Decoding the S1P-S1PR axis in cancer: Mechanisms, pathways and therapeutic horizons (Review)

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Abstract. Sphingosine-1-phosphate (S1P) and its five G protein-coupled receptors (S1PR1-S1PR5) regulate a broad range of processes that shape cancer progression, including proliferation, survival, angiogenesis, immune evasion and metastatic dissemination. Under physiological conditions, this signaling axis contributes to vascular integrity, immune cell trafficking and tissue homeostasis. In cancer, however, its output is not solely determined by ligand abundances. Rather, tumors reprogram the S1P-S1PR axis at a number of levels, coupling altered S1P production with receptor-specific changes in expression, localization and the signaling state to generate context-dependent malignant phenotypes. The present review provided a receptor-resolved synthesis of S1PR functions in cancer and examined the mechanisms that underlie pathway dysregulation, including transcriptional activation, epigenetic remodeling, microRNA loss, post-translational modifications and altered receptor trafficking and compartmentalization. It further discussed how metabolic amplification of S1P availability cooperates with receptor-level rewiring to sustain tumor progression, microenvironmental remodeling and therapeutic resistance. This framework positions the S1P-S1PR axis as a dynamically reprogrammed signaling network and highlights therapeutic strategies that concurrently target S1P production and receptor-mediated signaling as promising avenues for more-precise, biomarker-informed cancer treatment.

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1. Introduction

Sphingolipids are bioactive lipids that function both as structural components of eukaryotic membranes and as signaling mediators that regulate cell fates and tissue homeostasis (1). Among these metabolites, sphingosine-1-phosphate (S1P) has emerged as a central regulator of proliferation, survival, migration, vascular integrity and immune cell trafficking (2). Together with ceramide and ceramide-1-phosphate, S1P occupies a pivotal position within the sphingolipid network, in which shifts in the metabolite balance can profoundly influence cell behaviors (3).

In cancer, the biological effects of S1P are especially complex (4). Rather than generating a uniform downstream response, S1P propagates signals through five G protein-coupled receptors, S1PR1-S1PR5, each of which differs in expression patterns, downstream coupling and biological output (5). As a result, consequences of S1P signaling in tumors are determined not only by ligand availability but also by receptor identity and the receptor state (6). Depending on the tumor type and cellular context, individual S1P receptors can promote or restrain proliferation, survival, invasion, angiogenesis, immune evasion and metastatic dissemination (7).

Much of the research has focused on elevated S1P production as a driver of tumor progression, particularly through increased sphingosine kinase (SphK) activity and altered sphingolipid catabolism (8). Although this metabolic dimension is clearly important, a ligand-centric framework does not adequately explain the receptor-specific and context-dependent outputs observed across cancers (7). Instead, the pleiotropic

effects of S1P signaling are shaped by multilevel reprogramming of the S1P-S1PR axis, in which isoform-specific receptor expression is integrated with transcriptional and epigenetic regulation, microRNA (miRNA)-mediated repression and post-translational modifications (6,9). These regulatory layers converge with altered spatiotemporal organization, including receptor trafficking and compartmentalization, to convert a homeostatic signaling system into a context-dependent driver of malignancy (5,10). Malignant progression is therefore driven not simply by activation of the S1P pathway, but by reprogramming of the regulatory architecture that governs it (6).

The present review examined the S1P-S1PR system as a dynamically reprogrammed signaling network in cancer. It first summarized the receptor-specific functions of S1PR1-S1PR5 across tumor and microenvironmental contexts and then discussed the mechanisms through which tumors reprogram this axis, including transcriptional activation, epigenetic remodeling, loss of miRNA-mediated restraint, altered receptor trafficking and compartmentalization and coupling to ligand-rich metabolic states. Finally, it considered how this framework may inform therapeutic strategies that more effectively target both S1P production and receptor-mediated signaling in a biomarker-guided manner.

2. The S1P-S1PR axis in physiology and cancer

S1P is generated from sphingosine by the sphingosine kinases sphingosine kinase 1 (SphK1) and SphK2 and signals through five G protein-coupled receptors, S1PR1-S1PR5 (2,11,12). A defining feature of this pathway is its 'inside-out' signaling, whereby intracellularly generated S1P is exported by transporters such as SPNS2 and ATP-binding cassette family members, enabling autocrine and paracrine activation of cell-surface S1PRs (2,13). Under physiological conditions, this system contributes to vascular regulation, immune cell trafficking and tissue homeostasis. In cancer, however, it is frequently dysregulated through increased ligand production, reduced catabolism, and altered receptor expression (Fig. 1) (7,8,11). Importantly, signaling output is determined not only by ligand abundance, but also by receptor identity, localization and cellular context (5,6,11).

3. Receptor-specific outputs of S1PR signaling in cancer

Activation of S1PR1-S1PR5 engages phosphatidylinositol 3-kinase (PI3K)-AKT, mitogen-activated protein kinase-extracellular signal-regulated kinase (ERK), Rho-Rho kinase (ROCK), phospholipase C (PLC)-Ca^{2+}, signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB signaling, thereby shaping malignant phenotypes that include proliferation, survival, migration, epithelial-to-mesenchymal transition (EMT), angiogenesis, immune modulation and therapeutic responses (Table I) (8,11,14,15). However, these outputs are highly context dependent and vary according to receptor subtype, cellular lineage and microenvironmental state (5,7,8,14,16).

