**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 39573

**Manuscript Type:** REVIEW

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

Ng ML *et al.* S1P signalling in stem cells

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**Author contributions:** Sukocheva OA and Menschikowski M conceptualized the original idea, designed the review concept, and wrote introductory and conclusive parts of the study; Ng ML and Yarla NS collected the required data and wrote different chapters of the manuscript; Sukocheva OA and Ng ML draw the figures; all authors read and approved the final manuscript.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

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**Manuscript source:** Invited manuscript

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**Received:** April 27, 2018

**Peer-review started:** April 27, 2018

**First decision:** June 6, 2018

**Revised:** July 27, 2018

**Accepted:** August 5, 2018

**Article in press:**

**Published online:**

**Abstract**

Balanced sphingolipid signalling is important for 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 signalling. Unlimited proliferation (self-renewal) within the regulated environment is a hallmark of progenitor/stem cells that was recently associated with the S1P signalling network in vasculature, nervous, muscular, and immune systems. The S1P was shown to regulate progenitor-related characteristics in normal and cancer stem cells (CSCs) *via* G-protein coupled receptors S1Pn (*n* = 1 to 5). SphK/S1P axis is crucially involved in the regulation of embryonic development of vasculature and nervous system, hematopoietic stem cells 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 the differentiation to provide healthy lifelong function of blood, immune systems, and replacement of damaged or dead cells. Differentiation-related role of SphK/S1P remains poorly assessed. A few pioneering investigations explored pharmacological tools that target sphingolipid signalling and can potentially confine and direct self-renewal towards normal differentiation. Further investigation is required to test the role of SphK/S1P axis in regulation of self-renewal and differentiation.

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

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

Ng ML, Yarla NS, Menschikowski M, Sukocheva OA. Regulatory role of sphingosine kinase and sphingosine-1-phosphate receptor signalling in progenitor/stem cells. *World J Stem Cells* 2018; In press

**INTRODUCTION**

During an 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 were shown to rely on sphingolipid signalling cascade. An important member of 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 that, 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 S1Pn (*n* = 1 to 5)[8,9]. The 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 phosphor-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 steroid hormone estrogen[15,22,23] were shown to trigger SphK1/S1P signalling in different cells. Supporting the global role of 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 following 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 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 by not only limited number of divisions, but also higher level of directed lineage differentiation.

The core properties of ESCs 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 level of S1P is associated with increased mouse ESCs proliferation and higher expression of 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 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 unique capacity for self-renewal and multi-lineage differentiation. HSCs and downstream partially lineage-committed progenitor cells functions are tightly linked to their migratory properties especially during fetal development[33,34]. Although 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 HSCs/progenitor trafficking mechanism supports full occupancy of stem cell niches in all BM cavities[37,38]. The HSCs trafficking is directed by 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 migration of endothelial and lymphoid progenitor cells[39], suggesting that other sphingolipid family members should be tested for potential involvement in regulation of hematopoietic stem/progenitor cell functions.

S1P concentration in peripheral blood and lymph regulates HSCs and lymphocytes egress from lymphoid organs[34,37]. HSCs and progenitors express S1P1 receptor(s) that can sense blood plasma S1P and direct the 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 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 gradient of concentration serves as chemoattractant to direct the migration of S1P1-expressing cells from BM to peripheral blood[37,40]. Similarly, lymphocyte egress from lymph nodes was directed by 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 condition of low-S1P concentration environment 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 mice model allowed using specific S1P1 inhibitor W146 that confirmed key role of the receptor in BM retention of hematopoietic cells[44].

Three different S1P receptors including S1P1, S1P2, and S1P3 influenced 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 endothelial and red blood cell network, S1P synthesis and release from erythrocytes was required for embryonic vascular development[47]. S1P2 and S1P3 effects were considered as important, although as accessory or partially redundant in some studies[11,12].

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

S1P-producing enzyme, SphK1, is partially responsible for maintenance of the EPCs specific phenotype. SphK1 controlled the rate and direction of EPCs differentiation, although the enzyme expression level did not affect the hematopoietic compartment[53]. The authors detected high level of SphK1 activity in EPCs that was gradually decreased in more differentiated endothelial cells. Notably, SphK1 knockout mice demonstrated higher levels of circulating EPCs[53]. The data indicates on potential negative role of the enzyme in the regulation of vascular regeneration when presence of EPCs in circulation is highly desirable, although the question requires further investigation. Overexpression SphK1 facilitated the retaining of EPCs at the progenitor stage with probable delay in the following differentiation program that was not tested. Suggestively, SphK1 functions in EPCs can be replaced by SphK2. SphK2 role in the regulation of EPCs functioning remains unclear.

