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EDITORIAL

Gingival-derived mesenchymal stem cells: An endless resource for regenerative dentistry

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Abstract

The gingiva, the masticatory portion of the oral mucosa, is excised and discarded frequently during routine dental treatments and following tooth extraction, dental crown lengthening, gingivectomy and periodontal surgeries. Subsequent to excision, healing eventually happens in a short time period after gingival surgery. Clinically, the gingival tissue can be collected very easily and, in the laboratory, it is also very easy to isolate gingival-derived mesenchymal stem cells (GMSCs) from this discarded gingival tissue. GMSCs, a stem cell population within the lamina propria of the gingival tissue, can be isolated from attached and free gingiva, inflamed gingival tissues, and from hyperplastic gingiva. Comparatively, they constitute more attractive alternatives to other dental-derived mesenchymal stem cells due to the availability and accessibility of gingival tissues. They have unique immunomodulatory functions and well-documented self-renewal and multipotent differentiation properties. They display positive signals for Stro-1, Oct-4 and SSEA-4 pluripotency-associated markers, with some co-expressing Oct4/Stro-1 or Oct-4/SSEA-4. They should be considered as the best stem cell source for cell-based therapies and regenerative dentistry. The clinical use of GMSCs for regenerative dentistry represents an attractive therapeutic modality. However, numerous biological and technical challenges need to be addressed prior to considering transplantation approaches of GMSCs as clinically realistic therapies for humans.

Key words: Gingival-derived mesenchymal stem cells; Regenerative dentistry; Lamina propria of the gingiva; Gingiva; Stem cell therapy

Core tip: Current therapeutic interventions in dentistry depend on biomaterials such as metals, polymers, ceramics, and composites. These restorative synthetic dental materials cannot restore the physiological architecture and function of the tissue. Thus, dentistry should move from restorative to regenerative dentistry, with the ability to regrow damaged or missing teeth with their own dental stem cells. Regenerating an entire tooth or individual parts of the tooth require a suitable number

of specific stem cell populations for use and implantation. Considering their neural crest origin and ease of availability, gingival-derived mesenchymal stem cells should be considered as an attractive source for stem cells that can be used in regenerative dentistry.

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INTRODUCTION

New directions for biomaterials research in dentistry is focused mainly on two different aspects. The first field of investigation involves the use of existing technology, such as conventional dental materials with the use Polyethylene fiber (ribbond) and Panavia F cement to give additional strength to the reattached tooth fragment of vital maxillary anterior teeth and obtaining fracture resistance equal to an intact tooth[1]. This involves machineries that use the ER:Yag laser, which is a more conservative alternative to conventional acid-etching for aesthetic brackets[2]. The second field of investigation involves research about new features, such as biomimetic materials that use fiber reinforced composite and polyethylene fibers with nanohybrid composite as alternates to crown coverage for endodontically-treated molars[3]. In addition, computer-aided design/computer-aided manufacturing of customized devices is used to improve the standardization process in the evaluation of cell behavior on different biomaterials for *in vitro* research on biomedical scaffolds[4]. Furthermore, nanomaterials with the use of nanofillers are used to improve the mechanical properties of fiber-reinforced composites that are polymerized with light-curing and additional postcuring[5]. Lastly, stem cells are also used as a source for regenerative therapies in dental research and practice[6].

Gingiva is the band from the masticatory mucosal tissue that encircles the necks of erupted teeth, and is considered as one of the constituents of the periodontium. Anatomically, the gingiva is divided into free, attached and interdental areas. The attached gingiva is tightly bound to the cementum of the root and to the underlying periosteum of the maxillary and mandibular alveolar bone. Histologically, the gingiva is composed of stratified squamous epithelial tissue supported by a matrix of dense fibrous connective tissue stroma termed lamina propria. Developmentally, the connective tissue of the gingiva is derived from both the neural crest and the mesenchyme. In cranial regions, neural crest cells are thought to differentiate into a wide variety of ectomesenchymal and non-ectomesenchymal derivatives[7]. The formed ectomesenchyme plays a pivotal role in the formation of the soft and hard tissues of the head and neck region, such as the majority of facial connective tissues and the facial skeleton, while the non-ectomesenchymal derivatives consist of pigment cells, glia and neurons[8].

Consequently, stem cells have been recognized in different oral tissues, such as stem cells isolated from exfoliated deciduous teeth, bone marrow-derived stem cells isolated from orofacial bones, stem cells from the apical papilla and dental follicle, dental pulp stem cells isolated from dental pulp tissue, periodontal ligament stem cells, progenitor/stem cells from oral epithelium, periosteum-derived stem cells, salivary gland-derived stem cell and gingival-derived mesenchymal stem cells (GMSCs) from gingival lamina propria[9]. The gingiva represents the most accessible, abundant, conservative and minimally-invasive source for stem/progenitor cell isolation from the oral cavity[10]. GMSCs can be isolated from normal or inflamed gingiva, from the attached and free gingiva, and from hyperplastic gingiva. Periodontal lesions, albeit inflamed, retain healing potential as inferred by the presence of MSC-like cells with similar immunophenotypic characteristics to those found in healthy periodontal tissue[11]. These stem cells can be isolated through enzymatic digestion or explant culture, have the liability to differentiate into different mesenchymal lineages, and are also associated with immunomodulatory properties. Therapeutically, these cells were used for skin wound repair, tendon periodontal, and bone defect regeneration. They were also used to treat peri-implantitis, oral mucositis, experimental colitis, collagen-induced arthritis, and contact hypersensitivity. In addition, they also are known to have antitumor effects[12].

STUDY ANALYSIS

Our study, along with others, have launched the earliest appraisal on GMSCs and carried out several biological research investigations. In the head and neck region, GMSCs can be used as the cellular components for 3D bio-printing of scaffold-free nerve constructs to meet the increasing clinical demand for peripheral nerve repair and regeneration[13]. They could also be used as a strategy to treat accidental or surgery trauma, especially for cranial bones[14], as well as to treat gingival defects with a safe and effective innovative treatment method[15]. They also may help ameliorate the regeneration of partially-dissected submandibular salivary gland, especially when combined with fibrin glue[16], and have shown significant potential for periodontal tissue regeneration[17]. Although neither full nor partial biological tooth regeneration has been achievable, emerging opportunities in stem cell therapy may shift the paradigm in the future. The quality of stem cells is extremely important, as cells obtained from younger patients are of exceptionally higher value *vs.* older ones. In addition, their differentiation capacity, accessibility and possible immunomodulatory properties should be considered. Most of the regenerative studies have been done *in vitro* or in animal models,

and data from human clinical research remains scarce. The successful application of stem cells in the clinical practice of dentistry remains an elusive and challenging objective.