S1PR1 is the receptor most consistently linked to malignant phenotypes across solid and hematologic cancers (6,7,17). Acting predominantly through Gi, it activates ERK, PI3K-AKT, Rac and STAT3 to promote proliferation, survival, motility and inflammatory fitness (8,12,15). Particularly important is the S1PR1-STAT3 feedforward circuit, which sustains interleukin (IL)-6-dependent inflammatory signaling (18,19). S1PR1 also contributes to endothelial signaling, underscoring its role as a recurrent protumorigenic signaling node (10,20-22).

By contrast, S1PR2 often opposes S1PR1 and is generally linked to tumor-restraining functions (7,20). Through RhoA-ROCK signaling and inhibition of Rac activity, S1PR2 can restrict cytoskeletal plasticity, migration and invasion and its loss or downregulation is associated with more-aggressive behavior in several malignancies (7,11,23). However, this profile is not fixed. In selected settings, including epidermal growth factor receptor-driven tumors and liver disease, S1PR2 can be redirected towards protumorigenic outputs depending on the disease stage, signaling environment and metabolic context (16,24). In hepatocytes, S1PR2 contributes to metabolic and epigenomic homeostasis through conjugated bile acid-dependent activation of SphK2 and accumulation of nuclear S1P, a pathway linked to histone acetylation and hepatic lipid and sterol gene regulation; in nonalcoholic steatohepatitis-associated liver injury, disruption of this axis was associated with a glycine N-methyltransferase/S-adenosylmethionine imbalance, aberrant methylation and enhanced susceptibility to hepatocarcinogenesis (25-27). S1PR2 therefore illustrates that receptor identity alone does not determine biological outcomes.

S1PR3 is more consistently associated with aggressive disease and phenotypic plasticity (14,28). Through Gi- and Gq-dependent signaling, S1PR3 activates PI3K-AKT, ERK, PLC and calcium-dependent pathways that support survival, invasion and metastatic progression (12,15,23). In numerous solid tumors, its upregulation is linked to inflammatory signaling, matrix remodeling, the EMT and stemness-associated programs (7,19,28-30). Collectively, these observations place S1PR3 among the receptor programs most closely linked to invasive behaviors, adaptive plasticity and microenvironmental support in cancer (11,12).

S1PR4 and S1PR5 have more restricted physiological expression patterns, but increasing evidence indicates that they are important regulators of the immune context of cancer (7,31-33). S1PR4, which is enriched in hematopoietic tissues, is linked to immunosuppressive states and may also contribute to tumor-intrinsic signaling in aggressive breast cancer (15,19,34-37). S1PR5 is best known for its role in natural killer cell trafficking, but emerging evidence suggests context-dependent functions in solid tumors, including associations with immune surveillance, checkpoint responsiveness and clinical outcomes (38-41). Although their functions remain less well defined than those of S1PR1-S1PR3, current evidence suggests that both receptors influence cancer progression chiefly through immune and microenvironmental regulation (7,31,39).

Taken together, these receptor-resolved observations indicate that the S1P-S1PR axis is neither uniformly oncogenic nor uniformly tumor suppressive (7). Rather, each receptor defines a distinct signaling module whose output depends on the cellular compartment, microenvironmental state, and regulatory architecture that governs receptor expression and function (6,19). This diversity raises a central question for cancer biology: How do tumors selectively reshape receptor