S1P3 receptor axis influenced some specific S1P responses in EPCs. Patient-derived EPCs were tested for 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 S1P/S1P3 axis positively induced the CXCR4-dependent pathway signalling[55]. Furthermore, specific S1P1 receptor antagonist FTY720 increased the CXCR4-dependent chemotactic responsiveness and migration of human CD34+ lineage-committed progenitor cells[56]. Similarly, besides EPCs, S1P1 and S1P3 activation was required in regulation of CSCs migration[57,58].

S1P1 effects were tested in megakaryocytes, the thrombocyte lineage-specific progenitors. S1P1 was involved in initiation of the elongation of trans-endothelial pro-thrombocyte extensions into BM sinusoids and activated 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 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. Multistage process of myogenesis is preceded by myoblast division that is followed by terminal differentiation, cell merging into multinucleated myofibers, and maturation[61-63]. The initiation of myoblasts differentiation process is marked by progenitor cell cycle secession 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 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, 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, 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 were confirmed to regulate skeletal muscle biology[63]. Sphingolipids, can transduce signalling from growth factor and cytokine receptors as messengers and amplifiers in large variety of cells[11]. Consequently, the role of sphingolipids was questioned in regulation of myogenesis.

Traumatic tissue injury and following inflammatory activation of leukocytes and macrophages are marked by release of cytokines and growth factors that can stimulate skeletal muscle regeneration and remodelling[63,68]. One of the key-stone 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 kinin/kallikrein system that directs inflammation-linked responses in mesenchymal cells including fibroblasts, myofibroblasts, and smooth muscle cells[70]. Bradykinin was shown to induce myogenic differentiation in C2C12 myoblasts that was mediated by 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 S1P axis in bradykinin-induced myogenic differentiation[67].

Serving as a muscle trophic factor, S1P was suggested to play leading role in stimulation of myogenesis and regeneration provoked by various agents *via* transactivation of S1P2 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 was 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 S1P2 receptor in murine myoblasts C2C12. 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 corresponds to growth-stimulating signalling of S1P3 in tumours where the sphingolipid property to mediate IGF-1 effects is well recognized[11]. The myogenesis-stimulating role of S1P2 is partially unexpected as S1P2 anti-proliferative effects were observed previously 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 high specialization of stem cells and adjustments to pluripotency of S1P2 signalling network. Notably, S1P2 induced the myogenic differentiation program independently of acute S1P treatment[67]. Conclusively, pleiotropic role of SphK/S1P receptor axis in skeletal myoblasts was suggested reflecting the association of S1P receptor expression pattern with contrasting biological responses.

Proliferative and chemotactic effects of vascular endothelial growth factor (VEGF) signalling were also transduced by SphK/S1P network in muscle progenitor cells[74]. Previously, VEGF signalling pathway was shown to interact with 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 signalling complex[11,18]. The interaction was described as mutual as S1P enhanced levels of VEGF expression and transactivated VEGFR-2[11,18,75]. The role of S1P in 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 that assisted skeletal muscle healing[74]. Conditioned media with MSCs-secreted S1P stimulated C2C12 myoblast and satellite cell proliferation. 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 S1P2 and S1P3 receptors in 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 of S1P receptor expression levels. The authors also suggested that S1P signalling axis is a key component required for sphingolipid effects in proliferating muscle cells[76]. However, the authors observed that 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 were high in quiescent murine myogenic cells, but decreased during cell cycle initiation[78]. Constitutive expression of S1P3 resulted in 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 was supported by following experimental observations in the mdx mouse model of Duchenne muscular dystrophy. S1P3 knockdown produced a less severe muscle dystrophic phenotype indicating that S1P3-linked pathway repress cell cycle progression to direct myoblast functions[77].

