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Targeting sphingosine-1-phosphate signaling for cancer therapy

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Sphingosine-1-phosphate (S1P) is a potent pleotropic bioactive lipid mediator involved in immune cell trafficking, cell survival, cell proliferation, cell migration, angiogenesis and many other cellular processes. S1P either activates S1P receptors (S1PR1-5) through "inside-out signaling" or acts directly on intracellular targets to regulate various cellular processes. In the past two decades, much progress has been made in exploring S1P signaling and its pathogenic roles in diseases as well as in developing modulators of S1P signaling, including S1P agonists, S1P antagonists and sphingosine kinase (SphK) inhibitors. Ceramide and S1P have been defined as reciprocal regulators of cell fate, and S1P signaling has been shown to be crucial for the pathogenesis of various diseases, including autoimmune diseases, inflammation and cancer; therefore, targeting S1P signaling may curtail the process of pathogenesis and serve as a potential therapeutic target for the treatment of these diseases. In this review, we describe recent advances in our understanding of S1P signaling in cancer development (particularly in inflammation-associated cancer) as well as in innate and adaptive immunity, and we also discuss modulators of S1P signaling in cancer treatment.

sphingosine-1-phosphate, sphingosine, ceramide, cancer, inflammation, immunity

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INTRODUCTION

Sphingolipids are an essential class of plasma membrane lipids that are clustered in either lipid rafts or cholesterol-enriched membranes. These sphingolipids are biologically active signaling molecules as well as structural proteins that regulate many cellular processes and are involved in the pathogenesis of various diseases. Among these sphingolipids, the ceramide-sphingosine-sphingosine-1-phosphate (S1P) cascade has drawn considerable attention, as these molecules are involved in many diseases, including cancer, multiple sclerosis, asthma, rheumatoid arthritis and inflammatory bowel disease (IBD) (Edmonds et al., 2011; Pyne and Pyne, 2010; Spiegel and Milstien, 2011; Watters et al., 2011). Ceramide is deacetylated by ceramidase to generate sphingosine, which is further phosphorylated by sphingosine kinase 1 or 2 (SphK1 or SphK2) to generate S1P. S1P binds to a family of five G protein-coupled receptors known as S1PRs (S1PR1-5), which differentially mediate heterotrimeric G proteins to regulate various cellular processes. However, S1P can also directly induce intracellular signaling to regulate downstream signaling and cellular effects.

S1P was initially found to play critical roles in lymphocyte egress from lymphoid organs (Fujiwara et al., 2007), as S1P exists in higher concentrations in the blood and lymph than in lymphoid organs, which promotes lymphocyte migration toward higher S1P concentrations in the circulation. As such, targeting S1P may have immunosuppressive ef-

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fects, and this possibility has been investigated in organ transplantation and autoimmune diseases (Brinkmann and Lynch, 2002). Indeed, the S1P agonist FTY720 (fingolimod), which was developed by Novartis Pharmaceuticals, exhibited therapeutic effects against multiple sclerosis in clinical trials and was approved by the US Food and Drug Administration (FDA) in 2010 (Brinkmann et al., 2010). FTY720 binds to multiple S1PRs (1, 3, 4, 5) and induces their degradation, thereby acting as a "functional antagonist" and reducing the number of autoaggressive Th17 cells as well as directly acting on astrocytes and neurons (Brinkmann, 2009), which were considered to be involved in the mechanisms for the therapeutic effects against multiple sclerosis. In addition, FTY720 may also have other therapeutic effects against cancer, asthma, rheumatoid arthritis and IBD, which were summarized by Edmonds et al. (Edmonds et al., 2011).

Although targeting S1P signaling for the treatment of autoimmune diseases, organ transplantation and inflammation has been extensively investigated, the effects of targeting S1P for cancer treatment are still preliminary; to date, few clinical trials have explored the anti-tumor effects of S1P modulators. In the past few years, several preclinical studies have revealed that S1P signaling is involved in cancer cell growth, survival, and migration as well as in neovascularization, inflammation and drug resistance, which has been reviewed by Pyne et al. (Pyne and Pyne, 2010; Pyne et al., 2012). Intriguingly, S1P may play a critical role in inflammation-associated cancer due to its pleiotropic effect as a participant in the inflammatory pathway as well as in cancer progression (Nagahashi et al., 2014; Suh and Saba, 2015). The ceramide-S1P rheostat determines whether cells undergo apoptosis or survive (Espaillat, 2015). Moreover, S1P also affects cancer immunity by regulating lymphocyte circulation and localization and immune cell differentiation and survival, as well as by influencing various aspects of the immune response to cancer (Reimann, 2015). Therefore, targeting S1P signaling is likely to exert therapeutic effects in cancer. In this review, we will summarize the recent advances regarding S1P signaling in cancer cell development and its underlying signaling pathways, cancer immunity, and the current progress toward using S1P modulators as cancer therapeutics. We also hope to provide a basis for those interested in targeting S1P signaling for cancer therapy.

S1P SIGNALING

S1P is produced by the phosphorylation of sphingosine by either of two sphingosine kinases (SphK1 and SphK2). It is then exported into the extracellular microenvironment, where it binds to the extracellular region of G protein-coupled receptors known as S1PRs (1-5) to induce autocrine or paracrine "inside-out signaling" (Figure 1). SphK1 is located in the cytosol and translocates to the plasma membrane in the vicinity of sphingosine upon activation, which can be stimulated by growth factors such as platelet-derived growth factor (PDGF) (Hobson et al., 2001; Soliven et al., 2003), vascular endothelial growth factor (VEGF) (Hernandez-Coronado et al., 2016; Shu et al., 2002), and epidermal growth factor (EGF) (Adada et al., 2015; Doll et al., 2005; Paugh et al., 2008a; Sarkar et al., 2005). In addition, it plays essential roles in tumor angiogenesis and lymphangiogenesis (Anelli et al., 2010; Nagahashi et al., 2012). In contrast to oncogenic SphK1, either overexpression or downregulation of SphK2 has been shown to inhibit cell growth and promote apoptosis in a cell-dependent manner (Igarashi et al., 2003; Sankala et al., 2007). SphK2 and SphK1 have different subcellular distributions; the latter is mainly located in the endoplasmic reticulum, nucleus and mitochondria, while less is known about the function and regulation of SphK2.