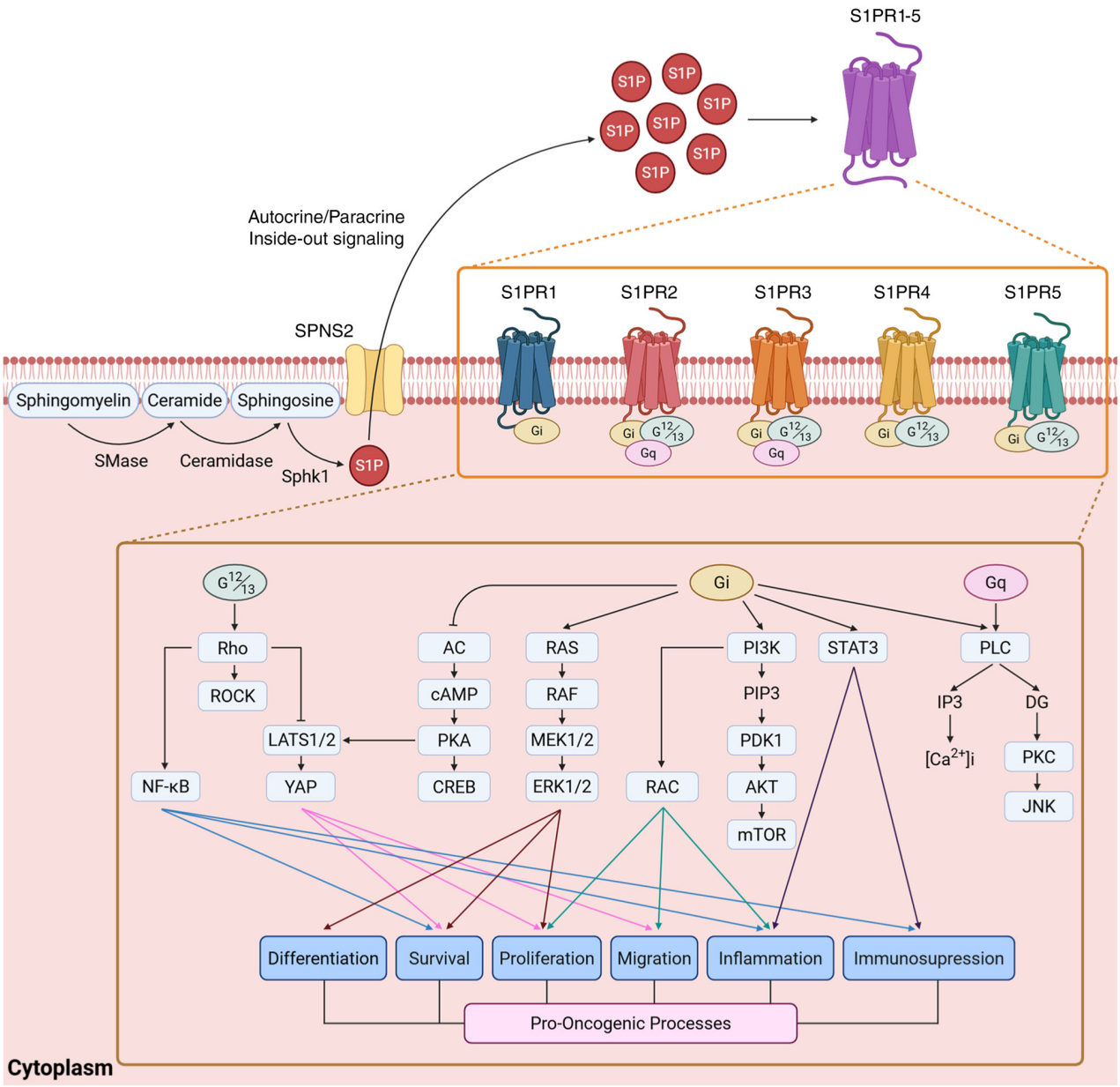

Figure 1. Overview of the S1P-S1PR signaling axis in cancer. Sphingomyelin is hydrolyzed to ceramide by SMase and ceramide is subsequently converted to sphingosine by ceramidase. Sphingosine is phosphorylated by SphK1 to generate S1P, which is exported by transporters such as SPNS2. Extracellular S1P binds S1PR isoforms and activates downstream Gi-, Gq- and G12/13-dependent signaling pathways, including Rho, AC, Ras, PI3K, STAT3 and PLC, thereby promoting tumor-associated processes. S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SMase, sphingomyelinase; SphK1, sphingosine kinase 1; SPNS2, spinster homolog 2; Gi, G protein alpha i; Gq, G protein alpha q; G12/13, G protein alpha 12/13; AC, adenylyl cyclase; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; PLC, phospholipase C.

abundance, localization, and signaling competence to favor malignant outputs? Addressing that question requires moving beyond receptor cataloging toward the upstream mechanisms that reprogram the axis in cancer.

4. Multilevel reprogramming of the S1P-S1PR axis in cancer

Although the tumor-promoting effects of S1P receptor signaling have been extensively described, the upstream mechanisms that dysregulate this axis in cancer remain incompletely understood (8). In malignant cells, the S1P-S1PR system is reprogrammed at multiple levels, including transcriptional and epigenetic control, posttranscriptional regulation, receptor trafficking and posttranslational modifications and changes in ligand availability (2,8). Together, these mechanisms alter receptor expression levels, receptor localization, and signaling competence, thereby sustaining aberrant pathway output (Fig. 2) (2,11). Understanding how these regulatory layers converge is essential for explaining how tumors convert a physiological homeostatic system into a context-dependent driver of survival, progression, and therapeutic resistance (11).

Transcriptional and epigenetic reprogramming. Under physiological conditions, expression of S1PR isoforms is tightly regulated in a tissue- and context-specific manner (11). In cancer,

Table I. Tumor-associated functions, G-protein coupling and principal downstream signaling pathways of S1P receptors (S1PR1-S1PR5).

