti, Italy; <sup>b</sup>StemTech Group, “G. D’Annunzio” University of Chieti-Pescara, Chieti, Italy; <sup>c</sup>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 pro-resolving 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, pro-resolving 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;00:1–7*

### 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 pro-resolving mediators. Among these, the so-called specialized pro-resolving 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 pro-resolving bioactions *in vitro* and *in vivo* [3]. Differently from classical anti-inflammatory molecules, SPMs modulate, without completely suppressing, pro-inflammatory 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 (LX)<sub>4</sub> (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 pro-resolving program?
2. Do SPMs exert pro-resolving 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. © 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.

## SPM BIOSYNTHESIS AND BIOACTIONS

### SPMs Derived from AA

#### LXs and Aspirin-Triggered LXs

LX (an acronym of “lipoxygenase interaction products”) A<sub>4</sub> and B<sub>4</sub> 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)A<sub>4</sub>, which is transferred to interacting PLT at sites of injury or thrombosis, where 12-LO converts LTA<sub>4</sub> 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[p]ETE). Following diapedesis and interactions of white blood cells with epithelial cells, 15-H(p)ETE is taken up by leukocyte 5-LO to produce LXA<sub>4</sub> and B<sub>4</sub> [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 LXA<sub>4</sub> and B<sub>4</sub> 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 LTA<sub>4</sub> hydrolase [21] and cytochrome P450 [20, 23]. Reduction of 18-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].

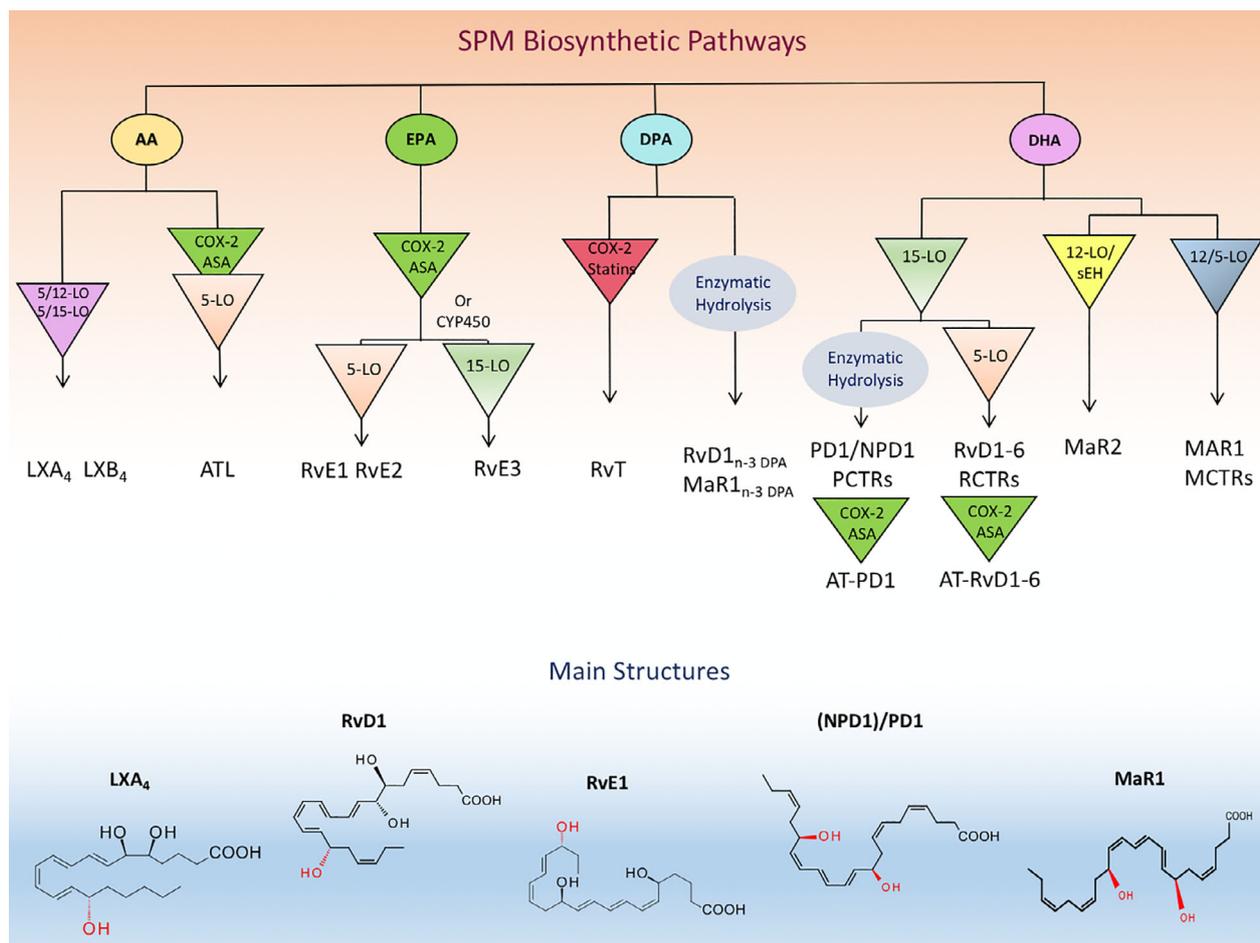
#### SPMs Conjugated in Tissue Regeneration