Currently, several members of the ATP-binding cassette family and spinster homolog 2 (Spns2) have been identified as S1P transporters in different cell types, such as ATP binding cassette subfamily C member 1 (ABCC1) in mast cells (Mitra et al., 2006), ATP binding cassette subfamily A member 1 (ABCA1) in astrocytes (Sato et al., 2007), ABCC1 and ATP binding cassette subfamily G member 2 (ABCG2) in breast cancer cells (Takabe et al., 2010), and Spns2 in endothelial cells (Fukuhara et al., 2012; Kawahara et al., 2009). When S1P is exported from the cell by these transporters, it binds to S1PRs (1–5) to regulate various cellular processes through autocrine and/or paracrine signaling. S1P receptors consist of seven hydrophobic transmembrane α-helices (TM1-TM7), a structure common to GPCRs spanning the lipid bilayer to form a polar internal tunnel (O'Sullivan and Dev, 2013). S1PR1 was previously known as endothelial differential gene 1 (EDG-1), the transcript of which was cloned and identified as an immediate-early gene expressed during differentiation of human endothelial cells into capillary-like tubules (Hla and Maciag, 1990) and has been shown to play an important role in angiogenesis (He et al., 2014; Liu et al., 2000; Yonesu et al., 2009). The five S1P receptors have different cell distributions and functions, and their roles particularly in cancer will be discussed below.

S1PR1 (EDG1) is predominantly expressed in immune cells, endothelial cells, cardiomyocytes, smooth muscle cells and neuronal cells and is essential for immune cell trafficking, endothelial barrier function, neovascularization and neurogenesis (Delgado and Martinez-Cartro, 2016). S1PR1 couples to G_i and activates the Ras/ERK, PI3K/AKT, PI3K/Rac, STAT3 and PLC signaling pathways to regulate cell proliferation, survival and migration (Takabe et al., 2008). S1PR1 is required for tumor angiogenesis as has been demonstrated using *in vivo* RNA interference (Chae et al., 2004). S1PR1 is induced by STAT3, and the activated S1PR1 can also activate STAT3 and upregulate IL-6 for reciprocal regulation, thereby accelerating tumor progression via persistent STAT3 activation in cancer cells