Receptor	Primary role in tumors	Main G-protein coupling	Major downstream pathways	Key tumor-relevant functions	(Refs.)
S1PR1	Mostly pro-oncogenic	Gi	PI3K-AKT, Ras-ERK1/2, PLC, Rac, STAT3, YAP	Promotes proliferation, survival, migration, the EMT, metastasis, and angiogenesis; sustains persistent STAT3 signaling and may reinforce senescence resistance, including through YAP-associated signaling in ovarian cancer.	(8,11, 12,82)
S1PR2	Mainly tumor-suppressive, but strongly context-dependent	G12/13, Gq, weak Gi	Rho-ROCK, Rac inhibition; in some liver settings PI3K-AKT-mTOR	Restrains proliferation, migration, invasion, and the EMT; promotes cell-cycle arrest and tissue confinement; may also support senescence and metabolic or epigenetic homeostasis, although it can exert pro-tumorigenic effects in specific contexts such as NAFLD-associated HCC.	(8,14,24, 26,83)
S1PR3	Largely pro-oncogenic	Gi, Gq, G12/13	PI3K-AKT, ERK, PLC-Ca^{2+}, Rho/ROCK, mTOR, STAT3	Drives tumor growth, stemness, the EMT, invasion, metastasis, inflammatory signaling, immune suppression, and therapy resistance; also contributes to cytoprotective autophagy and may promote T-cell exhaustion and resistance to PD-1 blockade.	(8,11, 78,84)
S1PR4	Primarily immune modulatory, with protumor effects in selected cancers	Gi, G12/13	ERK1/2; HER2-related crosstalk in breast cancer	Shapes the tumor immune microenvironment by limiting $CD8^+$ T-cell abundance and survival in a cell-intrinsic manner; loss of S1PR4 can enhance anti-tumor immunity, whereas tumor-intrinsic S1PR4 may promote progression in ER-negative breast cancer.	(8,36)

Table I. Continued.

Receptor	Primary role in tumors	Main G-protein coupling	Major downstream pathways	Key tumor-relevant functions	(Refs.)
S1PR5	Highly context-dependent; immune-regulatory and occasionally tumor-supportive	Gi, G12	ERK2, Ca^{2+} mobilization, Rac, AC, FAK, and PLC; involves CXCR4-associated signaling/crosstalk.	Regulates NK-cell egress and immune surveillance; in cancer, it has been linked to immune responsiveness and aggressive behavior in colorectal cancer, may exert protective effects in lung adenocarcinoma, and may influence NK-cell desensitization and macrophage polarization in a context-dependent manner.	(8,39, 41,85)

S1PR, sphingosine-1-phosphate receptor; S1PR1, sphingosine-1-phosphate receptor 1; S1PR2, sphingosine-1-phosphate receptor 2; S1PR3, sphingosine-1-phosphate receptor 3; S1PR4, sphingosine-1-phosphate receptor 4; S1PR5, sphingosine-1-phosphate receptor 5; Gi, G protein alpha i; Gq, G protein alpha q; G12, G protein alpha 12; G12/13, G protein alpha 12/13; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Ras, rat sarcoma; ERK, extracellular signal-regulated kinase; ERK1/2, extracellular signal-regulated kinase 1/2; ERK2, extracellular signal-regulated kinase 2; PLC, phospholipase C; Rac, Ras-related C3 botulinum toxin substrate; STAT3, signal transducer and activator of transcription 3; YAP, yes-associated protein; EMT, epithelial-mesenchymal transition; Rho, Ras homolog family member; ROCK, Rho-associated coiled-coil containing protein kinase; mTOR, mechanistic target of rapamycin; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; HER2, human epidermal growth factor receptor 2; CD8, cluster of differentiation 8; ER, estrogen receptor; Ca2+, calcium; AC, adenylyl cyclase; FAK, focal adhesion kinase; CXCR4, C-X-C motif chemokine receptor 4; NK, natural killer.

this architecture is frequently subverted by oncogenic and inflammatory signaling pathways that directly reshape receptor transcription (13,42). For example, IL-6-STAT3 signaling can induce S1PR1 transcription through promoter binding, thereby establishing a feedforward circuit that sustains aberrant STAT3 activation in tumor cells (18). Similarly, transforming growth factor-β (TGFβ)-mothers against decapentaplegic homolog 3 signaling upregulates S1PR3 in lung adenocarcinoma, promoting the EMT, migration and metastatic behavior (43).

By contrast, receptor subtypes with tumor-restraining functions are often transcriptionally suppressed. S1PR2 provides a prominent example (13). In diffuse large B cell lymphoma (DLBCL), forkhead box protein P1 (FOXP1) represses S1PR2 transcription, thereby relieving constraints on motility and proliferation (44). In other settings, viral oncogenesis may also indirectly alter receptor expression through changes in chromatin accessibility or promoter activity, as suggested for S1PR3 in Epstein-Barr virus-associated nasopharyngeal carcinoma (8,45). These observations indicate that tumor-associated signaling does not simply activate downstream pathways; it can selectively reshape the receptor landscape through transcriptional rewiring (8).

Epigenetic regulation provides an additional layer of control (8). DNA methylation, histone modification and chromatin remodeling can alter accessibility to S1PR loci and thereby reinforce malignant signaling states (8,46). In hematologic malignancies, disruption of the S1PR2 axis often occurs through multiple convergent mechanisms (47,48). In DLBCL, S1PR2 may be lost through recurrent mutations in the germinal center B cell-like subtype or through FOXP1-mediated repression in the activated B cell-like subtype (47). This loss can be further reinforced by hypermethylation of SMAD1, which impairs TGFβ-dependent induction of tumor-suppressive signaling (13,47). More broadly, nuclear S1P itself can influence chromatin regulation by inhibiting histone deacetylase (HDAC) 1 and HDAC2, thereby promoting histone acetylation and transcription of genes involved in cell-cycle control and survival (49). These findings place sphingolipid metabolism and chromatin regulation within the same regulatory framework and suggest that epigenetic remodeling is a central mechanism through which tumors reprogram receptor output (2,8).