Recent studies by Serhan et al. have identified distinct families of SPMs arising from the conjugation of epoxy-DHA to glutathione (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 LTC<sub>4</sub> 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-cysteinylglycyl-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  $\gamma$ -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,  $\omega$ -3 DPA is an  $\omega$ -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  $\omega$ -3 DPA SPM family are RvD1<sub>n-3</sub> DPA<sub>n</sub>, MaR1<sub>n-3</sub> DPA<sub>n</sub> [38], and RvD5<sub>n-3</sub> DPA<sub>n</sub> [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



**Figure 1.** Specialized pro-resolving lipid mediator biosynthetic pathways. Main biosynthetic routes, key enzymes, and structures are illustrated (see text for details).

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 pro-inflammatory 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 pro-resolving 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 metabolomics, we detected hPDLSC production of resolvins (both D and E series), PD1, MaR, LX, and ATL. Interestingly, prostaglandin (PG)E<sub>2</sub> was the most abundant lipid mediator formed by hPDLSC [4]. Although PGE<sub>2</sub> is released in the early phases of inflammation and carries pro-inflammatory 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, PGE<sub>2</sub> 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,

STEM CELL TYPE	SPM BIOSYNTHESIS	SPM AGONIST	SPECIES	SPM BIOACTIONS
 BM-MSC	Preconditioned with CO + AA LXA <sub>4</sub> ; LXB <sub>4</sub> ; ATL; RvD1,3,5 +DHA RvD1,2,3,5,6; ATL; RvD1,3; LXB <sub>4</sub> ; ATL; PD1			 Mouse survival - Bacterial clearance - Resolution of Inflammation  Organ Injury
	+ Alveolar epithelium = LXA <sub>4</sub>			 Resolution of acute lung injury
		LXB <sub>4</sub>		 SC radioprotection
ESC		LXA <sub>4</sub> , LXB <sub>4</sub>		 SC growth
NSC		PD1		 Neural and cardiac differentiation
hPDLSC		LXA <sub>4</sub> , 15-epi-LXA <sub>4</sub>		 SC proliferation
SCAP	RVD1-6; RVE2,3; PD1; MaR1; LXB <sub>4</sub> ; ATL	LXA <sub>4</sub>		 SC proliferation  SC migration  SC wound healing capacity  SC-induced Immunomodulation by PBMC  SC proliferation  SC wound healing capacity  SC chemokine secretion  SC growth factor secretion

**Figure 2.** Specialized pro-resolving 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 LXA<sub>4</sub> stimulated proliferation, migration, and wound healing capacity, while reducing chemokine and growth factor secretion.