PERSPECTIVE

Mesenchymal stem cells from adult gingival mucosa retain unique features, including multipotent differentiation capacity, neural crest origin, potent immunemodulatory properties, and fetal-like phenotypes. These features, with their ease of availability, noninvasive access to gingival tissue, and fast tissue regeneration after gingival excision, make gingiva a fascinating source for cell isolation and regenerative dentistry. These cells are attractive to treat diseases like dental caries and periodontitis, or to improve the regeneration of craniofacial bone[6]. In contrast to bone marrow-derived mesenchymal stem cells, these cells are more closely related to dental tissues. To achieve this goal, experimental animal studies should be accomplished to ensure the ability of these cells to form such dental structures. This step should then be followed up with clinical trials that involve an adequate population number.

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REVIEW

Regulatory role of sphingosine kinase and sphingosine-1-phosphate receptor signaling in progenitor/stem cells

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Abstract

Balanced sphingolipid signaling is important for the maintenance of homeostasis. Sphingolipids were demonstrated to function as structural components, second messengers, and regulators of cell growth and survival in normal and disease-affected tissues. Particularly, sphingosine kinase 1 (SphK1) and its product sphingosine-1-phosphate (S1P) operate as mediators and facilitators of proliferation-linked signaling. Unlimited proliferation (self-renewal) within the regulated environment is a hallmark of progenitor/stem cells that was recently associated with the S1P signaling network in vasculature, nervous, muscular, and immune systems. S1P was shown to regulate progenitor-related characteristics in normal and cancer stem cells (CSCs) *via* G-protein coupled receptors S1P*n* (*n* = 1 to 5). The SphK/S1P axis is crucially involved in the regulation of embryonic development of vasculature and the nervous system, hematopoietic stem cell migration, regeneration of skeletal muscle, and development of multiple sclerosis. The ratio of the S1P receptor expression, localization, and specific S1P receptor-activated downstream effectors influenced the rate of self-renewal and should be further explored as regeneration-related targets. Considering malignant transformation, it is essential to control the level of self-renewal capacity. Proliferation of the progenitor cell should be synchronized with differentiation to provide healthy lifelong function of blood, immune systems, and replacement of damaged or

dead cells. The differentiation-related role of SphK/S1P remains poorly assessed. A few pioneering investigations explored pharmacological tools that target sphingolipid signaling and can potentially confine and direct self-renewal towards normal differentiation. Further investigation is required to test the role of the SphK/S1P axis in regulation of self-renewal and differentiation.

Key words: Sphingosine-1-phosphate; Sphingolipids; Embryonic stem cells; Mesenchymal stem cells; Bone marrow hematopoietic stem cells; Sphingosine kinase; Progenitor

Core tip: The aim of this study is to review the role of sphingosine kinase, sphingosine-1-phosphate (S1P), and its receptors in the regulation of stem/progenitor cell function. Our analysis indicates that S1P receptor expression, localization, and specific downstream effectors influence the rate of self-renewal and differentiation of myogenic, hematopoietic, endothelial, neural, and cancer progenitor cells.

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INTRODUCTION

During organism growth, development, and adaptation to changed environmental conditions, orchestrated functioning of multiple processes supports physiological homeostasis. The synchronization should occur at the level of a single cell, such as controlled cell division and apoptosis, and at the level of organs and systems, such as directed angiogenesis, immune responses, and regeneration. Many of those biological processes have been shown to rely on the sphingolipid signalling cascade. An important member of the sphingolipid family, sphingosine-1-phosphate (S1P), is a bioactive signalling molecule. S1P effects are essential for structural and functional regulation of cell growth and survival. The main source of S1P is catabolic degradation of membrane glycosphingolipids and sphingomyelin, which results in production of sphingosine which, in turn, is phosphorylated by sphingosine kinases (SphK1 and SphK2)[1,2]. Supported by experimental evidence observed in *Sphk* knockout mice *in vivo*, SphK isozymes can partially balance metabolism for each other, although there are some SphK1- and SphK2-specific non-overlapping functions[3,4].

Suggestively, S1P is generated during membrane restructuring in all types of cells. Locally produced S1P can act either intracellularly or extracellularly. S1P can be released to the extracellular environment by erythrocytes[5], platelets[6], and endothelial cells[7]. Circulating S1P is an important signalling mediator and ligand for specific G protein-coupled receptors S1P*n* (*n* = 1 to 5)[8,9]. S1P1 is highly expressed in various tissues, but specifically in endothelial cells and vasculature. S1P2 and S1P3 are also broadly expressed, although their levels of expression demonstrated some function specificity. Activated S1P receptors trigger distinctive downstream effectors and respective responses[10,11]. Intracellularly produced S1P can be utilized in two different metabolic pathways[8,12]. Firstly, S1P can be recycled through ceramide synthesis by S1P-specific phosphatases[13]. Secondly, S1P can be irreversibly degraded by S1P lyase into phospho-ethanolamine and hexadecenal linked to a variety of intracellular signalling cascades[14].

Various growth stimulating agents, hormones, and cytokines, the canonical regulators of cell proliferation and survival, can activate SphK and stimulate S1P production. Hormones, cytokines, and growth factors including EGF[15], PDGF[16], IGF[17], VEGF[18], NGF[19], TGF[20], TNF[21], and the steroid hormone estrogen[15,22,23] were shown to trigger SphK1/S1P signaling in different cells. Supporting the global role of the sphingolipid network in regulation of proliferation, the list of SphK/S1P-inducing agents keeps growing. Recent experimental findings demonstrate that S1P and its network play a complex role in the regulation of stem/progenitor cell signalling in normal and malignant tissues.

Stem or progenitor cells are defined as undifferentiated cells with specific clonogenic potential, unlimited self-renewal capacity that is accompanied by directed differentiation into multiple (often limited to a specific number) cell lineages[24,25]. According to their programmed differentiation potential, stem cells are encoded for particular tissue regeneration and cell replacement. For instance, pluripotent embryonic stem cells (ESCs) can differentiate into cell-types of all the primary germ layers. Bone marrow (BM)-located adult stem cells are considered multipotent[26] or pluripotent[27,28]. Other groups of adult stem cells are oligopotent, bipotent, or unipotent and are represented by basal cells in the epidermis, spermatogonial stem cells, and satellite cells in skeletal muscles[28]. The cells with limited potency are often referred to as progenitor cells and include, for instance, endothelial progenitor cells (EPCs)[29] and pancreatic progenitor cells[30]. Progenitor cells are marked not only by limited number of divisions, but also higher levels of directed lineage differentiation.