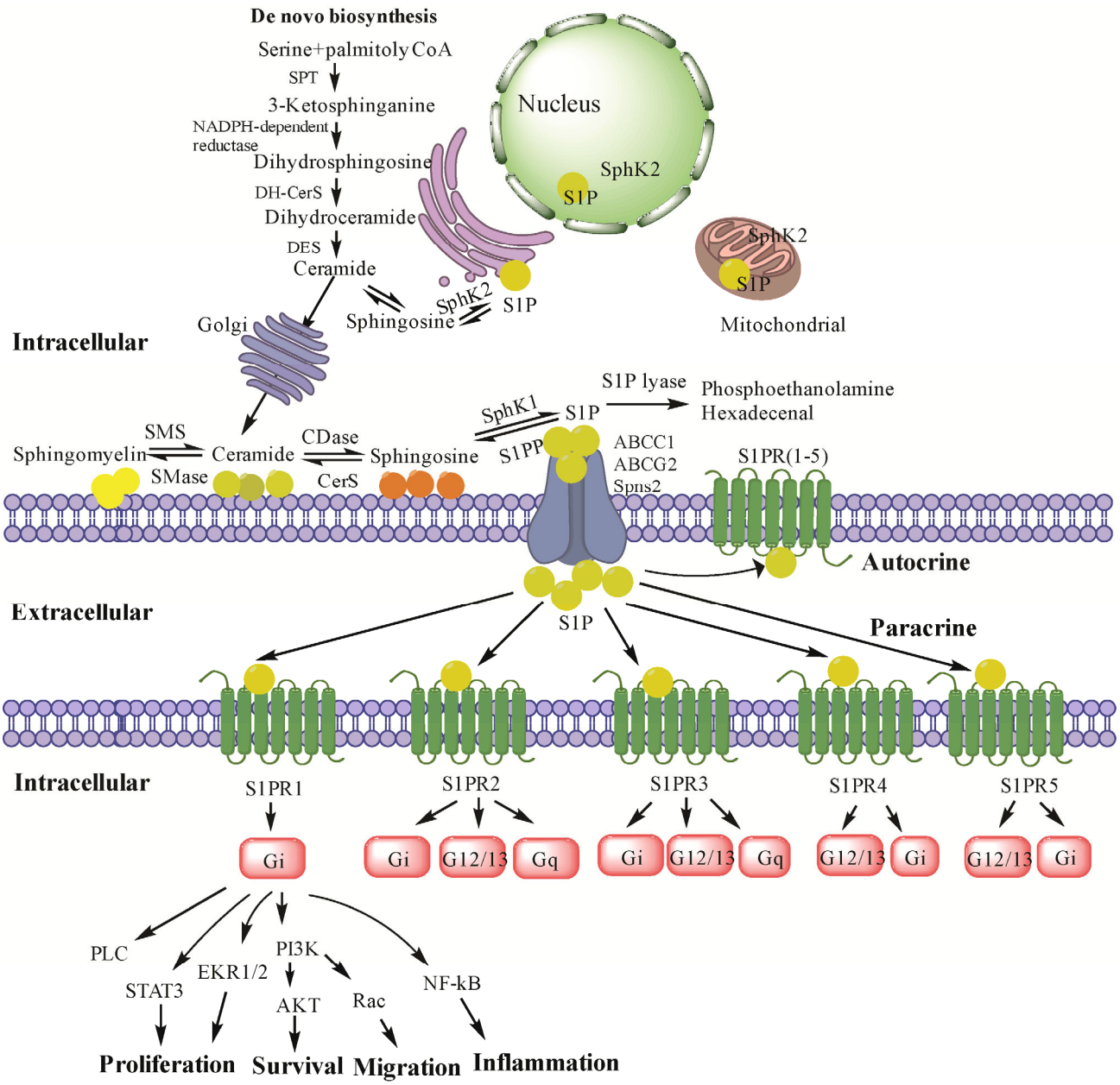

Figure 1 Schematic illustration of the S1P signaling pathway. Ceramide is produced either from sphingomyelin catalyzed by sphingomyelinase or from *de novo* biosynthesis by enzymatic cascade. Ceramide is deacetylated by ceramidase to generate sphingosine, which is further phosphorylated by sphingosine kinase 1 or 2 (SphK1 or SphK2) to generate S1P. S1P is exported outside of the cells by either ABC transporter family members ABCC1/ABCG2 or Spns2, and in an autocrine or paracrine manner, S1P binds to a family of five G protein-coupled receptors known as S1PRs (1–5), which differentially mediate heterotrimeric G proteins to regulate various cellular processes. For example, S1PR1 couples to G_i and then activate downstream signaling pathways, including the PI3K/AKT, PI3K/Rac, ERK1/2, STAT3, NF-κB and PLC pathways, to regulate cell survival, cell proliferation, cell migration, inflammation and other cellular processes. SPT, serine palmitoyl transferase; DH-Cers, dihydroceramide synthase; DES, dihydroceramide desaturase; SMS, sphingomyelinase synthase; SMase, sphingomyelinase; CDase, ceramidase; CerS, ceramide synthase; SphK1/2, sphingosine kinase 1/2; S1P, sphingosine-1-phosphate; S1PP, S1P-phosphatase.

and the tumor microenvironment (Lee et al., 2010). This positive feedback loop between S1PR1 and STAT3 has been demonstrated to contribute to chronic intestinal inflammation and colitis-associated colon cancer (Liang et al., 2013; Nagahashi et al., 2014) as well as to diffuse large B-cell lymphoma (DLBCL) (Liu et al., 2012; Paik et al., 2014). This feedback loop is also crucial to the formation of premetastatic niches for myeloid cell colonization (Deng et al., 2012) as well as to the accumulation of regulatory T cells in the tumor microenvironment (Priceman et al., 2014). In addition, S1PR1 has been implicated in the progression of subacute T-lymphoblastic lymphoma to acute T-lymphoblastic leukemia (Feng et al., 2010) and correlates with poor prognosis of non-muscle invasive urothelial car-

cinoma (Go et al., 2015); furthermore, it can also activate ERK to enhance cell survival (Rutherford et al., 2013; Waters et al., 2006) and promote cell migration in fibrosarcoma (Fisher et al., 2006), glioma (Yoshida et al., 2010) and Hodgkin lymphoma (Kluk et al., 2013).

S1PR2 (EDG5) is also widely expressed in immune cells as well as in the cardiovascular and central nervous systems, and it couples to G_i, G_q and $G_{12}/_{13}$. S1PR2-deficient mice showed increased tumor angiogenesis and growth in Lewis lung carcinoma and B16 melanoma xenograft models (Du et al., 2010), as well as the development of clonal B-cell lymphomas (Cattoretti et al., 2009). S1PR2 is repressed by forkhead box protein 1 (FOXP1) in activated B-cell (ABC) and germinal center B-cell (GCB)-DLBCL cell lines and is associated with FOXP1-mediated promotion of tumor cell survival in DLBCL (Flori et al., 2016). S1PR2 inhibits cell migration via activating RhoA and suppressing Rac1 in melanoma cells (Arikawa et al., 2003) and glioma cells (Malchinkhuu et al., 2008). In contrast, S1PR2 can mediate the invasive growth of cholangiocarcinoma cells stimulated by conjugated bile acids (Liu et al., 2014) and can also mediate Bcr-Abl1 stability and drug resistance to either imatinib or nilotinib via inhibition of PP2A to prevent Bcr-Abl1 dephosphorylation and proteasomal degradation (Salas et al., 2011). The opposing roles of S1PR2 are cell-dependent, although its exact role in tumor development still requires clarification.

S1PR3 (EDG3) is widely expressed in immune cells and in the heart, brain, lung, kidney, pancreas, intestine, thymus and spleen, and it couples to G_i, G_q and $G_{12}/_{13}$ (Kluk and Hla, 2002). S1P/S1PR3 signaling transcriptionally increases EGFR expression via the Rho kinase (ROCK) pathway in lung adenocarcinoma cells and also enhances EGF-stimulated cell proliferation, cell invasion and colony formation (Hsu et al., 2012). TGF-β treatment stimulates the binding and transactivation of SMAD3 to S1PR3 and promotes the growth of human lung adenocarcinoma cells in mice; additionally, pharmacological inhibition or knockdown of S1PR3 dramatically inhibits tumor growth and lung metastasis (Zhao et al., 2016). It also mediates the migration of gastric cancer cells in response to S1P stimulation (Yamashita et al., 2006) and the crosstalk between S1P and PDGFR to activate Akt signaling pathways (Baudhuin et al., 2004). In addition, in aldehyde dehydrogenase (ALDH)-positive breast cancer stem cells, S1PR3 is highly expressed and critical for promoting an ALDH-positive cell population and crosstalk with Notch1 to enhance tumor formation *in vivo* (Hirata et al., 2014; Wang et al., 2016).

S1PR4 (EDG6) has a restricted distribution and is mainly expressed in lymphocytic and hematopoietic cells (Graler et al., 1998), but its role in the immune system remains elusive. S1PR4 is associated with the migration of neutrophils from blood to tissue (Allende et al., 2011) and affects dendritic cell function and TH17-cell differentiation but has little impact on T cell function (Schulze et al., 2011). S1PR4 regulates Rho to influence cytoskeletal rearrangement and motility via G_i and $G_{12}/_{13}$ (Graler et al., 2003). S1PR4 signaling can interact with that of HER2, resulting in the stimulation of ERK1/2 in breast cancer cells (Long et al., 2010b) and is correlated with worse outcomes in estrogen receptor-negative breast cancer (Ohotski et al., 2012).