Myoblasts and fully differentiated muscle cells were marked by a heterogeneous expression pattern of S1P receptor subtypes. S1P1 was mostly found in cardiomyocytes, while S1P2/S1P3 receptors were expressed by cardiac progenitor cells[78]. S1P receptor activated Rho signalling that, in turn, switched in the proliferation of cardiac myoblasts. Notably, both S1P2 and S1P3 induced RhoA activation through Gα12/13 during myocardial regeneration indicating some redundancy of signalling pathways[78]. However, there is some specificity confirmed for different S1P receptor subtypes. For instance, during construction of the primary heart tube in zebrafish, S1P2 controlled proper endoderm formation and cardiac myoblasts migration[79]. Notably, in the other 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 receptor is unclear. Myoblasts and satellite cell differentiation capacity depends on cytoskeletal remodelling and can be controlled by gap junction proteins and particularly the connexin (Cx) 43[80]. It was shown that S1P induced 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 was linked to Cx43 expression/function *via* calpain/PKCα axis[76], although the involvement of S1P receptor was not 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 involvement of Rho/Rho kinase signalling downstream of S1P as profibrotic TGF1 effect[65]. Notably, S1P receptors are linked to various downstream effectors in myoblasts. For instance, S1P2 myogenic signalling was 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] was also activated in cardiac myoblasts[76], suggesting that S1P isoforms might be linked to the similar downstream 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 was 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 enhanced apoptosis induced by chemotherapy, radiation and ischemia in different cells[82]. Undetectable in resting skeletal muscle, S1P lyase level was upregulated after muscle injury[82]. Mdx mice model for muscular dystrophy was marked by skeletal muscle S1P lyase upregulation and S1P deficiency *in vivo*. Accordingly, pharmacological S1P lyase inhibition stimulated 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 3 myogenic microRNAs (miRNAs) including miR-1, miR-206, and miR-486[83]. The myotube formation was recovered in the cells treated with an S1P1 agonist, S1P2 antagonist, and combination treatments. Transfected with miR-1 or miR-206, the S1P lyase knockdown cells were able to reverse the inhibition of differentiation[83]. Considering that stem cells resistance to apoptosis is a keystone of the regeneration, pharmacological inhibition of S1P lyase during specific stages of myogenesis seems as attractive therapeutic approach to enhance muscular remodelling after injury[78,82].

Another sphingolipid C1P was also implicated in 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 phosphorylation of glycogen synthase kinase-3β and the product 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 induction of myoblast apoptosis and 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 if 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 the other 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. The S1P1 was involved in induction of adipose-derived stem cells growth by HDL[88].

Obesity and metabolic disorders might be associated with dysfunctional adipose progenitor cells and diabetes. Notably, multipotent pancreatic progenitor cells (MPCs) were suggested as a promising target for the treatment of type-1 diabetes mellitus[30]. MPCs are the stem cells with limited potency which 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 level of Notch and Hippo/YES signalling is also required to maintain tree-like branched epithelium and block early MPCs differentiation[90,91]. SphK/S1P/S1P2 axis was found to support the pancreatic progenitor differentiation[92]. S1P2, SphK1, and SphK2 expression levels were upregulated during pancreas second transition in the developing epithelium and co-localised with both trunk and tip progenitors[92]. S1P2 receptor activated YES-associated protein (YAP) and up-regulated connective tissue growth factor signalling important for 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 systems 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 that in turn is required to maintain normal Notch signalling and proper acinar and endocrine differentiation[92]. Given such an important role of S1P2 in regulation of MPCs differentiation, the role of S1R receptors in 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 SphK/S1P axis in 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 exhibited neuro-protective effects signalling as a mediator of nerve growth factor (NGF) in hippocampal neurons and pheochromocytoma PC12 cells[93,94]. During last couple of decades, several groups addressed the role of sphingolipids in neural progenitor cells. Neural progenitor/stem cells (NPSCs) demonstrated limited potency, although still promising to be useful for the treatment of Alzheimer’s disease[95], and brain or spinal cord injuries[96]. Besides insufficient proliferation rate, NPSCs maintain slow differentiation, and migration characteristics. However, similar to its effects in circulating immune cells in blood and lymph, extracellular S1P is a powerful chemoattractant for microglial cells in 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 co-ordinated S1P release from astrocytes. The extracellular S1P in autocrine or paracrine manner stimulated astrocytes differentiation mediated by S1P receptors[98]. Previously, it was demonstrated that cerebellar astrocytes express S1P1, S1P2, and S1P3 receptors[99]. The other study indicated that S1P3 is overexpressed under pro-inflammatory condition in astrocytes[100]. However, astrocytes are not true progenitor cells, but rather precursor cells. Furthermore, S1P receptor demonstrated heterogeneous expression in neural and neural progenitor cells[101,102]. For instance, up-regulation of S1P1 was noted in NPSCs that migrated out of the embryoid body/ESCs[103]. However, the level and role of S1P receptor subtypes in NPSCs remains controversial as different study demonstrated noticeable variations in S1P receptor expression[104].

In the presence of activated astrocytes, S1P further enhancing NPSCs differentiation, indicated by neurite outgrowth and arborisation[97,105]. Notably, neural precursors derived from ESC expressed all five S1P receptor mRNAs, although S1P2 and S1P3 mRNA levels were the highest[97,105]. S1P effect in neural progenitor cells was mediated by increased laminin expression and extracellular matrix (ECM) interactions with progenitor integrins. However, the role of particular S1P receptor subtypes was not verified. For instance, the role of S1P2 remains unclear. Kimura *et al*[106] demonstrated that NPSCs 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 mouse embryo. The enzyme was found to increase the NPSCs proliferation and survival during early sensory ganglia development[107]. Embryos with both *Sphk1* and *Sphk2* genes knockout 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 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 receptors pathways[107,111-117].

