Abstract

Sphingosine-1-phosphate (S1P) is a signalling lipid that regulates many cellular processes in mammals. One well-studied role of S1P signalling is to modulate T-cell trafficking, which has a major impact on adaptive immunity. Compounds that target S1P signalling pathways are of interest for immune system modulation. Recent studies suggest that S1P signalling regulates many more cell types and processes than previously appreciated. This review will summarise current understanding of S1P signalling, focusing on recent novel findings in the roles of S1P receptors in innate immunity.

KEYWORDS

G protein coupled receptors, Inhibitors, Innate immunity, Sphingolipid, Sphingosine-1-phosphate, S1P receptors

1 | INTRODUCTION

Sphingosine-1-phosphate (S1P) is a signalling lipid that is an important regulator in inflammation, angiogenesis, vascular permeability, brain and cardiac development, and cancer growth and metastasis (reviewed in N. J. Pyne et al., 2012; Pyne, McNaughton, et al., 2016; N. Pyne & Pyne, 2017; S. Pyne, Adams, & Pyne, 2016). S1P is able to affect many processes by signalling extracellularly through S1P receptors (S1PRs). One well-studied role of S1PR signalling is the modulation of T-cell trafficking, which has a major impact on adaptive immunity (Mandala et al., 2002; Matloubian et al., 2004). Compounds that target S1PRs are of interest for treatment of autoimmune diseases, the first of these compounds being FTY720 (fingolimod), which was approved in 2010 as a first line treatment for relapsing forms of multiple sclerosis (Brinkmann et al., 2010). Recent studies suggest that S1P signalling regulates many more cell types and processes than previously appreciated, including cells of the innate immune system (reviewed in Blaho & Hla, 2014; Garris, Blaho, Hla, & Han, 2014). The innate immune system is the first line of defence against infectious diseases. Understanding the interplay between S1PR signalling and the innate immune response is essential, not only to our understanding of S1P biology but also to design better therapeutics. This review will briefly summarise current understanding of S1P signalling, focusing on recent novel findings in the roles of S1PRs in innate immunity.

1.1 | S1P pathway overview

The S1P pathway in mammalian systems has been studied in depth (reviewed in Mendelson, Evans, & Hla, 2014; N. Pyne & Pyne, 2017; Rosen & Goetzl, 2005; Strub, Maceyka, Hait, Milstien, & Spiegel, 2010; Figure 1). S1P is produced by the phosphorylation of sphingosine by one of two sphingosine kinases (SK1 and SK2) (Wattenberg, Pitson, & Raben, 2006), which was approved in 2010 as a first line treatment for relapsing forms of multiple sclerosis (Brinkmann et al., 2010). Recent studies suggest that S1P signalling regulates many more cell types and processes than previously appreciated, including cells of the innate immune system (reviewed in Blaho & Hla, 2014; Garris, Blaho, Hla, & Han, 2014). The innate immune system is the first line of defence against infectious diseases. Understanding the interplay between S1PR signalling and the innate immune response is essential, not only to our understanding of S1P biology but also to design better therapeutics. This review will briefly summarise current understanding of S1P signalling, focusing on recent novel findings in the roles of S1PRs in innate immunity.
the receptors on different cell types and the coupling of receptors to different G-alpha subunits allow S1P to differentially exert its influence in numerous pathways (Figure 1, Table 1; reviewed in Blaho & Hla, 2014). S1P can also signal intracellularly both dependent and independent of extracellular S1PRs utilising several different proposed mechanisms (M. M. Adada et al., 2015; Canals et al., 2010; Park et al., 2016; Usatyuk et al., 2011).

1.2 | S1PRs and compounds that target them

S1PRs are a family of seven helix transmembrane G-protein coupled receptors that recognise and bind extracellular S1P to affect cellular processes. Sphingosine-1-phosphate receptor 1 (S1PR1) was the first of this family to be discovered during a screen for immediate early endothelial differentiation genes (EDG1) in 1990 (Hla & Maciag,
It was later found that S1P bound specifically to this receptor (Lee et al., 1998). From 1990 to 2000, four other specific high affinity receptors for S1P were discovered, S1PR2 (EDG5; Okazaki et al., 1993), S1PR3 (EDG3; Yamaguchi, Tokuda, Hatase, & Brenner, 1996), S1PR4 (EDG6; Gräler, Bernhardt, & Lipp, 1998), and S1PR5 (EDG8; Im et al., 2000). Each member of this family of proteins was found to bind extracellular S1P with high affinity (Spiegel, 2006). To better understand these receptors and to exploit their therapeutic potential, there have been concerted efforts toward the design of compounds that specifically target S1PRs.

