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PERSPECTIVES

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

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SUMMARY

Accumulating evidence indicates that stem cells (SCs) possess immunomodulatory, anti-inflammatory, and prohealing 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 (LX)A_4 (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?

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SPM Biosynthesis and Bioactions

SPMs Derived from AA

LXs and Aspirin-Triggered LXs

LX (an acronym of "lipoxygenase interaction products") A_4 and B_4 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_4, which is transferred to interacting PLT at sites of injury or thrombosis, where 12-LO converts LTA_4 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_4 and B_4 [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_4 and B_4 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_4 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 17*S*-hydroperoxy-DHA and 5-LO that catalyzes conversion into RvD1 [26]. In the presence of aspirin-acetylated COX-2, DHA is converted into 17*R*-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_4 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 $RvD1_{n-3\ DPA}$, $MaR1_{n-3\ DPA}$ [38], and $RvD5_{n-3\ DPA}$ [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

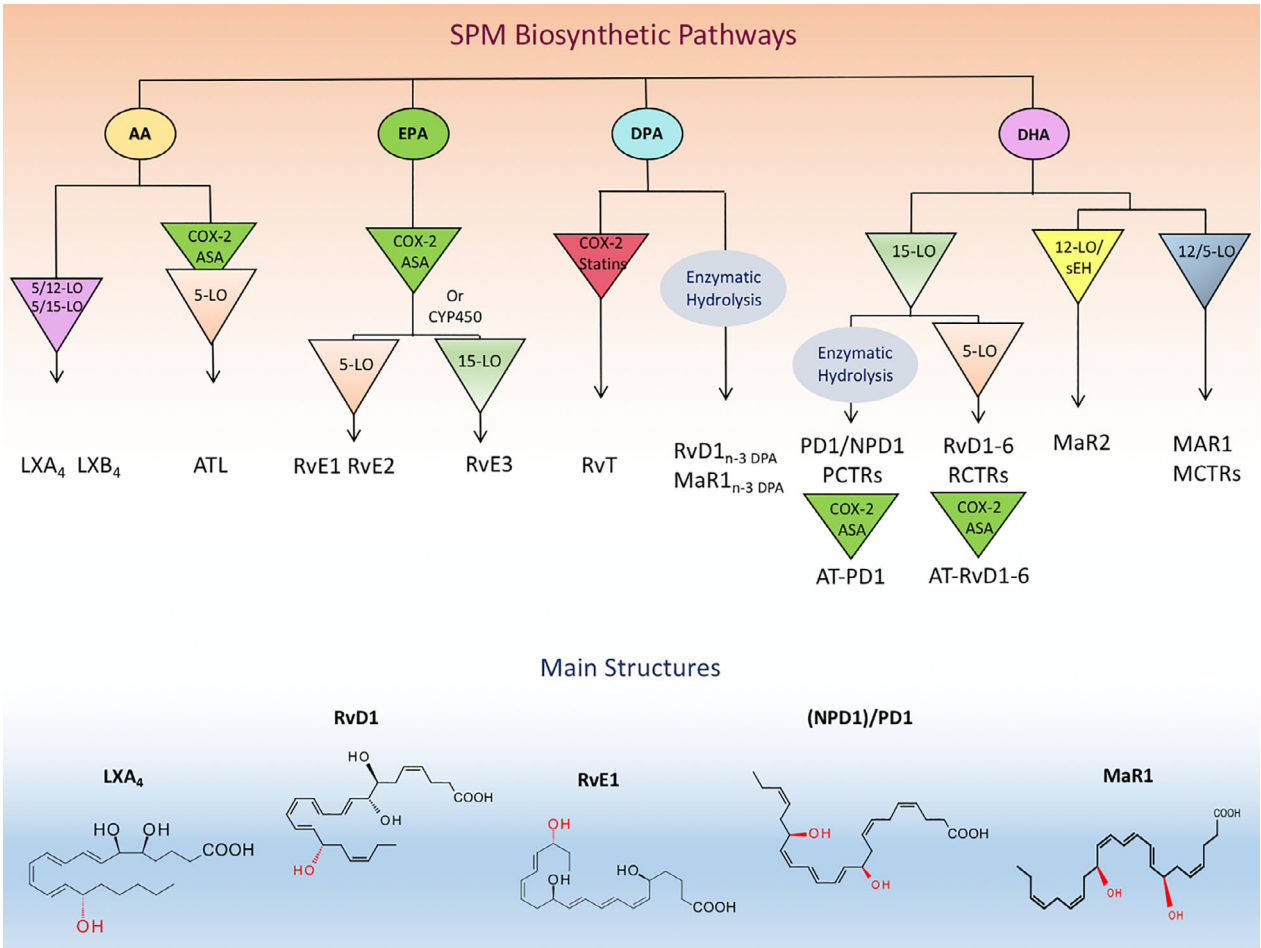

Figure 1. Specialized proresolving lipid mediator biosynthetic pathways. Main biosynthetic routes, key enzymes, and structures are illustrated (see text for details).

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 proinflammatory chemokines and cytokines as well as the expression of adhesion molecules, leukocyte transepithelial 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 metololipidomics, we detected hPDLSC production of resolvins (both D and E series), PD1, MaR, LX, and ATL. Interestingly, prostaglandin (PG)E_2 was the most abundant lipid mediator formed by hPDLSC [4]. Although PGE_2 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, PGE_2 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,