The core properties of ESC pluripotency are maintained by a group of lineage-specific transcription factors (TFs) such as Nanog, Oct4, and Sox2-NOS and their regulatory networks[31]. Recently, it was demonstrated that high intracellular levels of S1P is associated with

increased mouse ESC proliferation and higher expression of the cell surface pluripotency markers SSEA1 and Oct4[31]. The authors found that ESCs express high level of sphingosine phosphate lyase (SPL), an enzyme that catalyzes the S1P degradation, thus, keeping the intracellular level of S1P under tight control[32]. During the last decade, besides the detected effects in ESCs, the regulatory role of sphingolipids has been assessed in several types of precursor multipotent cells including neural, muscle, hematopoietic, endothelial, and mesenchymal progenitor/stem cells. S1P was suggested to functions as a trophic factor for many stem cell types. However, the role of sphingolipids in the regulation of cell renewal and differentiation remains only partially addressed. Here, we review and discuss recent advancement and development about the functional role of sphingosine kinase, S1P and S1P receptors in stem/progenitor cells.

SPHK/S1P/S1P RECEPTORS SIGNALLING IN HEMATOPOIETIC AND ENDOTHELIAL STEM/PROGENITOR CELLS

Hematopoietic stem cells (HSCs) represent the rare population of precursor cells that defines the blood composition and homeostasis. HSCs are characterized by their unique capacity for self-renewal and multi-lineage differentiation. HSCs and downstream partially lineage-committed progenitor cell functions are tightly linked to their migratory properties, especially during fetal development[33,34]. Although the majority of postnatal and adult HSCs/progenitors stay in BM specialized niches or cavities[35], some of the HSCs/progenitors belong to a highly migratory subpopulation that recirculates between BM and blood[36,37]. Suggestively, the HSC/progenitor trafficking mechanism supports full occupancy of stem cell niches in all BM cavities[37,38]. HSC trafficking is directed by an S1P blood/lymph/tissue gradient that is mostly maintained by SphK/S1P receptor and S1P-degrading enzyme S1P lyase network[38]. Notably, another well-studied sphingolipid, ceramide-1-phosphate (C1P), can also enhance the migration of endothelial and lymphoid progenitor cells[39], suggesting that other sphingolipid family members should be tested for potential involvement in the regulation of hematopoietic stem/progenitor cell functions.

S1P concentration in peripheral blood and lymph regulates HSC and lymphocyte egress from lymphoid organs[34,37]. HSCs and progenitors express S1P1 receptor(s) that can sense blood plasma S1P and direct stem cell migration[40]. Although water-insoluble S1P binds apolipoprotein M and circulates in peripheral blood mostly as a part of high-density lipoprotein (HDL) particles, the level of S1P is always higher in plasma and lymph compared to the S1P level in interstitial fluids of all organs, including thymus and lymph nodes[41,42]. The concentration gradient serves as a chemoattractant to direct the migration of S1P1-expressing cells from BM to peripheral blood[37,40]. Similarly, lymphocyte egress from lymph nodes is directed by the S1P gradient between lymphoid tissue and lymph[38]. The level of S1P1 receptor expression is a critical factor that regulates sensitivity to circulating S1P. Expressed in blood or lymph-circulating cell, S1P1 receptors are rapidly internalized and downregulated through G-protein coupled receptor kinase-2–mediated phosphorylation[43]. Inside of tissue, S1P1 is up-regulated under the condition of low-S1P concentration in interstitial fluids. The high level of S1P1 on tissue-located cells supports the traversing of cells from tissues towards high S1P in blood plasma or lymphatics. Animal HSCs also express S1P1 receptors that mediate stem cell trafficking from BM into peripheral blood[44]. The mouse model has allowed for the use of the specific S1P1 inhibitor W146, which confirmed a key role for the receptor in BM retention of hematopoietic cells[44].

Three different S1P receptors, including S1P1, S1P2, and S1P3, influence the development and function of the embryonic vasculature[45,46]. The S1P/S1P1 axis plays a leading role during embryonic vascularization and angiogenesis. Supporting a functional link between the endothelial and red blood cell network, S1P synthesis and release from erythrocytes is required for embryonic vascular development[47]. S1P2 and S1P3 effects are considered important, although as accessory or partially redundant in some studies[11,12].

Activated S1P1 receptor has been found to stimulate the proliferation of endothelial vascular (outgrowth) progenitors[48] and colony-forming cells[49]. Morphogenesis of the kidney vasculature is also mediated by S1P1 signalling. A hypothetical endothelial and hematopoietic precursor has been shown to express S1P1 receptor in the kidney. The receptor activation maintains an appropriate development of glomerular capillaries, arterial mural cell coating, and lymphatic vessel development[50]. Besides S1P1, S1P3 receptor positively directs capillary-like formation and EPC migration. Notably, S1P2 partially blocks the migratory capacity of mesenchymal progenitor cells, mesangioblasts, whereas SphK and/or S1P1/S1P3 are involved in the positive regulation of angiogenesis *in vivo*[20,45]. S1P2 signalling is clearly tissue-specific and can promote proliferation in different cells similarly to S1P1 and/or S1P3. Accordingly, small hepatocyte-progenitor and stem (oval) cell proliferation is positively associated with S1P2 and S1P4 expression during liver injury[51]. Furthermore, S1P2 promotes the growth of primary $CD34^+$ mononuclear cells obtained from chronic myeloid leukemia (CML) patients[52].

The S1P-producing enzyme SphK1 is partially responsible for the maintenance of the EPC-specific phenotype. SphK1 controls the rate and direction of EPC differentiation, although the enzyme expression level did not affect the hematopoietic compartment[53]. The authors detected high levels of SphK1 activity in EPCs, which gradually decreased in more differentiated endothelial

cells. Notably, *SphK1* knockout mice demonstrated higher levels of circulating EPCs[53]. The data suggests a potential negative role of the enzyme in the regulation of vascular regeneration when the presence of EPCs in circulation is highly desirable, although the question requires further investigation. Overexpression of SphK1 facilitates the retention of EPCs at the progenitor stage with probable delay in the following differentiation program, but that was not tested. Suggestively, SphK1 function in EPCs can be replaced by SphK2. The role of SphK2 in the regulation of EPC function remains unclear.

The S1P3 receptor axis influences some specific S1P responses in EPCs. Patient-derived EPCs were tested for the activation of G protein-coupled protein receptor C-X-C chemokine receptor 4 (CXCR4) signalling. CXCR4 axis is an important regulator of pluripotent cell development and function, as it is involved in the interaction between HSCs cells or hematologic and solid tumor cells and their protective microenvironment[54]. It was detected that the S1P/S1P3 axis positively induced the CXCR4-dependent signalling pathway[55]. Furthermore, the specific S1P1 receptor antagonist FTY720 increased CXCR4-dependent chemotactic responsiveness and migration of human $CD34^+$ lineage-committed progenitor cells[56]. Similarly, besides EPCs, S1P1 and S1P3 activation was required in the regulation of CSCs migration[57,58].

