

Lysophospholipid (S1P) receptors in GtoPdb v.2025.3

Victoria Blaho¹, Jerold Chun¹, Deron R. Herr², Danielle Jones¹ and Yasuyuki Kihara¹

1. Sanford Burnham Prebys Medical Discovery Institute, USA
2. Indiana State University Foundation, USA

Abstract

Sphingosine 1-phosphate (S1P) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [98]**) are activated by the endogenous lipid [sphingosine 1-phosphate](#) (S1P). Originally cloned as orphan members of the endothelial differentiation gene (*edg*) family [16, 125], the receptors are currently designated as S1P₁R through S1P₅R [75, 16, 125]. 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, 54]. 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 [103, 105]. The structures of S1P₁ [185, 70, 110, 189], S1P₂ [32], S1P₃ [118, 192], and S1P₅ [112, 190] are solved, and confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [70, 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](#) and [ozanimod](#) target S1P₁ and S1P₅, while [etrasimod](#) targets S1P₁, S1P₄ and S1P₅; and [ponesimod](#) targets S1P₁ alone, and all are FDA approved for the treatment of various MS forms [16, 125] and/or ulcerative colitis for ozanimod and etrasimod [147, 158]. 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, although most S1P₁ effects appear to involve functional antagonism [143, 37, 64, 65].

Contents

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Lysophospholipid (S1P) receptors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=135>

Introduction to Lysophospholipid (S1P) receptors

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=135>

Receptors

S1P₁ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=275>

S1P₂ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=276>

S1P₃ receptor

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S1P₄ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=278>

S1P₅ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=279>

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