To establish S1P role in regulation of neural cell survival, Saini *et al*[118] tested involvement of SphK1 in 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 cytoplasm to plasma membrane of oligodendrocytes. The effects coincided with enhanced S1P accumulation at the membrane compartment. Down regulation 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 on a concerted interaction among NT-3, SphK, Erk1/2 and PKC pathways[115,119]. A crosstalk between NT-3 and SphK1 has been also demonstrated in animal models of multiple sclerosis[120]. Notably, PTEN and Notch signalling mediated 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 oligodendrocytes development.

Survival-related mechanisms of S1P effects were linked to multiple signalling pathway. For instance, S1P can activate membrane S1P receptor(s) to induce CREB phosphorylation in the 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 anti-apoptotic protein Bcl-2 and downregulation of pro-apoptotic protein Bim in 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 cell[11]. Considering genomic and epigenetic regulation, SphK1 can trigger activation of various TFs including AP-1 and NF-kB that were shown to promote anti-apoptotic signalling[125-129]. Involvement of SphK/S1P/S1P3 receptor-dependent signalling in regulation of survival and differentiation of neural stem/progenitor cells is summarized in Figure 2

S1P receptor demonstrated 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 processes retraction[131]. Higher expression level and activation of S1P1 facilitated cell survival of oligodendrocyte progenitors and induced oligodendroglial differentiation[132]. NPSCs derived from ESCs expressed all five S1P receptor mRNAs, although the actual protein expression level was not tested[105].

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

SphK/S1P/S1P RECEPTOR SIGNALLING IN BREAST CSCs

Involvement of SphK/ S1P signalling axis in CSC functioning has been recently investigated in several malignancies including glioblastoma[136], melanoma[137], and 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 high level of heterogeneity, the CSCs yield the majority of cancers through continuous self-renewal and very limited differentiation. CSCs were reported to utilize similar molecular mechanisms as embryonic and normal adult stem cells. For instance, the CSCs self-renewal capacity was associated with Notch, Hedgehog and Wnt signalling pathways[139]. Sphingolipid and particularly S1P receptor signalling network were explored in breast CSCs models recently[140,141].

The stimulatory role of S1P and its effect on CSC proliferation were tested after 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 the CSC-induced metastasis *in vivo*[141]. The study suggests that toxic agents and AhR triggered epigenetic activity (histone modification) in CSCs that, in turn, induced transcriptional activation of S1Pr3. Increased release of S1P was also observed because of SphK1 activation. S1P3 knockdown strongly decreased CD44high/CD24low (supposedly stem) MCF-7 cell populations[141].

Another group using different CSC markers showed the 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 Notch signalling pathway. SphK1-overexpressing CSCs demonstrated an increased ability to develop tumours in nude mice *in vivo*. Tumorigenicity of these CSCs was also blocked by S1P3 knockdown and specific S1P3 antagonists TY52156 and CAY10444[140]. The study detected high expression levels of S1P3, but lower S1P2 in the ALDH-positive CSCs population. S1P activated Notch-dependent proliferation employing ligand-independent activation of Notch *via*, suggestively, p38MAPK[140]. Notably, breast cancer patient-derived CSCs contained SphK1+/ALDH1+ cells or S1PR3+/ALDH1+ cells[140] indicating on a leading role of this receptor in maintenance of self-renewal potential.

Conclusively, inhibition of S1P3 signalling seems like an attractive clinical target in treatment of breast cancers. One of the S1P receptor inhibitors, FTY720, might be suggested as beneficial clinical agent. FTY720 can provoke global cytoskeletal change that results in deformed and decreased filopodia formation, reduced the expression of integrins, induced apoptosis, blocked ability of cancer cells to adhere, and prevented 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 signalling was not tested in breast CSCs. FTY720 reactivated expression of silenced estrogen receptor  (ERα) and sensitized them to tamoxifen, the widely used chemotherapy agent in mammary cancer patients[144]. However, the potential interaction of FTY720 and tamoxifen signalling 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 signalling and promotes survival of CSCs. Notably, ER signalling and tamoxifen resistance were mediated by SphK1/S1P3 receptor signalling in MCF-7 cells[11]. Moreover, the estrogen was found to regulate breast CSC numbers through the FGF/Tbx3 signalling pathway that is also responsible for regulation of normal embryonic breast stem cells function[145]. Suggestive additive effect of tamoxifen and FTY720 in mammary CSC remains to be explored in future studies.