S1P1 effects were tested in megakaryocytes, the thrombocyte lineage-specific progenitors. S1P1 is involved in the initiation of the elongation of trans-endothelial pro-thrombocyte extensions into BM sinusoids and activates the subsequent shedding of thrombocytes[59]. During activation, platelets can release considerable amounts of S1P and further increase S1P concentration in blood plasma besides the release of the lipid from erythrocytes and endothelial cells[60]. The sudden local increase in S1P concentration is potentially associated with activation of immune cell migration. The role of platelet-derived S1P in the regulation of HSCs and/or progenitor trafficking requires further testing.

SPHK/S1P/S1P RECEPTORS SIGNALLING IN MUSCLE STEM/PROGENITOR CELLS

Skeletal muscles are formed by myoblasts, muscle cell progenitors. The multistage process of myogenesis is preceded by myoblast division, which is followed by terminal differentiation, cell merging into multinucleated myofibers, and maturation[61-63]. The initiation of the myoblast differentiation process is marked by progenitor cell cycle cessation accompanied by vigorous synthesis of myogenin and expression of muscle-specific proteins, including sarcomeric components and creatine kinase[61]. Represented by quiescent mononucleated satellite cells, adult muscle cell progenitors employ a similar differentiation program as developing myoblasts[62]. The satellite cells/myoblasts, although mitotically quiescent, can be induced to proliferate by physical trauma, weight bearing, or inflammation-induced trauma[64]. After multiple rounds of satellite cell divisions, the cell cycle stops and the newly produced cells fuse onto the existing damaged muscle fibers. This process was observed *in vitro* using C2C12 cells, a skeletal myoblast cell line derived from murine satellite cells[65-67]. Despite significant progress, the molecular mechanisms of myogenesis remain only partially explored. For instance, molecular regulation of muscle progenitor signalling and associated repair mechanisms remain largely unclear, although growth factors and cytokines have been confirmed to regulate skeletal muscle biology[63]. Sphingolipids can transduce signalling from growth factor and cytokine receptors as messengers and amplifiers in a large variety of cells[11]. Consequently, the role of sphingolipids has been examined in the regulation of myogenesis.

Traumatic tissue injury and subsequent inflammatory activation of leukocytes and macrophages are marked by the release of cytokines and growth factors that can stimulate skeletal muscle regeneration and remodelling[63,68]. One of the keystone recent discoveries demonstrated a direct link between sphingolipid signalling and trauma/inflammation-provoked responses in muscle progenitor cells[67]. Bradykinin and its related peptides are pro-inflammatory molecules and muscle-specific growth factors that mediate exudative and inflammatory phases of muscle healing[69,70]. Bradykinin is also the leading member of the kinin/kallikrein system, which directs inflammation-linked responses in mesenchymal cells including fibroblasts, myofibroblasts, and smooth muscle cells[70]. Bradykinin has been shown to induce myogenic differentiation in C2C12 myoblasts through SphK1, the specific S1P-transporter spinster homolog 2 (Spns2), and S1P2 receptor. Specific pharmacological inhibition and/or protein expression silencing was used to confirm the involvement of the S1P axis in bradykinin-induced myogenic differentiation[67].

Serving as a muscle trophic factor, S1P has been suggested to play a leading role in the stimulation of myogenesis and regeneration provoked by various agents *via* transactivation of the $S1P_2$ receptor pathway[65,66,71,72]. Extracellular S1P reduced serum-induced cell proliferation, promoted cell cycle exit, and up-regulated the expression of various differentiation markers in myoblasts. The S1P-dependent myogenic differentiation is mediated by S1P2, activation of ERK1/ERK2 and p38 MAPK, both identified as downstream effectors of S1P2[71]. Furthermore, insulin growth factor 1 (IGF-1) increased SphK activity and induced transactivation of the S1P2 receptor in C2C12 murine myoblasts. The activation was linked to the IGF-1 myogenic differentiation effect. Pharmacological inhibition of SphK, specific silencing of SphK1 or SphK2, and S1P2 receptor downregulation resulted in reduction of the IGF-1 pro-differentiating effect in myoblasts[66]. Interestingly, IGF-1 also activated S1P1/S1P3 receptors. Contrary to S1P2, S1P1/S1P3 negatively regulated the IGF-1-induced

mitogenic differentiation. Specific silencing of S1P1/S1P3 receptors notably stimulated myoblast proliferation[66]. The data correspond to the growth-stimulating signalling of S1P3 in tumors where the ability of sphingolipids to mediate IGF-1 effects is well recognized[11]. The myogenesis-stimulating role of S1P2 is partially unexpected, as S1P2 anti-proliferative effects were previously observed in various, although mostly not stem-like cells[11,12]. S1P2 was shown to inhibit Rac signalling and related cell migration contrary to its demonstrated effects in myoblasts[73]. However, the divergence might be associated with the high specialization of stem cells and adjustments to pluripotency of the S1P2 signalling network. Notably, S1P2 induced the myogenic differentiation program independently of acute S1P treatment[67]. Conclusively, the pleiotropic role of SphK/S1P receptor axis in skeletal myoblasts reflects the association of S1P receptor expression pattern with contrasting biological responses.

Proliferative and chemotactic effects of vascular endothelial growth factor (VEGF) signalling are also transduced by SphK/S1P network in muscle progenitor cells[74]. Previously, VEGF signalling pathway was shown to interact with the SphK/S1P axis in several types of normal[75] and malignant cells[12,18]. SphK activation and S1P1 expression can be induced by VEGF. S1P1 and VEGF receptor-2 (VEGFR-2) proteins were found to interact and form a signalling complex[11,18]. The interaction was described as mutual, as S1P enhanced the levels of VEGF expression and transactivated VEGFR-2[11,18,75]. The role of S1P in the mediation of VEGF myogenesis-related effects was confirmed in another study that tested the role of bone-marrow-derived mesenchymal stromal cells (MSCs) as regulators of myogenesis. MSCs synthesize and release a large amount of S1P, which assists in skeletal muscle healing[74]. Conditioned media with MSC-secreted S1P stimulated C2C12 myoblast and satellite cell proliferation. A similar effect was reached by exposure to VEGF, as the myoblast growth response to MSC-secreted VEGF also induced S1P release from C2C12 cells[74,75].