S1PR5 (EDG8) is mainly expressed in neuronal and immune cells (e.g., dendritic cells and natural killer cells) and couples to G_i and $G_{12/13}$. S1PR5 is required for natural killer cell trafficking, as knocking out S1PR5 impaired cell homing under steady-state conditions, and S1PR5 is also necessary to mobilize natural killer cells to the site of inflammation (Walzer et al., 2007). Activation of S1PR5 by S1P has been reported to induce the survival of mature oligodendrocytes through a G_i-sensitive pathway (Jaillard et al., 2005). S1PR5 is also essential for S1P-induced autophagy of prostate cancer cells (Chang et al., 2009).

In addition to its action on S1P receptors at the cell surface, S1P can also directly activate its intracellular targets. Alvarez SE et al. (Alvarez et al., 2010) showed that S1P specifically binds to the tumor-necrosis factor receptor-associated factor 2 (TRAF2) at its N-terminal Really Interesting New Gene (RING) domain and stimulates lysine-63-linked polyubiquitination of RIP1, phosphorylation of IκB kinase and IκBα, and the subsequent activation of NF-κB, thereby mediating TNF-α signaling via the canonical NF-κB activation pathway. S1P also binds to the histone deacetylases HDAC1 and HDAC2 and inhibits their enzymatic activity. Binding sites for S1P are selectively enriched at the promoters of the genes p21 and c-fos, where it enhances local histone H3 acetylation and influences the epigenetic regulation of gene expression (Hait et al., 2009). In mitochondria, S1P produced by SphK2 has been reported to interact with prohibitin 2 to regulate cytochrome c oxidase assembly and respiratory function (Strub et al., 2011). In mouse neurons, S1P directly binds to beta-site APP cleaving enzyme-1 (BACE1) and increases its proteolytic activity to promote amyloid-beta peptide (Aβ) production (Takasugi et al., 2011). Currently, the intracellular direct targets of S1P have not been fully identified, and it is likely that other targets will be discovered as research progresses.

THE CERAMIDE AND S1P RHEOSTAT

Ceramide is generated from two sources: the first is directly produced by sphingomyelinases via catalysis of sphingomyelin, and the other is *de novo* biosynthesis, which is catalyzed by an enzymatic cascade starting with serine and palmitoyl-CoA (Figure 1). The deacylation of ceramide by ceramidases generates sphingosine, which can be either acylated back to ceramide by ceramide synthase or further phosphorylated by sphingosine kinases to generate S1P. S1P can be dephosphorylated back to sphingosine by S1P phosphatases or irreversibly degraded to hexadecenal and phosphoethanolamine by S1P lyase. Therefore, ceramide is

regulated by the balance between synthesis either *de novo* or from sphingomyelin and its deacylation by ceramidase, and S1P levels are regulated by the balance between sphingosine kinases and S1P lyase.

The ceramide-sphingosine-S1P rheostat was first proposed in early 1996 by Cuvillier et al. (Cuvillier et al., 1996), who postulated that both ceramide and sphingosine could induce apoptosis while S1P enhances cell survival. Thus, the balance of ceramide and S1P levels determines cell fate. This concept was further validated in extensive studies, and opposing effects between ceramide and S1P are observed not only in apoptosis versus cell survival but also in cell motility and invasion, cell cycle regulation, senescence and autophagy (Espaillat, 2015). Extensive studies have demonstrated the pro-apoptotic effect of ceramide, and its intracellular targets, such as PP1 and PP2A (Lin et al., 2007; Ogretmen and Hannun, 2004), cathepsin D (Heinrich et al., 1999; Heinrich et al., 2000), protein kinase C (Sumitomo et al., 2002; Wang et al., 2005) and caspase 8 (Darios et al., 2003), have been identified as mediating this effect. In contrast, S1P has been shown to exert anti-apoptotic signals, such as increases in the anti-apoptotic proteins BCL-2 and MCL1 (which are downstream of AKT (Li et al., 2008; Sauer et al., 2005)), decreases in the pro-apoptotic proteins BAX and BAD (Avery et al., 2008; Betito and Cuvillier, 2006) or cytochrome c release (Cuvillier and Levade, 2001), mainly through inside-out signaling pathways.

Therefore, reprogramming the levels of ceramide and S1P would induce cell death or survival. Many studies have shown that the ceramide-sphingosine-S1P rheostat is functional in cancer cells. For instance, as observed in prostate cancer and leukemia cells, knocking down SphK1 increases the ceramide/S1P ratio and the rate of apoptosis and inhibits cell proliferation (Bonhoure et al., 2008; Pchejetski et al., 2005). By contrast, overexpression of SphK1 decreases the ceramide/S1P ratio and increases the expression of AKT and BCL-2 (Limaye et al., 2005), as well as reducing cytochrome c release and caspase 3 activation to enhance cell survival (Bonhoure et al., 2008); moreover, it can also induce resistance to chemotherapy (Baran et al., 2007; Sobue et al., 2008). Intriguingly, elevated expression of SphK1 and S1P has been found in a variety of cancers (Zhang et al., 2014), such as breast cancer (Maczis et al., 2016), gastric cancer (Li et al., 2009) and glioblastoma multiforme (GBM) (Van Brocklyn et al., 2005), and it is associated with cancer progression and chemoresistance (Ponnusamy et al., 2010). Based on this evidence, reprogramming the ceramide-S1P rheostat may have anti-tumor effects and sensitize cells to chemotherapy in cancer treatments.

S1P IN INFLAMMATION-ASSOCIATED CANCER

The SphK1/S1P axis has been reported to play a crucial role in cancer development through a variety of mechanisms, including enhancing cell survival, cell proliferation, angiogenesis and metastasis, as well as increasing resistance to chemotherapy. For example, high expression of SphK1 correlates with poor survival and induced resistance to tamoxifen in ER^+ breast cancer patients (Long et al., 2010a; Watson et al., 2010). Elevated SphK1 is also associated with poor prognosis in patients with GBM, and treatment with the SphK1 inhibitor SK1-I attenuated AKT-mediated cell growth, migration and invasion *in vitro* as well as reducing the growth and vascularization of GBM xenografts *in vivo* (Kapitonov et al., 2009). Either knockdown or inhibition of SphK1 can sensitize pancreatic cancer cells to gemcitabine and prostate cancer cells to radiotherapy as a result of lowering the S1P/ceramide ratio (Guillermet-Guibert et al., 2009; Pchejetski et al., 2010). S1P is also involved in the progression of hematopoietic malignances (Stevenson et al., 2011). More intriguingly, recent evidence linking S1P and SphK1 to inflammation and cancer is increasing and even more compelling in light of the connection of chronic inflammation with cancer progression (Nagahashi et al., 2014; Shida et al., 2008; Suh and Saba, 2015).