Posttranscriptional regulation. Posttranscriptional mechanisms, particularly those mediated by miRNAs, are also important determinants of receptor abundance (50). Several tumor-suppressive miRNAs, including miR-148a, miR-363 and miR-133b, directly target the 3' untranslated region of S1PR1 mRNA and thereby limit receptor expression (12,50). Loss of these constraints can increase S1PR1 abundance and reinforce oncogenic phenotypes (51). In hepatocellular carcinoma, depletion of miR-148a promotes invasion and metastasis, whereas in nasopharyngeal carcinoma, downregulation of miR-133b was more strongly linked to proliferative signaling (50-52).

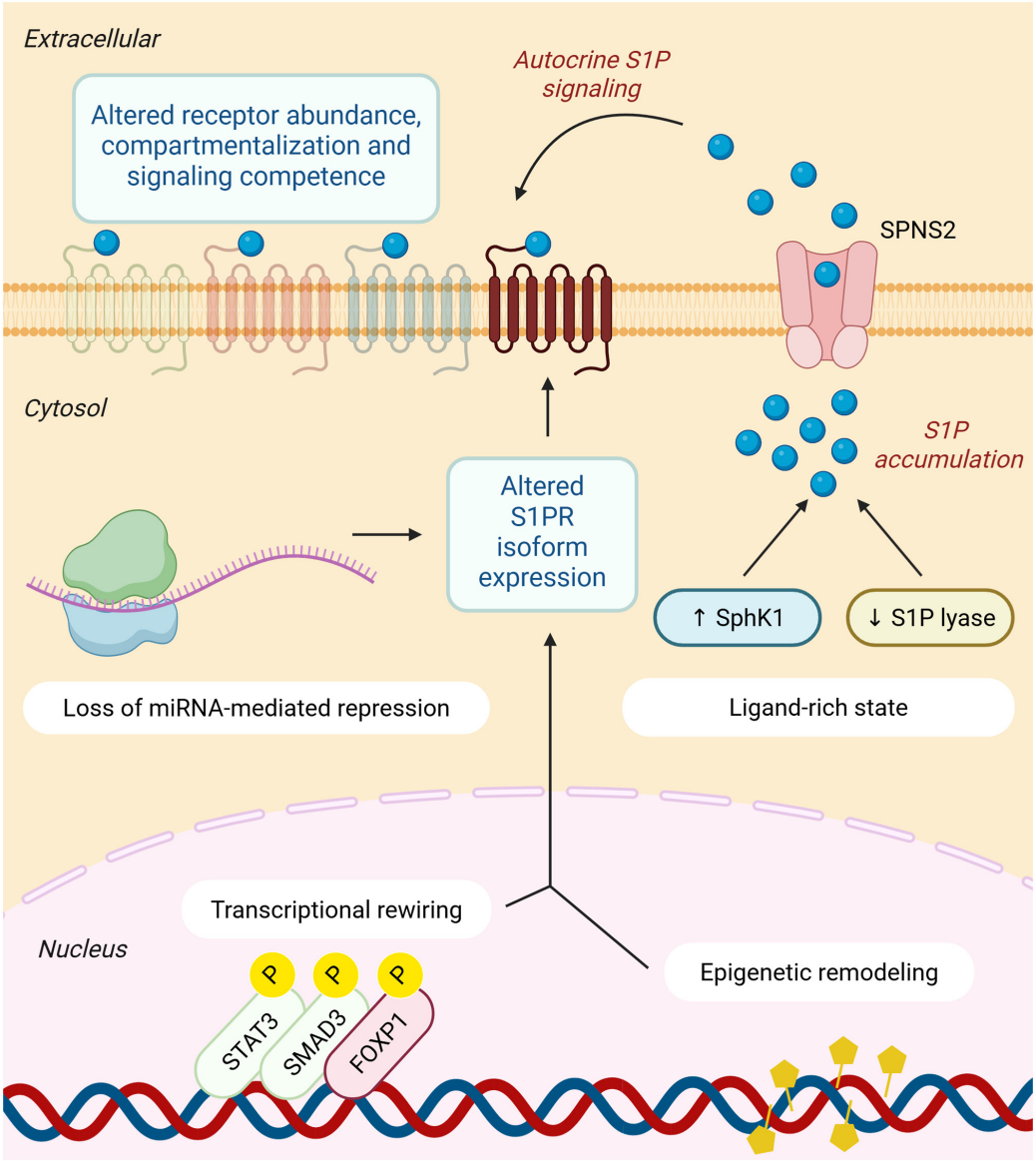

Figure 2. Multilevel reprogramming of the S1P-S1PR axis in cancer. Within tumor cells, the S1P-S1PR axis is reprogrammed at multiple levels. Transcriptional rewiring, epigenetic remodeling and loss of miRNA-mediated repression reshape S1PR isoform expression and receptor abundance. In parallel, increased SphK1 activity and reduced S1P lyase activity create a ligand-rich state that promotes intracellular S1P accumulation and S1P signaling in the tumor microenvironment. Together, these changes alter receptor abundance, compartmentalization and signaling competence at the plasma membrane, converting a homeostatic pathway into a context-dependent driver of malignancy. S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SphK1, sphingosine kinase 1; miRNA, microRNA.