**CONCLUSION**

SphK/S1P receptor network has emerged as 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 signalling in normal progenitor and CSC 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 exerts protective effect on oligodendrocytes survival counteracting ceramide-induced apoptosis[103,147] (Figure 3). The role of SphK/S1P receptor signalling in regulation of normal progenitor function looks very attractive. SphK/S1P/S1P receptor signalling should be explored as promising strategy to promote tissue regeneration in acute myocardial infarction, muscular degeneration, and various neurological pathologies. While induction of SphK/S1P signalling might be useful to boost regeneration and survival of normal stem/progenitor cells, inhibition of 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 signalling correlated with poor prognosis in breast cancer patients[1,11] and promoted mammary CSCs expansion[140,141].

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**P-Reviewer:** SaekiK,Tanabe S, Wakao H **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Cell and tissue engineering

**Country of origin:** Australia

**Peer-review report classification**

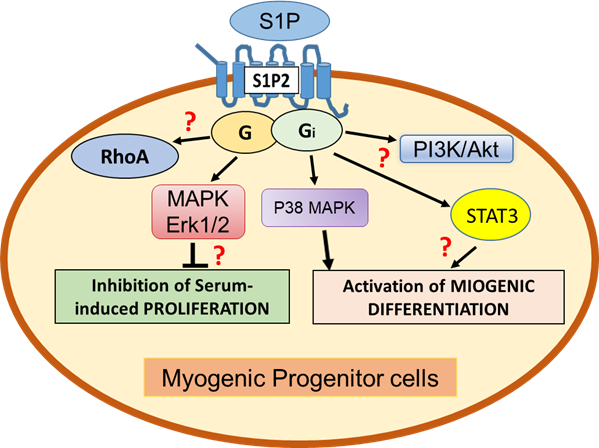
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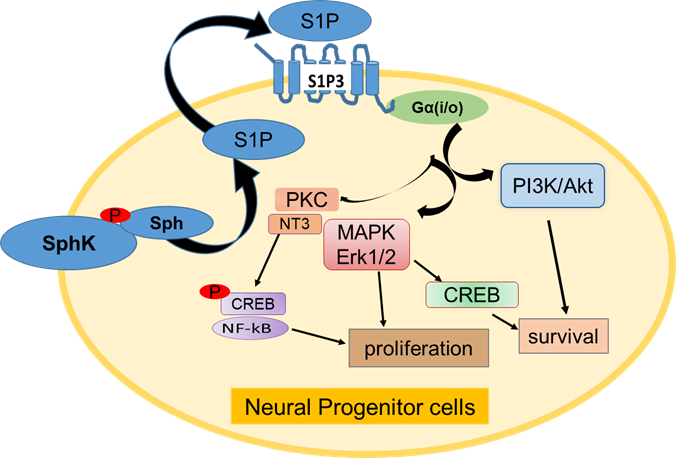
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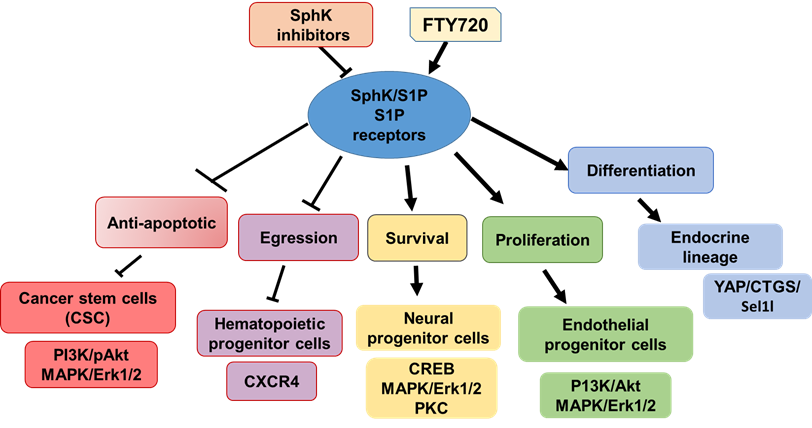
Grade E (Poor): 0



**Figure 1 Diversion of myogenic stimulation at the S1P2 receptor level (hypothetical scheme).** Activation of S1P2 receptor signalling 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.



**Figure 2 Sphingosine kinase/sphingosine-1-phosphate signalling 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-kB TFs. SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate; CREB: cAMP-response element binding protein; NT3: Neurotrophin 3; TF: Transcription factor.

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**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.