Notably, the involvement of $S1P_2$ and $S1P_3$ receptors in the regulation of myogenesis was detected more than a decade ago[76]. Meacci *et al*[76] observed that myogenic differentiation was accompanied by a significant variation in S1P receptor expression levels. The authors also suggested that the S1P signalling axis is a key component required for sphingolipid effects in proliferating muscle cells[76]. However, the authors observed that the S1P2 receptor is down-regulated during myogenesis, while SphK was enhanced in differentiating C2C12 myoblasts[77]. Suggestively, S1P2 and S1P3 can be activated during different stages of myogenesis and stimulate alternative biological responses in regular and progenitor muscle cells. For instance, S1P3 levels are high in quiescent murine myogenic cells, but decrease during cell cycle initiation[78]. Constitutive expression of S1P3 resulted in the suppression of satellite cell cycle progression. S1P3-null satellite cells exhibited enhanced proliferation. Acute cardiotoxin-induced muscle regeneration was promoted in S1P3-null myoblasts *in vivo,* marked by bigger muscle fibers compared to control mice. The data are supported by experimental observations in the mdx mouse model of Duchenne muscular dystrophy. S1P3 knockdown produced a less severe muscle dystrophic phenotype, indicating that the S1P3-linked pathway represses cell cycle progression to direct myoblast functions[77].

Myoblasts and fully differentiated muscle cells are marked by a heterogeneous expression pattern of S1P receptor subtypes. S1P1 has been mostly found in cardiomyocytes, while S1P2/S1P3 receptors are expressed by cardiac progenitor cells[78]. S1P receptor activates Rho signalling, which in turn, switches in the proliferation of cardiac myoblasts. Notably, both S1P2 and S1P3 induce RhoA activation through $G\alpha12/13$ during myocardial regeneration, indicating some redundancy of signalling pathways[78]. However, there is some specificity for different S1P receptor subtypes. For instance, during construction of the primary heart tube in zebrafish, S1P2 controls proper endoderm formation and cardiac myoblast migration[79]. Notably, in another study, S1P2 negatively regulated satellite cell migration, while S1P1/S1P4 facilitated the S1P migratory effect in myoblast cells[72].

Considering muscle-specific cytoskeletal remodeling, the role of specific S1P receptors is unclear. Myoblasts and satellite cell differentiation capacity depends on cytoskeletal remodelling and can be controlled by gap junction proteins, particularly connexin (Cx) 43[80]. It has been shown that S1P induces p38 MAPK activation, phosphorylation of Cx43 and association of Cx43 with cortactin and F-actin, followed by murine C2C12 myoblasts differentiation[81]. S1P-induced C2C12 myoblast differentiation and transient receptor potential canonical 1 (TRPC1) channel activity have been linked to Cx43 expression/function *via* calpain/PKCα axis[76], although the involvement of S1P receptor has not been demonstrated.

Transforming growth factor beta 1 (TGFβ1), inflammation-associated pleiotropic cytokine, was shown to control skeletal muscle regeneration *via* S1P3 receptor signalling[65]. TGFβ1 increased levels of SphK1 in C2C12 myoblasts in a Smad-dependent manner and stimulated the expression of S1P3 receptors that resulted in induction of fibrosis. The study demonstrated the involvement of Rho/Rho kinase signalling downstream of S1P as profibrotic TGFβ1 effect[65]. Notably, S1P receptors are linked to various downstream effectors in myoblasts. For instance, S1P2 myogenic signalling is mediated by activated phosphatidylinositol 3-kinase (PI3K)[72] and signal transducer and activator of transcription 3 (STAT3)-dependent pathways[82]. The biological meaning of the divergence of S1P receptor signalling requires further clarification (Figure 1). For instance, Rho signalling that can mediate S1P effects in non-pluripotent cells[73] is also activated in cardiac myoblasts[76], suggesting that S1P isoforms might be linked to similar downstream

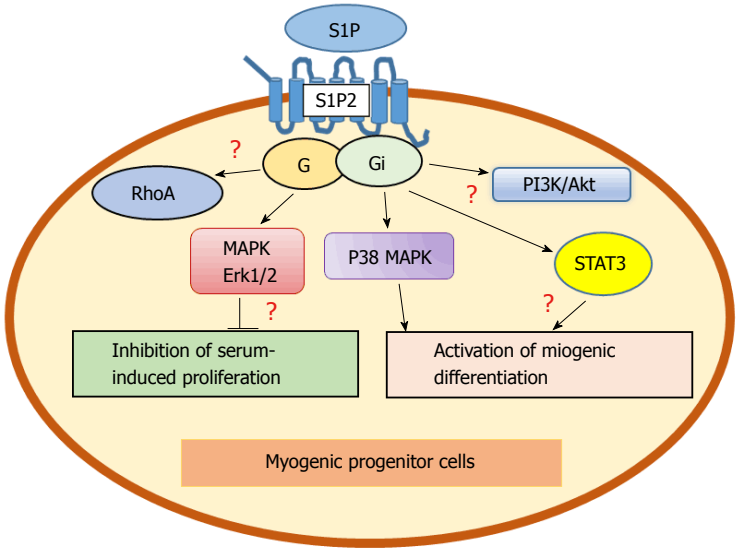

Figure 1 Diversion of myogenic stimulation at the S1P2 receptor level (hypothetical scheme). Activation of S1P2 receptor signaling results in dual effects in muscle progenitor cells: Erk1/2 mediates inhibition of serum-induced proliferation, while p38MAPK[78,79], phosphatidylinositol 3-kinase (PI3K)[72] and activator of transcription 3 (STAT3)-dependent pathways[82] are required for S1P-trigerred activation of myogenic differentiation. The role of RhoA signaling is unclear. Question marks indicate unclear signaling regulation. S1P: Sphingosine-1-phosphate.

effectors independently of pluripotency. Future studies should clarify how S1P receptors induce different effects in normal, malignant, and progenitor cells using similar downstream effectors.

It has been shown that myogenesis is regulated not only by SphK/S1P receptors, but also by other S1P metabolizing enzymes, including S1P lyase. The lyase irreversibly catabolizes S1P at carbon bond C(2-3), producing hexadecenal and ethanolamine-phosphate. The lyase enhances apoptosis induced by chemotherapy, radiation and ischemia in different cells[82]. Undetectable in resting skeletal muscle, the S1P lyase level is upregulated after muscle injury[82]. The mdx mouse model for muscular dystrophy was marked by skeletal muscle S1P lyase upregulation and S1P deficiency *in vivo*. Accordingly, pharmacological S1P lyase inhibition stimulated an increase in muscle S1P levels and myoblast recruitment, thus advancing mdx skeletal muscle regeneration[82]. S1P lyase knockdown cells demonstrated increased levels of intra- and extra-cellular S1P, but decreased myotube formation and delayed induction of three myogenic microRNAs (miRNAs) including miR-1, miR-206, and miR-486[83]. Myotube formation was recovered in cells treated with an S1P1 agonist, S1P2 antagonist, and combination treatments. Transfection with miR-1 or miR-206 allowed the S1P lyase knockdown cells to reverse the inhibition of differentiation[83]. Considering that stem cell resistance to apoptosis is a keystone of regeneration, pharmacological inhibition of S1P lyase during specific stages of myogenesis seems like an attractive therapeutic approach to enhance muscular remodelling after injury[78,82].