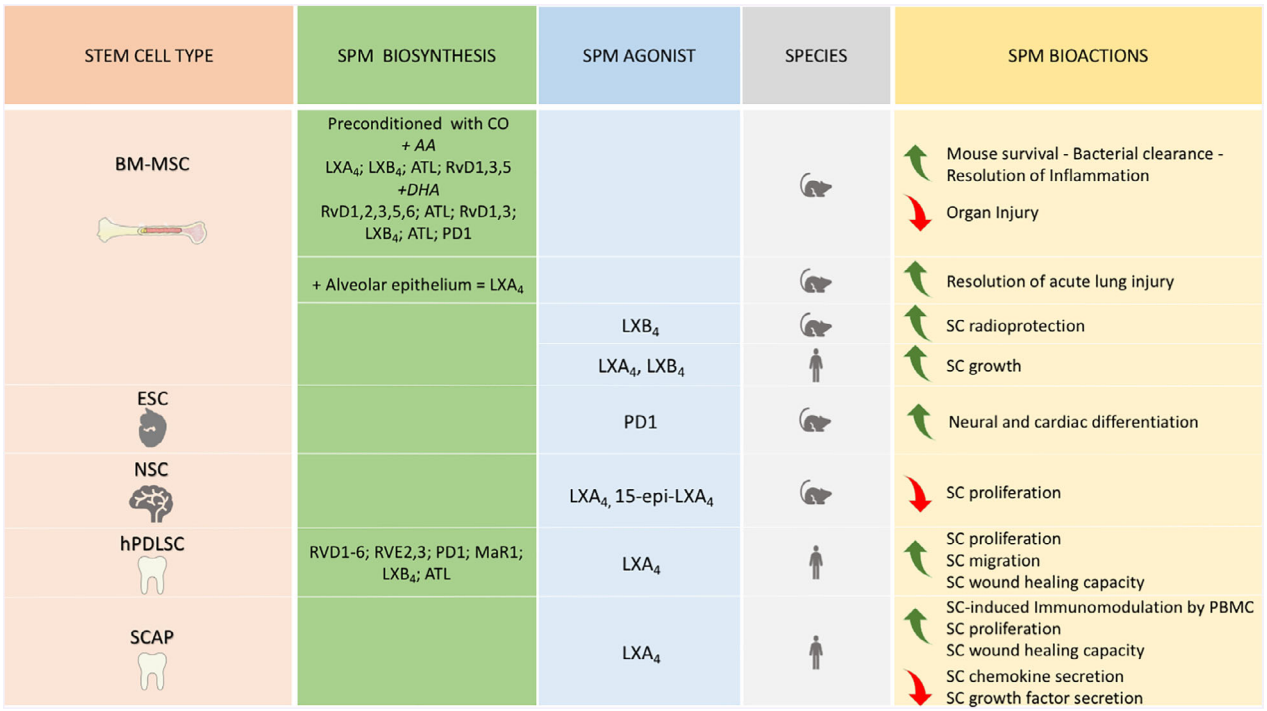

Figure 2. Specialized proresolving lipid mediator (SPM) biosynthesis and bioactions in stem cells (SCs). Direct evidence of SPM biosyntheis has been so far obtained in human periodontal ligament stem cells (hPDLSC) and in mouse bone marrow mesenchymal stromal cells (BM-MSC) preconditioned with carbon 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_4 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 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 LXA_4 formation during coculture of human BM-MSC with human alveolar epithelial type II cells, suggesting that LXA_4 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 form the human placenta (hAECs), 24 hours after bleomycin challenge enhanced LXA_4 formation as well as the expression of the LXA_4 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 LTA_4 as well as by LXB_4 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_4 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 by LXA_4 [4]. Similar results were obtained with SCs from the dental apical papilla (SCAP), which express the LXA_4 receptor (see below). In