This regulatory logic extends across the receptor family (50). miR-9 suppresses both S1PR1 and S1PR3 and miR-125b is also reported to negatively regulate S1PR1 in lung carcinoma (53,54). In cancer, these interactions may be disrupted by genomic loss of miRNA loci, defective Dicer or Drosha processing, or repression by oncogenic signaling pathways (54,55). The result is not merely loss of fine-tuning, but a permissive state in which increased receptor abundance amplifies downstream signaling (54).

Other forms of posttranscriptional regulation may further stabilize this rewired state (42). Long non-coding (lnc)RNAs have been implicated in multidrug resistance and related oncogenic phenotypes, although their receptor-specific roles within the S1P axis remain less clearly defined (2,56). Taken together, these findings indicate that posttranscriptional deregulation can serve as a critical intermediate between oncogenic signaling and receptor overactivity, enabling tumors to sustain pathological S1P signaling even in the absence of direct genomic alterations (11,50).

Receptor localization, trafficking, and posttranslational control. Tumor-associated rewiring of the S1P-S1PR axis also occurs at the level of receptor trafficking, membrane organization and post-translational modifications (57,58). Under physiological conditions, receptor internalization and recycling help constrain signaling duration and preserve responsiveness to extracellular gradients (59). In cancer, these controls may be altered in ways that prolong receptor residence at the plasma membrane or otherwise favor sustained signaling output (57).

S1PR1 provides one example of this principle. Its localization within lipid raft or caveolin-enriched membrane domains is linked to receptor clustering, internalization and efficient downstream coupling. Disruption of this spatial organization may impair normal desensitization and favor persistent G protein-mediated signaling (59,60). Similarly, adaptor proteins such as phosphatidylinositol 3,4,5-triphosphate-dependent Rac exchanger 1 protein can interfere with agonist-induced receptor endocytosis and thereby prolong receptor signaling at the cell surface (57). These observations support the broader view that the strength of receptor signaling depends not only on how much receptor is expressed, but also on whether the receptor remains properly trafficked and spatially constrained (57,61).

Post-translational modifications add further complexity. N-Linked glycosylation is implicated in the efficient surface delivery and stabilization of S1PR1 and S1PR5 (60,62,63). Lipid modifications, particularly palmitoylation, may likewise promote receptor partitioning into signaling-competent membrane microdomains, thereby supporting efficient downstream coupling and pathway output (60,64). Emerging evidence also suggests that non-canonical forms of GPCR organization, including altered β-arrestin dynamics, may modulate S1PR desensitization in selected systems (57,59). Although these mechanisms remain less established than transcriptional or epigenetic reprogramming, they raise the possibility that tumors enhance signaling not only by increasing receptor expression levels but also by preserving receptors in a signaling-competent state (2,57).

De novo receptor expression vs. functional reactivation. Cancer cells may exploit the S1P-S1PR axis through two complementary strategies (11). The first is ectopic expression of receptor isoforms that are normally restricted to other tissues (34,35). The second is functional reactivation or stabilization of receptors that are already constitutively expressed but are normally subject to tighter regulatory control (18,57).

Examples of *de novo* receptor expression highlight how tumors can expand the signaling repertoire available to them (11). In T-cell large granular lymphocyte leukemia, aberrant induction of the S1PR5 lineage-restricted receptor is linked to constitutive ERK1/2 activation and enhanced pro-survival signaling, suggesting that acquisition of this receptor program may create a selective therapeutic vulnerability (62,65). Similarly, S1PR4, which is typically associated with hematopoietic tissues, can be induced in estrogen receptor-negative breast cancer, where it amplifies human epidermal growth factor receptor 2-linked signaling and correlates with a poor prognosis (2,35). In such settings, tumors do not simply intensify an existing signaling axis; they acquire receptor programs that are not normally part of the tissue context (34).

At the same time, S1PR1-S1PR3 can be functionally reprogrammed without requiring *de novo* expression (2). Ligand-rich tumor microenvironments, altered receptor trafficking and changes in membrane organization may all favor persistent activation of constitutively expressed receptors (11,57). In this way, tumors can strengthen signaling output either by acquiring new receptor modules or by stabilizing existing ones in a hyperactive state (34,57). This distinction between *de novo* receptor expression and functional reactivation provides a useful conceptual framework for understanding how cancers expand or intensify S1P signaling in different settings (11).

Ligand availability and receptor signaling state cooperate to drive hyperactivation. Persistent activation of the S1P-S1PR axis in cancer reflects the convergence of metabolic dysregulation and receptor-level rewiring (2,11). In numerous tumors, SphK1 is upregulated, increasing S1P production, whereas reduced activity of sphingosine-1-phosphate lyase promotes further accumulation of intracellular and extracellular S1P (8). These changes create ligand-rich conditions that favor chronic pathway activation, tumor progression, and therapeutic resistance (2).