The SphK1/S1P axis is involved in the pathogenesis of both inflammation and cancer, and targeting S1P signaling has shown therapeutic effects in the treatment of inflammation-associated diseases such as multiple sclerosis, rheumatoid arthritis and IBD (Watters et al., 2011). As such, targeting SphK1/S1P signaling to curtail processes critical to the development of inflammation and its associated cancer may be promising, as this approach may essentially "kill two birds with one stone". In the following sections, we will discuss colitis-associated colon cancer (CAC), which represents one of the most convincing forms of evidence linking the processes of inflammation and carcinogenesis.

Crohn's disease and ulcerative colitis are two types of inflammatory disease of the gut collectively known as IBD, and patients with IBD exhibit an increased risk of developing colon cancer, described as CAC. Indeed, either upregulating SphK1 or downregulating S1P lyase resulted in elevated S1P levels, which have been observed in mouse models of colon cancer and in human colorectal cancer specimens (Kawamori et al., 2009; Kawamori et al., 2006; Kohno et al., 2006; Oskouian et al., 2006). Ablation of SphK1 reduced dextran sodium sulfate (DSS)-induced colitis, aberrant crypt formation and colon cancer development in mouse models (Snider et al., 2009)—together, these findings suggest that S1P accumulation contributes to inflammation and colon cancer development. The upregulation of SphK1 enhances S1P production and colon cancer development; however, the molecular mechanisms that promote CAC development remain elusive. Liang et al. (Liang et al., 2013) found that SphK2-null mice exhibited elevated SphK1 and S1P levels and persistent amplification of signaling pathways involving NF-κB, IL-6, STAT3 and S1PR1 in colitis and CAC. Activation of STAT3 in cancer

cells can also induce S1PR1 expression and IL-6 production, and the increased S1PR1 signals a positive feedback loop to persistently activate STAT3, thereby resulting in malignant progression (Lee et al., 2010). NF-κB and STAT3 are two key transcription factors for the development of CAC (Bollrath et al., 2009; Greten et al., 2004; Grivennikov et al., 2009). Activation of NF-κB increases the expression of pro-inflammatory cytokines such as IL-6 and TNF-α, which in turn stimulate NF-κB and STAT3 to promote CAC; indeed, these molecules are elevated in patients with active ulcerative colitis (Li et al., 2010) and colorectal cancer (Popivanova et al., 2008). In addition to acting on cell surface S1P receptors, S1P can directly target intracellular targets such as TRAF2 to activate NF-κB signaling in response to TNF-α stimulation (Alvarez et al., 2010). Therefore, the S1P/S1PR1/STAT3/NF-κB/IL-6/TNF-α signaling axis plays a crucial role in the development of CAC. In addition, S1P signaling contributes to innate and adaptive immunity, including monocyte and macrophage activity, lymphocyte trafficking and cytokine signaling (Aoki et al., 2016; Rivera et al., 2008b), all of which may be implicated in the development of CAC. Therefore, further elucidation of these connections and of the gut microbiome, intestinal mucosal integrity and endoplasmic reticulum stress will clarify the role of S1P signaling in CAC development and provide a basis for the use of S1P modulators for treatment of CAC and other inflammation-associated cancers with a similar pathogenesis.

S1P AND CANCER IMMUNITY

It is well known that the S1P/S1PRs axes regulate the trafficking of various immune cells, including B and T lymphocytes, dendritic cells, macrophage and natural killer cells (Rivera et al., 2008a; Schwab and Cyster, 2007); thus, it is likely that S1P signaling is involved in the immune response to cancer. S1P is present at higher concentrations in the blood and lymph than in lymphoid organs and the thymus, and this differential is essential for lymphocyte egress (Matloubian et al., 2004). Treatment with FTY720 prevents lymphocyte egress from lymph nodes, which results in decreased circulating lymphocytes (Jeffery et al., 2011). Interestingly, S1P signaling has different effects on the trafficking of different T cell subtypes. S1P/S1PR1 signaling promotes Treg accumulation but inhibits $CD8^+$ T cell recruitment and activation in tumor tissues from breast and melanoma xenograft models, suggesting that S1P/S1PR1 induces an immunosuppressive microenvironment to promote tumor growth (Priceman et al., 2014). An increase in S1PR1 in $CD4^+$ T cells promotes JAK/STAT3-dependent Treg tumor migration. Consistent with this finding, treatment with FTY720 can inhibit regulatory T cell proliferation *in vitro* and *in vivo* as well as abrogate the immunosuppressive microenvironment (Wolf et al., 2009).

S1P/S1PR1 can promote Th2 and Th17 cell differentiation while decreasing Th1 cell differentiation. Activation of S1P/S1PR1 induced the differentiation of $CD4^+$ T cells to Th17 T cells in response to IL-1β, IL-6 and TGF-β1 (Huang et al., 2007; Liao et al., 2007) while suppressing IFNγ production and Th1 T cell differentiation in S1PR1-transgenic T cells (Dorsam et al., 2003; Graler et al., 2005). In addition, S1P can impair the ability of dendritic cells to initiate the Th1 cell response but can promote the Th2 cell response (Idzko et al., 2002). Since Th17 cells are essential for the development of IBD (Hundorfean et al., 2012; Monteleone et al., 2011) and CAC (De Simone et al., 2013; Punkenburg et al., 2016) and Th1 cells mediate IFNγ production and the anti-tumor response (Kennedy and Celis, 2008), the preferential augmentation of Th17 cells and suppression of Th1 cells by S1P signaling facilitates the development of IBD and CAC. Moreover, S1PR1 has been reported to impact STAT3 signaling, and overexpression of STAT3 can potentiate Th17 cell differentiation and increase the expression of IL-17 downstream genes, such as IL-23 and RORγt, both of which contribute to a positive feedback loop that increases Th17 cell differentiation and inhibits Th1 cell polarization (Yang et al., 2007; Zhou et al., 2007), which is one of the reasons S1P signaling is preferred in Th17 cell differentiation. However, the signaling pathways involved in this process remain elusive.