Another sphingolipid C1P has been implicated in the regulation of skeletal muscle regeneration. C1P induced myoblast proliferation and myoblast cell cycle progression without activation of a putative G(i)-coupled C1P receptor[84]. C1P stimulated the phosphorylation of glycogen synthase kinase-3β and the production of retinoblastoma gene, and enhanced cyclin D1 protein levels. Furthermore, various downstream target proteins, including phosphatidylinositol 3-kinase/Akt, ERK1/2, and the mammalian target of rapamycin, mediated C1P signalling in myoblasts. Interestingly, C1P did not influence the induction of myoblast apoptosis or myogenic differentiation[84]. Previous knowledge of C1P signalling is limited to the demonstrated effects in fibroblasts and macrophages, thus, demanding further investigation of C1P role in progenitor cells.

According to the recently developed theory, brown adipose cells are derived from a mesenchymal progenitor that shares some similarity with muscle cell precursor cells and expresses Myf5-Cre proteins, while white adipocytes originate from a Myf5-negative precursor[85]. According to another theory, adipocytes arise from a vascular bed and originate from a subset of endothelial cells[86]. While the theory is clarified, S1P was revealed to promote differentiation of C3H10T1/2 multipotent mesenchymal stem cells into osteogenic rather than adipogenic progenitors[87]. Furthermore, adipose tissue itself was shown to contain stem cell progenitors. The adipose stromal-vascular cell fraction is an abundant source of both multipotent and pluripotent progenitor cells, defined as adipose-derived stem cells. S1P1 is involved in the induction of adipose-derived stem cell growth by HDL[88].

Obesity and metabolic disorders might be associated with dysfunctional adipose progenitor cells and diabetes. Notably, multipotent pancreatic progenitor cells (MPCs)

have been suggested as a promising target for the treatment of type-1 diabetes mellitus[30]. MPCs are stem cells with limited potency that proliferate and differentiate into three distinct lineages, including insulin-producing β cells, acinar cells, and ductal cells. The early MPCs were classified by the expression of the TFs Pdx1, Ptf1a, and Sox9, some of them known as mesenchymal progenitor markers[89]. High levels of Notch and Hippo/YES signalling are also required to maintain tree-like branched epithelium and block early MPC differentiation[90,91]. The SphK/S1P/S1P2 axis was found to support pancreatic progenitor differentiation[92]. S1P2, SphK1, and SphK2 expression levels were upregulated during pancreas second transition in the developing epithelium and co-localized with both trunk and tip progenitors[92]. S1P2 receptor activated YES-associated protein (YAP) and up-regulated connective tissue growth factor signalling important for the survival of endocrine and acinar pancreatic progenitors. S1P signalling decreased Notch regulation of lineage allocation necessary for endocrine and acinar specification[92]. *S1P2 receptor*-null embryos demonstrated high perinatal mortality marked by pathological hematopoietic and vascular system phenotypes[46]. Expression of a negative posttranscriptional regulator of Notch signalling protein Sel1l was also influenced by S1P2 signalling. S1pr2 inhibition resulted in the loss of the Sel1l protein, which in turn is required to maintain normal Notch signalling and proper acinar and endocrine differentiation[92]. Given such an important role of S1P2 in the regulation of MPC differentiation, the role of S1R receptors in the regulation of differentiation should be further explored in future studies.

Conclusively, the sphingolipid signalling network is a potential therapeutic target to influence myogenesis, adipogenesis, and associated metabolic pathologies including diabetes. Pharmacological control over sphingolipid signalling should be tested during induction of muscle regeneration, aging, inflammation and trauma-associated muscle fibrosis. The role of the SphK/S1P axis in the regulation of adipose cell precursor function and adipose-derived stem cell differentiation remains to be clarified in future studies.

SPHK/S1P/S1P RECEPTORS SIGNALLING IN NEURAL STEM/PROGENITOR CELLS

S1P signalling exhibited neuro-protective effects as a mediator of nerve growth factor (NGF) in hippocampal neurons and pheochromocytoma PC12 cells[93,94]. During the last couple of decades, several groups have addressed the role of sphingolipids in neural progenitor cells. Neural progenitor/stem cells (NPSCs) have limited potency, though they are still promising to for the treatment of Alzheimer's disease[95] and brain or spinal cord injuries[96]. Besides insufficient proliferation rates, NPSCs maintain slow differentiation and migration characteristics. However, similar to its effects on circulating immune cells in blood and lymph, extracellular S1P is a powerful chemoattractant for microglial cells in the brain. More effective than fibroblast growth factor (FGF), S1P is a powerful stimulator of neurogenesis[97] (Figure 2). S1P can mediate FGF signalling in different neural cells. It was found that FGF coordinates S1P release from astrocytes. The extracellular S1P, through autocrine or paracrine mechanisms, stimulates astrocyte differentiation mediated by S1P receptors[98]. Previously, it was demonstrated that cerebellar astrocytes express S1P1, S1P2, and S1P3 receptors[99]. Another study indicated that S1P3 is overexpressed in astrocytes under pro-inflammatory conditions[100]. However, astrocytes are not true progenitor cells, but rather precursor cells. Furthermore, S1P receptor demonstrates heterogeneous expression in neural and NPSCs[101,102]. For instance, up-regulation of S1P1 was noted in NPSCs that migrate out of the embryoid body/ESCs[103]. However, the level and role of S1P receptor subtypes in NPSCs remains controversial, as different studies have demonstrated noticeable variations in S1P receptor expression[104].

In the presence of activated astrocytes, S1P further enhances NPSCs differentiation, indicated by neurite outgrowth and arborization[97,105]. Notably, neural precursors derived from ESCs express all five S1P receptor mRNAs, although S1P2 and S1P3 mRNA levels are the highest[97,105]. The effect of S1P on NPSCs is mediated by increased laminin expression and extracellular matrix (ECM) interactions with progenitor integrins. However, the role of particular S1P receptor subtypes has not been verified. For instance, the role of S1P2 remains unclear. Kimura *et al*[106] demonstrated that NPSC migration to sites of injury was inhibited by S1P2 activation.

The role of SphK/S1P in neural stem cells has been explored by Meng *et al*[107]. The authors detected SphK1 expression in neuron and progenitor cells of nascent trigeminal and dorsal root ganglia of the mouse embryo. The enzyme was found to increase NPSC proliferation and survival during early sensory ganglia development[107]. Embryos with both *Sphk1* and *Sphk2* genes knocked out displayed clear developmental defects marked by fewer neurons and progenitor cells in trigeminal and dorsal root ganglia[107]. This finding supports the previously shown data of crucial involvement of SphK1/S1P axis in the regulation of cell growth and survival in the developing neural system[107-110]. According to the proposed mechanism, sphingolipids are involved in neural cell signalling downstream of p75 and/or neurotrophin receptor pathways[107,111-117].