SPM profiling in SCs may provide valuable predictive information regarding their pro-resolving 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 LXA<sub>4</sub> formation during coculture of human BM-MSC with human alveolar epithelial type II cells, suggesting that LXA<sub>4</sub> 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 LXA<sub>4</sub> formation as well as the expression of the LXA<sub>4</sub> 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, pro-resolving, tissue-repairing pathways are promoted.

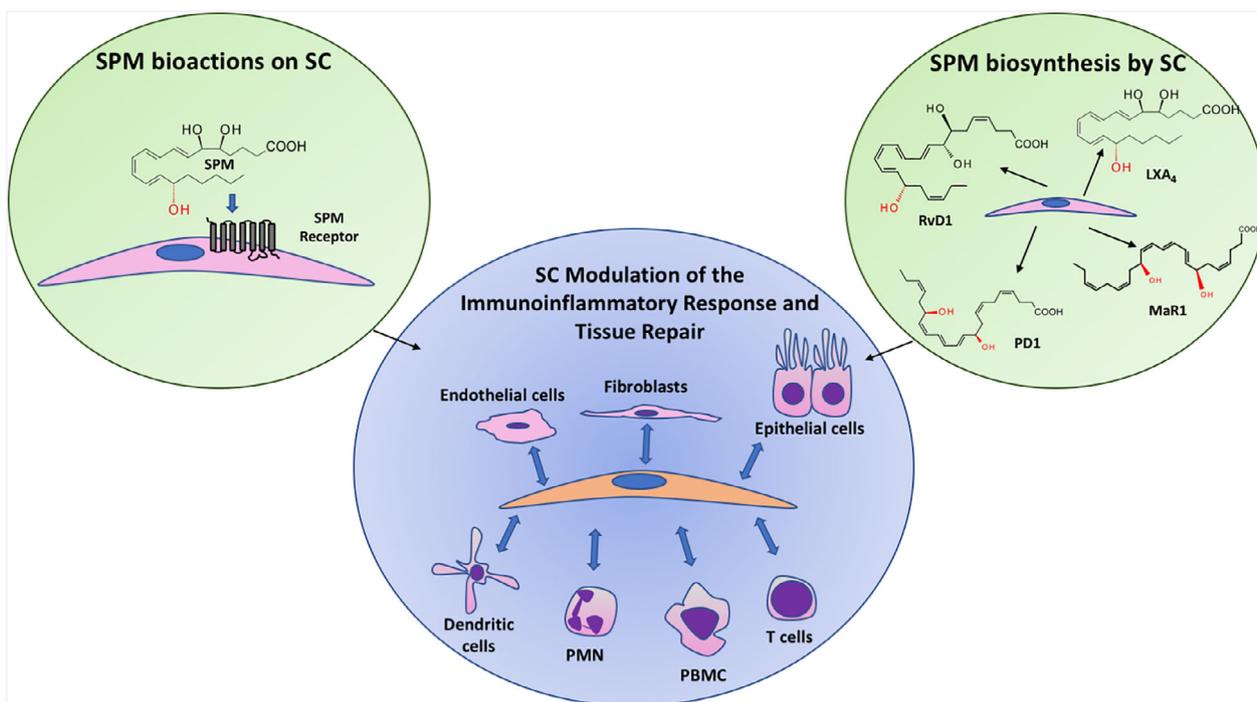
#### IMPACT OF SPMs ON SC BIOLOGY

Early work showed radioprotection by the LX precursor LTA<sub>4</sub> as well as by LXB<sub>4</sub> 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, LXA<sub>4</sub> has been proposed as regulator of neural SC proliferation and differentiation [57]. Moreover, PD1 supplementation of mouse embryonic SCs potentially promotes neuronal and cardiac differentiation [49]. We observed stimulation of hPDLSC proliferation, migration, and wound healing by LXA<sub>4</sub> [4]. Similar results were obtained with SCs from the dental apical papilla (SCAP), which express the LXA<sub>4</sub> receptor (see below). In this model, LXA<sub>4</sub> also inhibited chemokine and growth factor secretion, enhancing the immunomodulatory properties of peripheral blood mononuclear cells [58]. These results suggest that modulation of resident SCs may account for the beneficial actions of SPMs in periodontal disease [59]. A schematic representation of known SPM pathways and bioactions in SCs is illustrated in Figure 2, whereas Figure 3 depicts a schematic representation of the impact that exogenous or endogenous SPMs may have on SC pathophysiology.