However, ligand abundance alone does not fully explain the signaling output (11). Functional studies indicated that receptor abundance, localization and signaling competence are equally important determinants of pathway strength (57,59). In Epstein-Barr virus-positive nasopharyngeal carcinoma, for example, both elevated S1P and increased S1PR3 expression are required to drive migration and silencing S1PR3 markedly attenuates S1P-dependent effects (45). Likewise, in breast cancer, co-expression of S1P and S1PR1 establishes an autocrine signaling loop that promotes invasion and angiogenesis (2,18). These examples illustrate a broader principle: Tumors exploit both metabolic and receptor-level mechanisms to amplify signaling beyond what either mechanism could achieve alone (11).

This convergence has important conceptual and therapeutic implications (8). It suggests that the malignant consequences of S1P signaling emerge not simply from excess ligands, nor solely from altered receptor expression, but from coordinated rewiring of both (2,11). Accordingly, effective interventions may require simultaneous consideration of ligand production, the receptor state and cellular context (8).

Genetic alterations as context-specific exceptions. Although the preceding sections emphasize that most tumor-associated rewiring of the S1P-S1PR axis is driven by non-genetic mechanisms, focal genomic alterations provide instructive exceptions that help clarify the oncogenic or tumor-suppressive functions of specific receptor isoforms (13,66). In most solid tumors, receptor dysregulation appears to predominantly arise through transcriptional, epigenetic, posttranscriptional, metabolic and post-translational reprogramming rather than through recurrent coding alterations (47). Even so, selected genetic lesions offer important insight into how individual receptors constrain or promote malignant behaviors in defined disease contexts (48).

The clearest example is S1PR2 in DLBCL, where recurrent loss-of-function mutations disrupt a tumor-suppressive signaling axis involved in growth control, cytoskeletal organization and tissue compartmentalization (48). These lesions often coexist with additional perturbations, including guanine nucleotide-binding protein subunit alpha-13 inactivation or SMAD1 loss, which further weaken receptor-dependent restraint (47,48). In this setting, genetic disruption of S1PR2 helps define a receptor program that normally limits malignant expansion and dissemination (48).

By contrast, S1PR3 amplification was described in ependymomas, where recurrent gain of the 9q22.1 locus, often together with SHC-transforming protein 3, promotes signaling

Table II. S1PR-targeting agents and S1P-axis inhibitors with relevance to cancer.

Drug	Target	Cancer relevance	(Refs.)
Fingolimod	S1PR1/3/4/5 modulator	Broad preclinical antitumor activity; suppresses stemness	(11,86)
Siponimod	S1PR1/5 modulator	Selective next-generation comparator; limited direct cancer data	(86)
Ozanimod	S1PR1/5 modulator	Clinically validated selectivity; potential translational relevance	(86,87)
Ponesimod	S1PR1 modulator	Highly selective S1PR1 reference drug	(88)
ACT-209905	S1PR1 modulator	Glioblastoma growth/migration inhibition; TMZ sensitization	(77)
JTE-013	S1PR2 antagonist	Mechanistic probe; worsens NASH-HCC *in vivo*	(26)
KRX-725-II	S1PR3 antagonist	Anti-angiogenic/antitumor concept	(78)
Opaganib	SphK2 inhibitor	Upstream anti-S1P therapeutic strategy	(12)
PF-543	SphK1 inhibitor	Preclinical anti-tumor S1P-axis inhibition	(12,89)

S1PR1, sphingosine-1-phosphate receptor 1; S1PR2, sphingosine-1-phosphate receptor 2; S1PR3, sphingosine-1-phosphate receptor 3; S1PR4, sphingosine-1-phosphate receptor 4; S1PR5, sphingosine-1-phosphate receptor 5; SphK1, sphingosine kinase 1; SphK2, sphingosine kinase 2; S1P, sphingosine-1-phosphate; TMZ, temozolomide; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma.

programs linked to tumor growth and survival (67,68). Although this appears to be a more context-restricted event, it is consistent with the broader association of S1PR3 with aggressive and invasive phenotypes (69).

These examples are informative, but they do not define the dominant pattern across cancers (11). Rather, they underscore that although genomic lesions can shape receptor output in selected settings, most tumor-associated changes in the S1P-S1PR axis arise through non-genetic rewiring (2,47,66). Beyond these genetic exceptions, the broader reprogramming of the S1P-S1PR axis is likely sustained by interacting non-genetic regulatory layers. Transcriptional activation may be stabilized by epigenetic remodeling, whereas loss of miRNA-mediated repression can further increase receptor abundance once permissive chromatin states are established (42,70). In parallel, altered trafficking and posttranslational regulation may retain receptors in signaling-competent membrane compartments, allowing ligand-rich microenvironments to convert increased receptor abundances into sustained pathway activation (2,57). The S1P-S1PR axis is therefore most plausibly reprogrammed through convergent, mutually reinforcing layers of control rather than through any single dominant lesion, a framework that may help explain how modest changes across multiple levels collectively sustain oncogenic signaling and therapeutic resistance (2,11).

5. Therapeutic implications of targeting a reprogrammed signaling axis

If malignant progression depends on multilevel reprogramming of the S1P-S1PR axis, then therapeutic interventions must account not only for receptor identity but also for ligand availability, receptor signaling competence and cellular context (8,11). This perspective shifts the therapeutic question away from whether the pathway is active and toward how it has been rewired in a given tumor setting (13).