To establish a role for S1P in the regulation of neural cell survival, Saini *et al*[118] tested the involvement of SphK1 in the neurotrophin-3 (NT-3) signalling pathway. It was found that SphK1 mediates NT-3–dependent activation of cAMP-response element binding protein (CREB) in cultured oligodendrocyte progenitors. NT-3 increased SphK1 activation and translocation from the cytoplasm to the plasma membrane of oligodendrocytes.

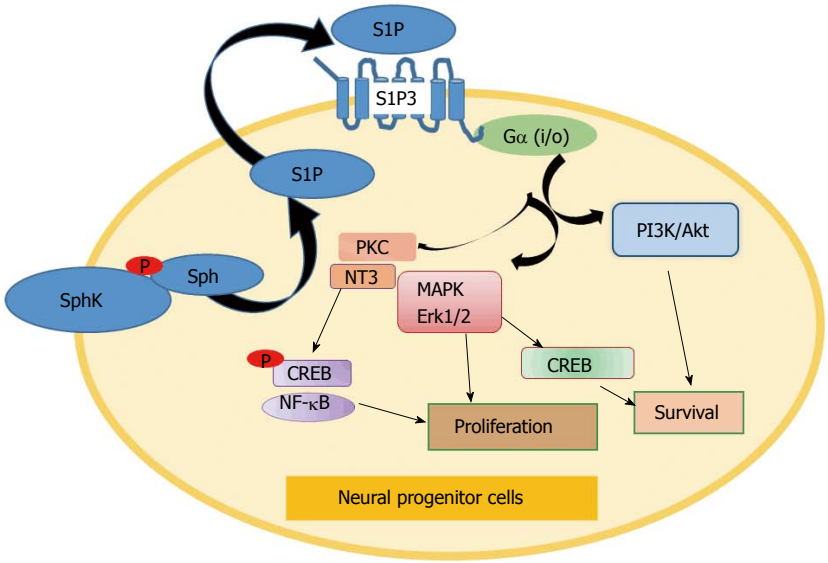

Figure 2 Sphingosine kinase/sphingosine-1-phosphate signaling axis in neural stem/progenitor cells (hypothetical scheme). Activation of S1P3 receptor signaling and activation of neural cell progenitor differentiation are mediated by various downstream effectors including PKC, PI3K/Akt, MAPK/Erk1/2, NT3, and CREB/NF-κB TFs. SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate; CREB: cAMP-response element binding protein; NT3: Neurotrophin 3; TF: Transcription factor.

The effects coincided with enhanced S1P accumulation at the membrane. Downregulation of SphK1 facilitated apoptosis in oligodendrocyte progenitors induced by growth factor deprivation. Inhibition of Erk1/2 and PKC also blocked NT3- and S1P-induced CREB phosphorylation, indicating a concerted interaction among NT-3, SphK, Erk1/2 and PKC pathways[115,119]. Crosstalk between NT-3 and SphK1 has been also demonstrated in animal models of multiple sclerosis[120]. Notably, PTEN and Notch signalling mediate the anti-fibrotic effects of dihydro-S1P in systemic sclerosis[121]. However, a complexity of functional crosstalk between NT-3 and SphK signalling requires further clarification during oligodendrocyte development.

Survival-related mechanisms of S1P effects were linked to multiple signalling pathways. For instance, S1P can activate membrane S1P receptor(s) to induce CREB phosphorylation in oligodendroglial progenitors[122-124]. Downstream S1P receptor effects were mediated by activation of Erk1/2 and PKC-dependent pathways in progenitor cells[102,122]. Another signalling mechanism was associated with activation of growth factor signalling[93]. For instance, platelet-derived growth factor (PDGF) receptor was shown to activate SphK1 in oligodendrocytes[123]. In turn, SphK1 mediated PDGF-dependent up-regulation of mRNAs encoding the Kv1.5 and Kv1.6 K^+ channels during oligodendrocyte proliferation[124]. Furthermore, SphK1 promoted survival of oligodendrocyte progenitors *via* upregulation of the anti-apoptotic protein Bcl-2 and downregulation of the pro-apoptotic protein Bim in a CREB-dependent manner. The mechanism is based on the established SphK1-dependent regulation of a balance between pro-apoptotic and anti-apoptotic Bcl-2 proteins shown in normal and cancer cells[11]. Considering genomic and epigenetic regulation, SphK1 can trigger the activation of various TFs, including AP-1 and NF-κB, which were shown to promote anti-apoptotic signalling[125-129]. Involvement of SphK/S1P/S1P3 receptor-dependent signalling in the regulation of survival and differentiation of neural stem/progenitor cells is summarized in Figure 2.

S1P receptor demonstrates heterogeneous expression in neural cells. Brain white matter cells contain the highest expression of S1P2[130]. S1P5 is expressed by mature oligodendrocytes where the receptor regulates survival and cell process retraction[131]. Higher expression level and activation of S1P1 facilitates survival of oligodendrocyte progenitors and induces oligodendroglial differentiation[132]. NPSCs derived from ESCs express all five S1P receptor mRNAs, although the actual protein expression level was not tested[105].

The level of S1P receptor subtype requires utter attention, as a large group of S1P receptor agonists/antagonists has been developed to target the receptor signalling in the central nervous system. For instance, FTY720, a S1P receptor agonist, can cross the blood-brain barrier and target NPSCs[133]. FTY720 advanced clinical trials were efficient for the treatment of multiple sclerosis. Restoration and protection of neural cells by FTY720 signalling has been shown for astrocytes and oligodendrocytes[132,134]. Moreover, FTY720 increased the viability and neurogenicity of irradiated NPSCs from the hippocampus[135], thus promising to serve as a healing agent for neurological diseases[133] (Figure 3).