Other efforts have focused on naïve T cells and memory T cells affected by S1P signaling. Memory T cells are considered to be "antigen-experienced" and are subdivided into $CCR7^+CD45RA^-$ T central memory (T_{CM}) and $CCR7^-$-$CD45RA^-$ T effector memory (T_{EM}) subsets (Sallusto et al., 2004). Interestingly, treatment with FTY720 preferentially blocks $CCR7^+$ T_{CM} and naïve T cells but not $CCR7^-$ T_{EM} cells (Brinkmann, 2009; Kebir et al., 2007), suggesting that FTY720 acts on the early stages but not the later stages of the immune response. This may be because S1P signaling regulates T cells by competing with the CCL21/CCR7 chemokine receptor axis, which is a mechanism for retaining T cells in tissues (Pham et al., 2008). S1P also promotes macrophage homing and migration, increases endothelial barrier function (Singer et al., 2005), and enhances the endocytic function of mature dendritic cells via S1PR3 (Maeda et al., 2007). S1PR5 is the predominant S1P receptor expressed in natural killer cells and can promote natural killer cell trafficking via S1PR5 (Jenne et al., 2009; Konig et al., 2010). In addition, S1P signaling regulates the trafficking of neutrophils, hematopoietic progenitors and mast cells (Ishii et al., 2009; Jolly et al., 2004; Konig et al., 2010), but the relationship between this process and cancer pathogenesis requires further clarification.

Taking these findings together, S1P signaling is involved in both innate and adaptive immunity, both of which are crucial to cancer development. S1P signaling has been shown to induce an immunosuppressive microenvironment to promote tumor growth, but further studies are required to fully clarify the role of S1P signaling in the immune

response to cancer with regard to all types of immune cells in xenograft tumor models and patient samples, particularly in inflammation-associated tumors.

MODULATORS OF S1P SIGNALING IN CANCER TREATMENT

To date, various types of modulators of S1P signaling have been developed, including S1P agonists, S1P antagonists and sphingosine kinase inhibitors, and these modulators have been well described in the literature (Bigaud et al., 2014; Delgado and Martinez-Cartro, 2016; Edmonds et al., 2011). Below, we will focus on the effects of modulators of S1P signaling on the treatment of cancer (Table 1).

S1P agonists

FTY720 is an S1P agonist that functions as an antagonist by binding to S1PR1, S1PR3, S1PR4 and S1PR5 to stimulate the internalization and degradation of these receptors, resulting in their downregulation. Moreover, it can also directly inhibit the activity of SphK1 (Brinkmann et al., 2010). FTY720 potently prevented S1P-induced Ca^{2+} mobilization and migration in vascular endothelial cells, inhibited tumor vascularization and growth in a melanoma model (LaMontagne et al., 2006), and very strongly inhibited angiogenesis in a subcutaneous Lewis lung carcinoma (LLC1) tumor model (Schmid et al., 2007). In a CAC model, FTY720 interferes with the SphK1/S1P/S1PR1 amplification loop (which leads to persistent NF-κB and STAT3 activation and IL-6 production) and dramatically reduced tumor growth and multiplicity during CAC induction. Impressively, even after the tumors were initiated, FTY720 still inhibited tumor growth and development and prevented the amplification loop involving SphK1, S1P, and S1PR1 (Liang et al., 2013). In a hepatocellular carcinoma model, FTY720 induces apoptosis through the activation of protein kinase C (PKC)-delta signaling (Hung et al., 2008). FTY720 sensitizes prostate cancer cells to radiotherapy by inhibiting SPHK1 and reducing tumor growth and metastasis without toxic side effects (Pchejetski et al., 2010). FTY720 also suppresses the aggressiveness of androgen-independent prostate cancer cells, possibly by acting through Runx2 (Chua et al., 2009). FTY720 demonstrated anti-tumor activity via PP2A-dependent apoptosis in leukemia (Neviani et al., 2007; Toop et al., 2016), lung cancer (Saddoughi et al., 2013; Simon et al., 2011) and colon cancer (Cristobal et al., 2014). Notably, high doses of FTY720 could also inhibit its activity, leading to the accumulation of

Table 1 S1P modulators in cancer treatment

S1P Modulators	Targets	Cancer models	Functions
S1P agonists			
FTY720	S1PR1, S1PR3, S1PR4, S1PR5, SphK1	Melanoma, Lewis lung carcinoma, colon cancer, hepatocellular carcinoma, prostate cancer, leukemia	Anti-growth, anti-angiogenesis and anti-migration, anti-inflammation, pro-apoptosis
Siponimod	S1PR1, S1PR3	Not yet tested	
SEW2817	S1PR1	Leukemia	Pro-apoptosis
AUY954	S1PR1	Not yet tested	
Ponesimod	S1PR1	Not yet tested	
KRP-203	S1PR1, S1PR4	Not yet tested	
S1P antagonists			
W146	S1PR1	Not yet tested	
VPC23019	S1PR1, S1PR3	Bladder carcinoma	Anti-migration
VPC44116	S1PR1, S1PR3	Hodgkin lymphoma	Anti-migration
NIBR0213	S1PR1	Not yet tested	
JTE-013	S1PR2	Renal tumor	Anti-proliferation
TY52156	S1PR3	Not yet tested	
CYM50358	S1PR4	Not yet tested	
SphK inhibitors			
Saphingol	SphK1	Not yet tested	
DMS	SphK1	Not yet tested	
SK1-I	SphK1	Leukemia, glioblastoma, cholangiocarcinoma	Anti-growth, pro-apoptosis
SKI-II	SphK1, SphK2	Prostate cancer, colon cancer, breast cancer, lung cancer, head and neck squamous cell carcinoma	Anti-proliferation, anti-inflammation, pro-apoptosis
PF-543	SphK1, SphK2	Head and neck squamous cell carcinoma, colorectal cancer	Anti-proliferation, pro-apoptosis
ABC294640	SphK2	Prostate cancer, colon cancer and breast cancer, pancreatic cancer, non-small cell lung cancer, hepatocellular carcinoma, cholangiocarcinoma	Anti-proliferation, anti-inflammation, pro-apoptosis
K145	SphK2	Leukemia, breast cancer	Anti-proliferation

sphingosine and the subsequent activation of JNK and P38 to induce apoptosis (Hung et al., 1999).