#### 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 LXA<sub>4</sub>-specific binding to this receptor in PMN [60]. Subsequent work determined that other pro-resolving



**Figure 3.** Scheme of specialized pro-resolving lipid mediator (SPM) involvement in stem cells (SCs) pathobiology. SPM binding to its cognate receptor expressed by SCs (upper left) in conjunction with SPM generation by SCs (upper right) can regulate SC-governed pathways involved in immunoregulation, inflammation resolution, and tissue repair through interactions with blood as well as resident cells (center).

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 pro-resolving 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 LXA<sub>4</sub> [4].

Consistent with our findings, Viswanathan et al. reported FPR1 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 LXA<sub>4</sub> 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<sup>-</sup>c-Kit<sup>+</sup>Sca-1<sup>+</sup> 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 LXA<sub>4</sub> 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 SC 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.

#### AUTHOR CONTRIBUTIONS

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

#### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

#### REFERENCES

- Munir H, Ward LSC, Mcgettrick HM. Mesenchymal stem cells as endogenous regulators of inflammation. *Adv Exp Med Biol* 2018;1060:73–98.
- Sugimoto MA, Vago JP, Perretti M et al. Mediators of the resolution of the inflammatory response. *Trends Immunol* 2019;40:212–227.
- Chiang N, Serhan CN. Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. *Mol Aspects Med* 2017;58:114–129.
- 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.
- Serhan CN, Hamberg M, Samuelsson B. Trihydroxytetraenes: A novel series of compounds formed from arachidonic acid in human leukocytes. *Biochem Biophys Res Commun* 1984;118:943–949.
- Edenius C, Haeggstrom J, Lindgren JA. Transcellular conversion of endogenous arachidonic acid to lipoxins in mixed human platelet-granulocyte suspensions. *Biochem Biophys Res Commun* 1988;157:801–807.
- 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;85:772–780.
- Romano M, Chen XS, Takahashi Y et al. Lipoxin synthase activity of human platelet 12-lipoxygenase. *Biochem J* 1993;296:127–133.
- Brezinski DA, Nesto RW, Serhan CN. Angioplasty triggers intracoronary leukotrienes and lipoxin A4. Impact of aspirin therapy. *Circulation* 1992;86:56–63.
- Gangemi S, Luciotti G, D'Urbano E et al. Physical exercise increases urinary excretion of lipoxin A4 and related compounds. *J Appl Physiol* 2003;94:2237–2240.
- Edenius C, Kumlin M, Bjork T et al. Lipoxin formation in human nasal polyps and bronchial tissue. *FEBS Lett* 1990;272:25–28.
- 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 lipoxins. *J Clin Invest* 1993;92:1572–1579.
- 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.
- 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.
- Planagumà A, Pfeffer MA, Rubin G et al. Lovastatin decreases acute mucosal inflammation via 15-epi-lipoxin A4. *Mucosal Immunol* 2010;3:270–279.
- Gutierrez AD, Sathyanarayana 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.
- Lee JY, Han SH, Park MH et al. Neuronal SphK1 acetylates COX2 and contributes to pathogenesis in a model of Alzheimer's Disease. *Nat Commun* 2018;9:1479.
- 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.
- Ridker PM, Hurwitz 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.
- 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.
- Arita M, Bianchini F, Aliberti J et al. Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J Exp Med* 2005;201:713–722.
- 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.
- Haas-Stapleton EJ, Lu Y, Hong S et al. *Candida albicans* modulates host defense by biosynthesizing the pro-resolving mediator resolvin E1. *PLoS One* 2007;2:e1316.
- Tjonahen E, Oh SF, Siegelman J 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.
- Isobe Y, Arita M, Matsueda S et al. Identification and structure determination of novel anti-inflammatory mediator resolvin E3, 17,18-dihydroxyeicosapentaenoic acid. *J Biol Chem* 2012;287:10525–10534.
- 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.
- 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.
- 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.
- Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. *FASEB J* 2017;31:1273–1288.
- 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.
- Serhan CN, Fredman G, Yang R et al. Novel proresolving aspirin-triggered DHA pathway. *Chem Biol* 2011;18:976–987.
- Serhan CN, Yang R, Martinod K et al. Maresins: Novel macrophage mediators with potent antiinflammatory and proresolving actions. *J Exp Med* 2009;206:15–23.
- Dalli J, Ramon S, Norris PC et al. Novel proresolving and tissue-regenerative resolvin and protectin sulfido-conjugated pathways. *FASEB J* 2015;29:2120–2136.
- Dalli J, Sanger JM, Rodriguez AR et al. Identification and actions of a novel third maresin conjugate in tissue regeneration: MCTR3. *PLoS One* 2016;11:e0149319.
- Dalli J, Vlasakov I, Riley IR et al. Maresin conjugates in tissue regeneration biosynthesis enzymes in human macrophages. *Proc Natl Acad Sci USA* 2016;113:12232–12237.
- de la Rosa X, Norris PC, Chiang N et al. Identification and complete stereochemical assignments of the new resolvin conjugates in tissue regeneration in human tissues that stimulate proresolving phagocyte functions and tissue regeneration. *Am J Pathol* 2018;188:950–966.
- 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;186:962–973.
- Dalli J, Colas RA, Serhan CN. Novel n-3 immunoresolvents: Structures and actions. *Sci Rep* 2013;3:1940.
- 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.
- Dalli J, Chiang N, Serhan CN. Elucidation of novel 13-series resolvins that increase with atorvastatin and clear infections. *Nat Med* 2015;21:1071–1075.
- Recchiuti A, Cianci A, Simiele F et al. Lipoxins, resolvins and the resolution of inflammation. In: Steinhilber D, ed. *Lipoxygenase in inflammation*. Switzerland: Springer International Publishing, 2016:211–239.