SPHK/S1P/S1P RECEPTOR SIGNALLING IN BREAST CSCS

Involvement of the SphK/S1P signalling axis in CSC

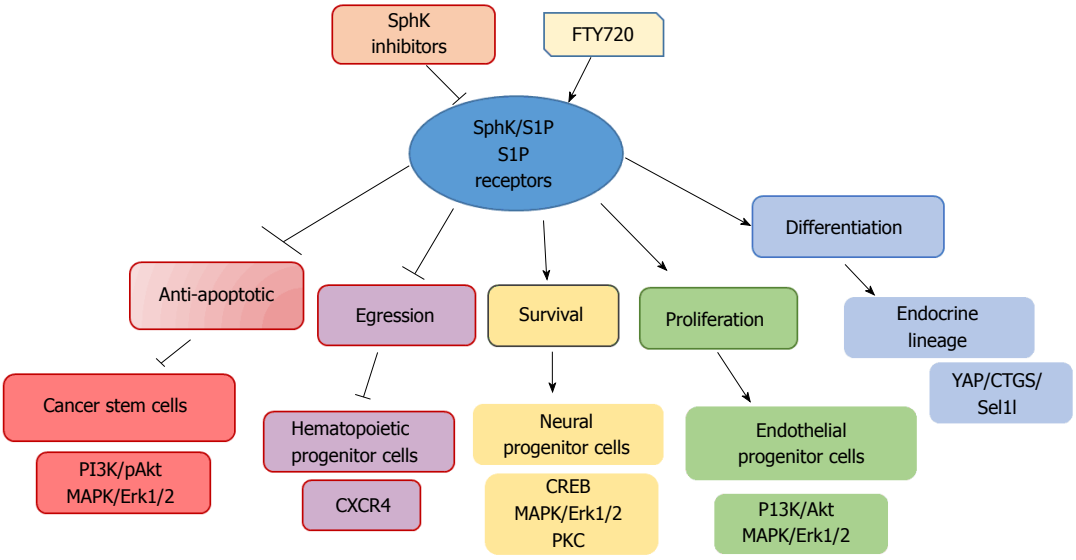

Figure 3 Differentiating effects of sphingosine kinase/sphingosine-1-phosphate inhibition and S1P receptor activation on downstream signaling pathways in various stem/progenitor cells. SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate; CREB: cAMP-response element binding protein; YAP: YES-associated protein.

functioning has been recently investigated in several malignancies, including glioblastoma[136], melanoma[137], hepatocellular carcinoma[138], and breast adenocarcinoma[139,140]. Considering the established role of sphingolipid signalling in mammary carcinomas, this study addressed the role of S1P receptors only in breast CSCs.

According to a cancer progenitor theory, mammary cancers originate from a small population of tumour-initiating cells. Marked by strong survival characteristics and a high level of heterogeneity, CSCs yield the majority of cancers through continuous self-renewal and very limited differentiation. CSCs have been reported to utilize similar molecular mechanisms as embryonic and normal adult stem cells. For instance, CSC self-renewal capacity has been associated with Notch, Hedgehog and Wnt signalling pathways[139]. Sphingolipid and particularly the S1P receptor signalling network has been recently explored in breast CSC models[140,141].

The stimulatory role of S1P and its effect on CSC proliferation was tested after the treatment of breast cancer cells with environmental carcinogens phthalate and benzyl butyl phthalate. These agents activate aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that is known to regulate quiescence, self-renewal, and differentiation of HSCs[142]. Activated AhR stimulated SphK1/S1P/S1PR3 signalling and promoted CSC-induced metastasis *in vivo*[141]. The study suggests that toxic agents and AhR triggered epigenetic activity (histone modification) in CSCs, which in turn, induced transcriptional activation of S1Pr3. Increased release of S1P was also observed because of SphK1 activation. S1P3 knockdown strongly decreased $CD44^{high}/CD24^{low}$ (supposedly stem) MCF-7 cell populations[141].

Another group used different CSC markers and demonstrated a key regulatory role of S1P3 in mammary CSCs[140]. S1P enhanced the mammosphere-forming capacity of aldehyde dehydrogenase (ALDH)-positive CSCs *via* S1P3 and associated induction of the Notch signalling pathway. SphK1-overexpressing CSCs demonstrated an increased ability to develop tumors in nude mice *in vivo*. The tumorigenicity of these CSCs was also blocked by S1P3 knockdown and the specific S1P3 antagonists TY52156 and CAY10444[140]. The study detected high expression levels of S1P3, but lower S1P2 in the ALDH-positive CSC population. S1P activated Notch-dependent proliferation, employing ligand-independent activation of Notch *via* p38MAPK[140]. Notably, breast cancer patient-derived CSCs contained SphK1+/ALDH1+ cells or S1PR3+/ALDH1+ cells[140], indicating a leading role for this receptor in the maintenance of self-renewal potential.

Conclusively, inhibition of S1P3 signaling seems like an attractive clinical target in the treatment of breast cancers. One of the S1P receptor inhibitors, FTY720, might be a beneficial clinical agent. FTY720 can provoke global cytoskeletal change that results in deformed and decreased filopodia formation, reduced expression of integrins, apoptosis, decreased cancer cell adhesion, and prevention of metastasis[143]. These diverse multifunctional effects of FTY720 suggest an ability to interact with more than one specific target in tested cells (Figure 3). Thus, the exact mechanisms of FTY720 signaling was not tested in breast CSCs. FTY720 reactivated expression of the silenced estrogen receptor α (ERα) and sensitized them to tamoxifen, the widely used chemotherapy agent in mammary cancer patients[144]. However, the potential interaction of FTY720 and tamoxifen signaling remains unclear in CSCs. Tamoxifen is the tissue-specific ER agonist/antagonist/modulator shown to inhibit proliferation of ER-positive breast cancer cells. However, prolonged

tamoxifen treatment up-regulates Wnt signaling and promotes survival of CSCs. Notably, ER signaling and tamoxifen resistance were mediated by SphK1/S1P3 receptor signaling in MCF-7 cells[11]. Moreover, estrogen was found to regulate breast CSC numbers through the FGF/Tbx3 signaling pathway, which is also responsible for the regulation of normal embryonic breast stem cell function[145]. An additive effect of tamoxifen and FTY720 in mammary CSCs remains to be explored in future studies.

CONCLUSION

The SphK/S1P receptor network has emerged as a key mediator of stem cell proliferation, survival and differentiation. The essential function of S1P receptor(s) for vascular and neural development has been proven in genetic knockout mice[146]. Considering the very high survival capacity of stem/progenitor cells, the activation of SphK/S1P signaling in normal progenitor and CSCs seems highly likely. S1P regulates cell proliferation and survival mainly through increased phosphorylation of p42/44-MAPK/Erk1/2 and PI3K/Akt, the two major chain reaction arms responsible for anti-apoptotic effects (Figures 2 and 3). In neurodegenerative disease, the S1P receptor agonist FTY720 may exert protective effects on oligodendrocyte survival, counteracting ceramide-induced apoptosis[103,147] (Figure 3). The role of SphK/S1P receptor signaling in the regulation of normal progenitor function looks very attractive. SphK/S1P/S1P receptor signaling should be explored as a promising strategy to promote tissue regeneration in acute myocardial infarction, muscular degeneration, and various neurological pathologies. While induction of SphK/S1P signaling might be useful to boost regeneration and survival of normal stem/progenitor cells, inhibition of the SphK/S1P-dependent survival pathway should be considered for cancer treatment/prevention[1,11,108,140]. Suggesting potential useful application of S1P receptor inhibitors in various CSCs, an increase in SphK/S1P3 signaling correlated with poor prognosis in breast cancer patients[1,11] and promoted mammary CSCs expansion[140,141].

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