A variety of other S1P agonists, including siponimod, SEW2871, AUY954, ponesimod and KRP-203, have been developed, and their functions in immunosuppression and anti-inflammatory pathways have been intensively investigated, but research on the anti-tumor activity of these compounds has been limited. Siponimod (BAF312) is an agonist of S1PR1 (EC_{50}: 0.4 nmol L^{-1}) and S1PR3 (EC_{50}: 5 μmol L^{-1}) and was discovered via a high-throughput screening program in 2004 (Hale et al., 2004). It is currently in clinical trials for the treatment of multiple sclerosis and psoriasis (Olsson et al., 2014; Vaclavkova et al., 2014). SEW2871 is a selective S1PR1 agonist (EC_{50}: 13 nmol L^{-1}) that has been reported to induce lymphocytopenia (Huwiler and Pfeilschifter, 2008). Interestingly, SEW2871 and FTY720 both enhance the natural killer cell-mediated lysis of K562 tumor cells (Rolin et al., 2010). In an experimental colitis model, SEW2871 protected epithelial cell apoptosis and improved barrier function in IL-10-deficient mice, which was associated with fewer $CD4^+$ T cells in the colon lamina propria and with the attenuation of established colitis (Dong et al., 2014; Dong et al., 2015). SEW2871 has also been shown to have other functions, including ameliorating ischemic acute renal failure (Lien et al., 2006), improving cognitive function (Asle-Rousta et al., 2013) and prolonging survival after heterotopic heart allograft (Ni et al., 2015). AUY954 is structurally related to SEW2871 and is also a selective S1PR1 ligand (EC_{50}: 1.2 nmol L^{-1}) (O'Sullivan and Dev, 2013). It has been shown to prevent allograft rejection (Pan et al., 2006) and to combat experimental autoimmune neuritis (Zhang et al., 2009). Ponesimod is a selective S1PR1 agonist (EC_{50}: 9 nmol L^{-1}) that has been reported to reduce blood lymphocytes and attenuate lymphocyte-mediated tissue inflammation (D'Ambrosio et al., 2015; Piali et al., 2011), and this compound is currently in clinical trials for the treatment of multiple sclerosis (D'Ambrosio et al., 2016). KRP-203 is a potent agonist of S1PR1 and S1PR4 and was initially developed for treating graft rejection in heart transplantation (Shimizu et al., 2005; Suzuki et al., 2006) and renal transplantation (Suzuki et al., 2006); however, it has also shown efficacy against autoimmune myocarditis (Ogawa et al., 2007) and chronic colitis (Song et al., 2008).

S1P antagonists

The binding of FTY720 to its receptors results in the internalization and degradation of the receptors, an act defined as "functional antagonism". Thus, it is likely that S1P antagonists would directly compete with the ligand to block the downstream signaling, and this hypothesis was supported after knockdown of S1PR1 in T cells (Allende and Proia, 2002). Unlike S1P agonists, S1PR1 antagonists do not cause either transient receptor activation or internalization. W146 was the first S1PR1 antagonist developed (K_i: 77 nmol L^{-1}) (Sanna et al., 2006), but it failed to inhibit lymphocyte egress due to poor pharmacokinetic properties (Tarrason et al., 2011). VPC44116 and VPC23019 interfere with S1P to prevent the activation of S1PR1 (K_i: 30 nmol L^{-1}) and S1PR3 (K_i: 300 nmol L^{-1}) (Foss et al., 2007) as well as block the cell migration of urinary bladder carcinoma (Davis et al., 2005) and Hodgkin lymphoma (Kluk et al., 2013) cells. NIBR0213 is a potent and selective S1PR1 antagonist (IC_{50}: 2 nmol L^{-1}) that induced long-lasting reduction of peripheral blood lymphocytes and showed therapeutic efficacy in an experimental model of autoimmune encephalomyelitis (Quancard et al., 2012). There are also other subtype-selective antagonists of S1P receptors, including JTE-013, TY52156, and CYM50358. JTE-013 is an antagonist of S1PR2 (IC_{50}: 17 nmol L^{-1}); it was used as chemical probe to block S1PR2 and demonstrated anti-proliferative activity at S1PR2 via induction of connective tissue growth factor expression (Li et al., 2008). TY52156 was developed by Murakami A et al. in 2010 as an antagonist against S1PR3 (K_i: 111 nmol L^{-1}). It could directly inhibit S1P-mediated vascular contraction by activating calcium and Rho in vascular smooth muscle cells (Murakami et al., 2010). CYM50358 antagonizes the activity of S1PR4 (IC_{50}: 25 nmol L^{-1}) by mediating the pro-apoptotic effect of TGFβ in skeletal muscle cells (Cencetti et al., 2013). Taking these findings together, there has been substantial progress in the development of S1P antagonists; however, these compounds have not been tested in cancer models. Therefore, more studies are needed to evaluate the anti-tumor activity of the S1P antagonists.