- 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, Raicevic G, Boufker HI 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 Tsoyi 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 Prockop 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 immunomodulation: 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 JL, 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 phagocytes. *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 Serhan 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 Dufton 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, Mattoscio D et al. Transcriptional regulation of the human FPR2/ALX gene: Evidence of a heritable genetic 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 peptide 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* 2007;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. Formyl peptide receptors promotes neural differentiation in mouse neural stem cells by ROS generation and regulation of PI3K/AKT signaling. *Sci Rep* 2017;7:1–16.
- 71 Heo SC, Kwon YW, Jang IH et al. WKYMVM-induced activation of formyl peptide receptor 2 stimulates ischemic neovasculogenesis by promoting homing of endothelial colony-forming cells. *STEM CELLS* 2014;32:779–790.
- 72 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.
- 73 Chen K, Singh VK, Tang P et al. Deficiency in *Fpr2* results in reduced numbers of *Lin<sup>+</sup>Kit<sup>+</sup>Sca1<sup>+</sup>* myeloid progenitor cells. *J Biol Chem* 2018;293:13452–13463.
- 74 Lee HY, Kim HS, Bae Y-S et al. Activation of formyl peptide receptor 2 by WKYMVM enhances emergency granulopoiesis through phospholipase C activity. *BMB Rep* 2018;51:418–423.
- 75 Chiang N, Dalli J, Colas RA et al. Identification of resolvin D2 receptor mediating resolution of infections and organ protection. *J Exp Med* 2015;212:1203–1217.
- 76 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.
- 77 Bang S, Xie YK, Zhang ZJ et al. GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. *J Clin Invest* 2018;128:3568–3582.
- 78 Berger BS, Acebron SP, Herbst J et al. Parkinson's disease-associated receptor GPR37 is an ER chaperone for LRP6. *EMBO Rep* 2017;18:712–725.
- 79 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.
- 80 Bruno S, Deregius MC, Camussi G. The secretome of mesenchymal stromal cells: Role of extracellular vesicles in immunomodulation. *Immunol Lett* 2015;168:154–158.