this model, LXA_4 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 FPRL1, FPR2, and FPR2/ALX, was the first to be identified as a receptor for a SPM. Studies by Fiore et al. demonstrated LXA_4-specific binding to this receptor in PMN [60]. Subsequent work determined that other proresolving

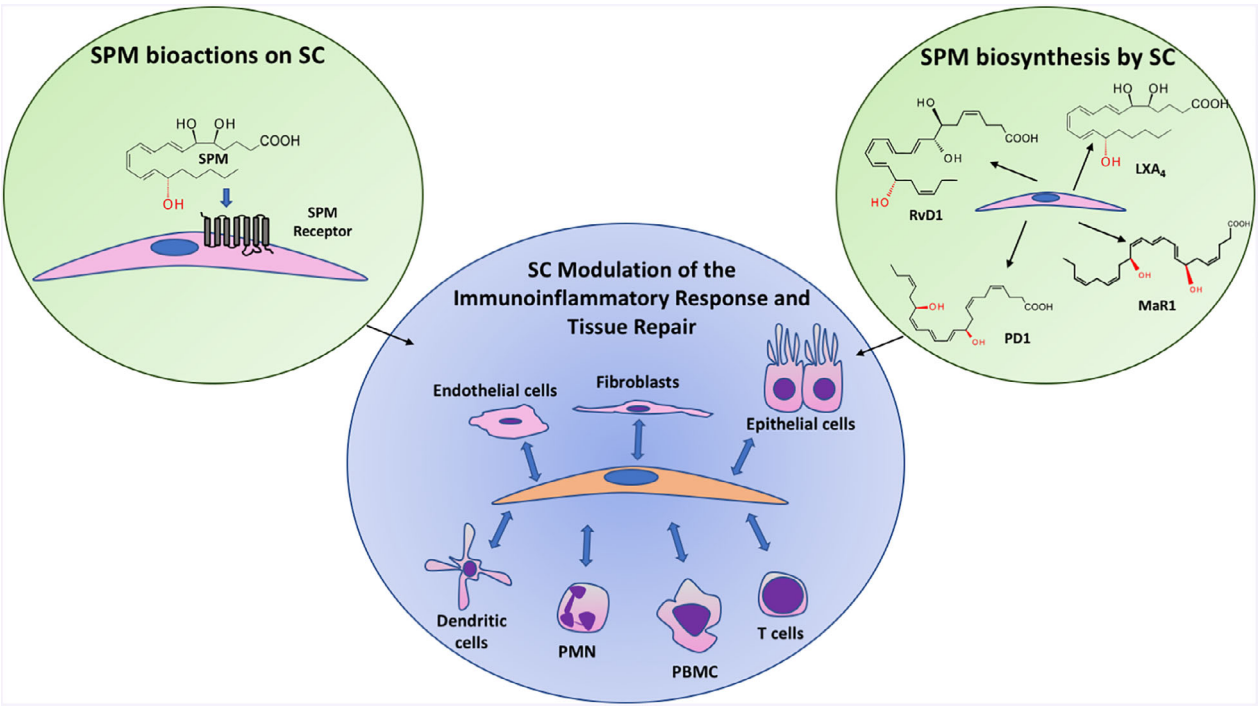

Figure 3. Scheme of specialized proresolving lipid mediator (SPM) involvement in stem cells (SCs) pathobiology. SPM binding to its cognate receptor expressed by SCs (top-left) in conjunction with SPM generation by SCs (top-right) can regulate SC-governed pathways involved in immunoregulation, inflammation 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 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 LXA_4 [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 LXA_4 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 $Lin^{-}c\text{-}Kit^{+}Sca\text{-}1^{+}$ 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 LXA_4 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.

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.

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