Lysophospholipid (S1P) receptors in GtoPdb v.2023.1

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Abstract

Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [96]) are activated by the endogenous lipid sphingosine 1-phosphate (S1P). Originally cloned as orphan members of the endothelial differentiation gene (edg) family [16, 123], the receptors are currently designated as S1P1R through S1P5R [73, 16, 123]. Their gene nomenclature has been codified as human S1PR1, S1PR2, etc. (HUGO Gene Nomenclature Committee, HGNC) and S1pr1, S1pr2, etc. for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function. All S1P receptors (S1PRs) have been knocked-out in mice constitutively and in some cases, conditionally.

S1PRs, particularly S1P1, are expressed throughout all mammalian organ systems. Ligand delivery occurs via two known carriers (or "chaperones"): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by S1P1 in multiple cell types [18, 53]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems.

Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression systems, targeted deletion of the different S1PRs, and most recently, mouse models that report in vivo S1P1R activation [101, 103]. The structures of S1P1 [180, 69, 108, 184], S1P2 [32], S1P3 [116, 187], and S1P5 [110, 185] are solved, and confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [69, 17]. fingolimod (FTY720), the first FDA-approved drug to target any of the lysophospholipid receptors, binds as a phosphorylated metabolite to four of the five S1PRs, and was the first oral therapy for multiple sclerosis (MS) [35]. Second-generation S1PR modulators siponimod, ozanimod, and ponesimod that target S1P1 and S1P3 are also FDA approved for the treatment of various MS forms [16, 123]. In 2021, ozanimod became the first S1PR modulator to be FDA approved for the treatment of ulcerative colitis [145]. The mechanisms of action of fingolimod and other S1PR-modulating drugs now in development include binding S1PRs in multiple organ systems, e.g., immune and nervous systems, although the precise nature of their receptor interactions requires clarification [141, 37, 63, 64].

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**References**


29. Cencetti F, Bernacchioni C, Tonelli F, Roberts E, Donati C and Bruni P. (2013) TGFβ1 evokes myoblast...
apo1otic response via a novel signaling pathway involving S1P4 transactivation upstream of Rho

signalling axis protects against obesity-induced metabolic dysfunction. *Adipocyte* **11**: 69-83

chip variants identifies S1PR4 and other loci influencing blood cell traits. *Nat Genet* **48**: 867-76


(2011) FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte
sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc Natl Acad Sci USA* **108**: 751-6


Opportunities for Treating Multiple Sclerosis and Other Disorders. *Annu Rev Pharmacol Toxicol* **39**: 149-
170 [PMID:30625282]


38. Contos Jj, Ye X, Sah VP and Chun J. (2002) Tandem genomic arrangement of a G protein (Gna15) and G


40. Debien E, Mayol K, Bijoux V, Daussy C, De Aguer MG, Taillardet M, Dagany N, Brinza L, Henry T and
Dubois B et al. (2013) S1PR5 is pivotal for the homeostasis of patrolling monocytes. *Eur J Immunol* **43**: 
1667-75 [PMID:23519784]

JR et al. (2016) Discovery of Tetrahydropyrazolopyridine as Sphingosine 1-Phosphate Receptor 3
(S1P3)-Sparing S1P1 Agonists Active at Low Oral Doses. *J Med Chem* **59**: 1003-20 [PMID:26751273]

(2007) Identification of Leu276 of the S1P1 receptor and Phe263 of the S1P3 receptor in interaction
with receptor specific agonists by molecular modeling, site-directed mutagenesis, and affinity studies.

Bergeijk J and Buttari F et al. (2018) Stimulation of S1PR5 with A-971432, a selective agonist, preserves
brain-blood barrier integrity and exerts therapeutic effect in an animal model of Huntington’s disease.
*Hum Mol Genet* **27**: 2490-2501 [PMID:29688337]


LB et al. (2016) HDL activation of endothelial sphingosine-1-phosphate receptor-1 (S1P1) promotes
regeneration and suppresses fibrosis in the liver. *JCI Insight* **1**: e87058 [PMID:28018969]

46. Donovan EE, Pelanda R and Torres RM. (2010) S1P3 confers differential S1P-induced migration by
autoreactive and non-autoreactive immature B cells and is required for normal B-cell development. *Eur J
Immunol* **40**: 688-98 [PMID:20039302]

Human Naive and Memory T Cells Display Opposite Migratory Responses to Sphingosine-1 Phosphate. *J
Immunol* **200**: 551-57 [PMID:29237776]

HJ et al. (2022) Sphingosine 1-Phosphate Receptor 5 (S1P5) Knockout Ameliorates Adenine-Induced Nephropathy. Int J Mol Sci 23 [PMID:35409312]


Sclerosis Modulated by S1P Signaling: Immediate-Early Astrocytes (ieAstrocytes). eNeuro 5 [PMID:30255127]


121. McQuiston T, Luberto C and Del Poeta M. (2011) Role of sphingosine-1-phosphate (S1P) and S1P receptor 2 in the phagocytosis of Cryptococcus neoformans by alveolar macrophages. *Microbiology (Reading, Engl.)* **157**: 1416-27 [PMID:21292747]


Discovery of BAF312 (Siponimod), a Potent and Selective S1P Receptor Modulator. *ACS Med Chem Lett* **4**: 333-7 [PMID:24900670]