SphK inhibitors

The dynamic balance between ceramide and S1P can determine cell fate; therefore, the enzymes regulating this balance are potential anticancer targets. Inhibition of SphK would increase the ceramide/S1P ratio to induce apoptosis. Since SphK1 is elevated in various cancers and correlates with a poor prognosis for survival (Van Brocklyn et al., 2005), SphK1 inhibitors have been intensively investigated for the treatment of cancer. FTY720 is both an agonist of S1P and an inhibitor of SphK1 (Tonelli et al., 2010); thus, the anti-tumor activity of FTY720 may be partially attributable to the direct inhibition of SphK1 activity. The first compound found to inhibit SphK1 activity is the competitive inhibitor saphingol (DHS) (Buehrer and Bell, 1992). In addition, DMS, an N-methylated metabolite of sphingosine, was later observed to be more potent than saphingol (Yatomi et al., 1996). Saphingol and DMS also have many other targets, such as protein kinase C (Igarashi et al., 1989), 3-phosphoinositide-dependent kinase 1 (King et al., 2000), and ceramide kinase (Sugiura et al., 2002), so they are non-specific SphK inhibitors with significant hepatotoxicity and hemolysis (Kedderis et al., 1995). SK1-I

(BML258; (2R, 3S, 4E)-N-methyl-5-(4′-pentylphenyl)-2-aminopent-4-ene-1,3-diol) is an SphK1-selective inhibitor and has been shown to inhibit cell growth and induce the apoptosis of leukemia cells (Paugh et al., 2008b; Yang et al., 2015b), glioblastoma cells (Kapitonov et al., 2009) and cholangiocarcinoma cells (Chen et al., 2015). SKI-II (2-(p-hydroxyanilino)-4-(p-chlorophenyl) thiazole), as the first non-lipid SphK inhibitor, is a non-competitive inhibitor with improved selectivity (French et al., 2003). It was designed to inhibit SphK1 but was also found to inhibit SphK2 with a lower potency. SKI-II has been shown to inhibit proliferation and induce apoptosis in a number of cell lines, including prostate cancer cells (Tonelli et al., 2013) and mammary adenocarcinoma cells (French et al., 2006). It also attenuates ulcerative colitis in dextran sulfate sodium-treated mice (Maines et al., 2008). Moreover, SKI-II has been shown to sensitize cancer cells to either doxorubicin-induced DNA damage (Huwiler et al., 2011) or radiation therapy (Sinha et al., 2011). PF-543 is a potent SphK1 inhibitor with 100 times more potency toward SphK2 and has been shown to dramatically decrease the S1P levels and increase the sphingosine levels (Schnute et al., 2012). Later, it was reported that PF-543 could induce SK1 proteasomal degradation and reduce DNA synthesis (Byun et al., 2013) as well as exert potent anti-proliferative and cytotoxic effects in colorectal cancer cells (Ju et al., 2016).

ABC294640 is a first-in-class selective SphK2 inhibitor developed in 2010 (French et al., 2010) that can inhibit the proliferation of a broad array of cancer cells (including prostate, colon and breast cancer) by depleting the S1P levels in a dose-dependent manner. Later, it was shown to have anti-tumor effects both *in vitro* and *in vivo* on several cancer types, including non-small cell lung cancer (Guan et al., 2016; Yang et al., 2015a), prostate cancer (McNaughton et al., 2016; Venant et al., 2015), and pancreatic cancer (Lewis et al., 2016). Interestingly, ABC294640 showed efficacy against Crohn's disease and in the suppression of CAC (Chumanevich et al., 2010; Maines et al., 2010; Xun et al., 2015). In addition, the combination of ABC294640 and sorafenib has been reported to potentiate the effects of sorafenib on hepatocellular carcinoma (Beljanski et al., 2011b), cholangiocarcinoma (Ding et al., 2016) and pancreatic adenocarcinoma (Beljanski et al., 2011a). K145 (3-(2-amino-ethyl)-5-[3-(4-butoxyl-phenyl)-propylidene]-thiazolidine-2,4-dione) is also a selective SphK2 inhibitor that can decrease the S1P levels and inhibit the proliferation of human leukemia U937 cells and the growth of U937 tumors in nude mice. This antitumor activity was also confirmed in a syngeneic mouse model by implanting murine JC breast cancer cells in BALB/c mice (Liu et al., 2013). These studies suggested that SphK2 could be a therapeutic target in some cancer types. Since there may be off-target effects of these compounds, more research is required to further evaluate the inhibitors in parallel with gene knockdown studies.

CONCLUSION AND FUTURE PERSPECTIVES

S1P is a pleotropic bioactive sphingolipid metabolite that is involved in various physiological and pathological cellular processes. In the past two decades, much progress has been made in exploring S1P signaling and its pathogenic roles in disease as well as in developing modulators of S1P signaling, including S1P agonists, S1P antagonists and SphK inhibitors. S1P signaling is a crucial regulator of immune cell responses and inflammation and has been implicated in the pathogenesis of many autoimmune diseases such as multiple sclerosis and rheumatoid arthritis as well as in inflammation and cancer. The S1P agonist FTY720 acts as a functional antagonist and has been shown to exert therapeutic efficacy against multiple sclerosis in clinical trials. Therefore, it is likely that S1P signaling modulators would have therapeutic effects against other autoimmune diseases, inflammation or cancer.

S1P signaling is well recognized as participating in many aspects of cancer development, including cell survival, cell proliferation, cell migration, angiogenesis and immune responses, as well as drug resistance to chemotherapy; thus, targeting this pathway may have great therapeutic potential for cancer. Indeed, S1P modulators and SphK inhibitors have been shown to possess anti-tumor activity and to enhance the sensitivity of chemotherapy in a variety of cancers. However, more work is required for understanding the actions of S1P modulators in the treatment of cancer. First, it remains unknown which subtypes of cancer are most sensitive to S1P modulators. Since S1P signaling is involved in both inflammation and cancer, it is hypothesized that inflammation-associated cancers are the most suitable, and extensive evidence has indeed shown the therapeutic efficacy of S1P modulators in CAC treatment, which is associated with blocking the SphK1/S1P/S1PR1/NF-κB/STAT3 amplification loop. These studies are still preliminary, and more inflammation-associated cancer models must be tested using different S1P modulators to refine which subtypes of cancer are most sensitive to pharmacological modulation of S1P signaling and its biomarkers. Second, the impact of S1P signaling on innate and adaptive immunity has not been fully clarified in tumor models and requires further study, especially in immunocompetent mouse tumor models. Third, more potent and specific modulators of S1P signaling must be developed in order to maximize the therapeutic efficacy and minimize off-target cytotoxicity. We hope to determine the most suitable cancer subtypes for the use of potent and specific S1P modulators and to identify biomarkers for predicting and monitoring drug efficacy in an effort to move toward clinical trials for the treatment of cancer.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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