Direct receptor targeting. Pharmacological modulation of S1PRs represents one major strategy for therapeutic interventions (11). Several S1PR-targeting agents, initially developed or approved for autoimmune diseases, are now being explored for antitumor applications (Table II) (71,72). For example, the selective S1PR1/5 modulator, siponimod, is reported to overcome chemoresistance in ovarian carcinoma by suppressing S1PR1-dependent p-STAT3 signaling (73). Other studies link a receptor-directed intervention to inhibition of S1PR3-dependent AKT-ERK signaling in renal cell carcinoma or to suppression of metabolic programs such as Yes-associated protein-c-MYC signaling in osteosarcomas (74,75).

Next-generation compounds with greater receptor selectivity may offer additional advantages (76). ACT-209905, a selective S1PR1 modulator, has shown activity in glioblastoma models and can enhance sensitivity to temozolomide (77). Likewise, S1PR3 antagonists, including TY-52156 and related pepducins, have demonstrated anti-angiogenic and immunomodulatory effects in preclinical systems (28,78). These findings support the idea that receptor-selective targeting may interrupt discrete malignant signaling modules rather than broadly suppressing all S1P signaling (23,76).

Targeting upstream S1P production. As elevated S1P availability is a recurring driver of receptor activation, upstream metabolic targeting provides a complementary therapeutic approach (8). SphK1 is of particular interest given its frequent upregulation in cancer and its role in maintaining ligand-rich microenvironments (2). In principle, inhibition of SphK activity can attenuate both tumor cell-intrinsic and microenvironmental S1P signaling (12). Similarly, S1P-neutralizing strategies, including antibody-based approaches such as sphingomab, have shown antitumor activity in preclinical models (79).

This upstream approach is especially attractive within the framework advanced in the present review, because it addresses one major component of pathway reprogramming: Metabolic amplification of the ligand supply (2,8). However, metabolic targeting alone may be insufficient in settings where receptor abundance, receptor localization, or downstream coupling have also been rewired to favor persistent signaling (8,42).

Combined targeting strategies. The coordinated nature of S1P axis reprogramming argues strongly for combination approaches (42). If tumors exploit both increased ligand

production and receptor-level rewiring, then simultaneous targeting of S1P synthesis and receptor-mediated signaling may produce more-durable pathway suppression than either approach alone (42). This concept is supported by experimental observations in which ligand availability and receptor expression cooperate to drive malignant phenotypes (35).

Combination strategies may also extend beyond the S1P pathway itself (42). Pairing S1PR-directed agents with chemotherapy, radiotherapy, targeted kinase inhibitors, or immune checkpoint blockade could prove particularly effective in tumors where S1P signaling contributes to therapeutic resistance, stromal crosstalk, or immune exclusion (12,80). Similarly, selective S1PR3 antagonism may complement immunotherapy by reducing macrophage polarization toward suppressive states and by mitigating T-cell exhaustion in selected settings (28). Although these approaches remain largely preclinical, they align closely with the reprogramming model developed in this review.

Biomarker and safety considerations. Despite its promise, therapeutic targeting of the S1P-S1PR axis is complicated by the physiological importance of this pathway in vascular and immune homeostasis (69). Even receptor-selective agents can produce organ-specific on-target toxicities, most notably bradycardia and macular edema (71,76). A distinct liability arises from interference with physiological lymphocyte trafficking, which may lead to functional immunosuppression rather than direct organ toxicity (11,76). These liabilities highlight the challenge of targeting a pathway whose physiological roles are closely intertwined with its pathological functions (23).

For this reason, future progress will depend not only on improved pharmacology but also on improved patient stratification (23). Biomarkers that capture receptor expression, ligand-rich states, transcriptional programs such as STAT3 activation, or immune-context features may help identify tumors most likely to benefit from pathway-directed interventions (12,28). More-selective agonists, antagonists, or biased modulators may further improve the therapeutic window by preferentially targeting disease-relevant signaling outputs while minimizing adverse effects linked to normal physiology (62,76).

Taken together, these considerations suggest that the most effective therapeutic strategies will likely be those that treat the S1P-S1PR axis not as a uniform pathway, but as a reprogrammed signaling network whose vulnerabilities vary across tumor types and biological contexts (13).

6. Conclusions

The S1P-S1PR axis is best understood not as a simple ligand-driven pathway, but as a dynamically reprogrammable signaling network in cancer (11). Its output is determined not only by S1P abundance, but also by receptor identity and by the regulatory mechanisms that govern receptor expression, localization and signaling competence across tumor and microenvironmental compartments (11,13). Tumors exploit this plasticity through coordinated transcriptional, epigenetic, posttranscriptional, trafficking and metabolic alterations, thereby converting a homeostatic signaling system into a context-dependent driver of tumor progression and therapeutic resistance (42,81). This framework supports biomarker-guided strategies that target both ligand production and receptor-mediated signaling according to the specific configuration of the axis in a given tumor (12,23).

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Author contributions

YTC, CFL, and IHW contributed to the conceptualization and development of the review. YTC and CFL drafted the manuscript and prepared the figures. CFL conducted the literature analysis and HYL critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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