FTY720 was the first compound discovered that targets S1PRs. FTY720 is an analogue of sphingosine that was originally derived from myriocin in 1995 and was found to have potent immunosuppressant activity (Adachi et al., 1995). This compound, like its analogue sphingosine, is phosphorylated in vivo by sphingosine kinases, particularly by SK2 (Allende et al., 2004; Kharel et al., 2005). Phosphorylated FTY720 binds S1PR1, 3, 4, and 5 (Albert et al., 2005). Treatment with FTY720 causes lymphopenia in the blood, and sequestration of lymphocytes in lymph nodes (Brinkmann et al., 2002; Mandala et al., 2002). Sequestration of lymphocytes is mediated by the agonism of S1PR1 by phosphorylated FTY720 that leads to a functional antagonism once the receptor has been internalised and degraded (Oo et al., 2007). This is a simplified explanation of the effect of phosphorylated FTY720 on lymphocyte egress, as this effect appears to be the result of multiple factors on multiple cell types and is outside the scope of this review (reviewed in Cyster & Schwab, 2012; Garris et al., 2014).

FTY720, under the name Gilenya® (fingolimod; Novartis AG, Basel Switzerland), is approved by the United States Food and Drug administration as a first line treatment for relapsing remitting multiple sclerosis. Additionally, BAF312 (siponimod), and RPC1063 (ozanimod), derivatives of FTY720, recently met their primary endpoint in Phase III clinical trials as treatments for secondary progressive multiple sclerosis, respectively (Althoff & Fiorin, 2016; Gonzalez et al., 2016; Hou et al., 2017; Nussbaum et al., 2015; Obinata & Hla, 2012; N. Pyne & Pyne, 2017).

### Table 1: Sphingosine-1-phosphate receptor summary

| Receptor  | Expression on immune cells                                                                 | G-α subunit | Downstream pathways                                                                                       | Compounds                  | References                                                                 
|-----------|-------------------------------------------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------|
| S1PR1     | T cell, B cell, NK cell, macrophage, monocyte, neutrophil, eosinophil/mast cell, dendritic cell | Gαi         | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac, migration                          | FTY720 (fingolimod)        | (Gonzalez et al., 2017; Obinata & Hla, 2012; N. Pyne & Pyne, 2017)        |
|           |                                                                                           | Gα, G12/13  | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac (activated by PI3K, opposed by Rho), Rho/Rho kinase, ERM phosphorylation | JTE013                     | (M. Adada et al., 2013; M. M. Adada et al., 2015; Hou et al., 2015; McQuiston et al., 2011) |
| S1PR2     | B cell, macrophage, monocyte, eosinophil/mast cell, dendritic cell                         | Gα, G12/13  | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac (activated by PI3K, opposed by Rho), Rho/Rho kinase, ERM phosphorylation | FTY720 (fingolimod)        | (Amadeep Bajwa et al., 2016; Blaho & Hla, 2014; Hou et al., 2017; Nussbaum et al., 2015) |
| S1PR3     | B cell, macrophage, monocyte, neutrophil, eosinophils/mast cell, dendritic cell           | Gα, G12/13  | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac (activated by PI3K, opposed by Rho), Rho/Rho kinase, ERM phosphorylation | FTY720 (fingolimod)        | (Amadeep Bajwa et al., 2016; Blaho & Hla, 2014; Hou et al., 2017; Nussbaum et al., 2015) |
| S1PR4     | T cell, B cell, macrophage, monocyte, neutrophils, eosinophil/mast cell, dendritic cell   | Gα, G12/13  | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac (activated by PI3K, opposed by Rho), Rho/Rho kinase, ERM phosphorylation | FTY720 (fingolimod)        | (Amadeep Bajwa et al., 2016; Blaho & Hla, 2014; Hou et al., 2017; Nussbaum et al., 2015) |
| S1PR5     | NK cell, eosinophil/mast cell, patrolling monocytes                                         | Gα, G12/13  | Adenylyl cyclase (inhibitory), Ras/ERK, PI3K/Akt/eNOS, PLC/Ca²⁺, Rac, migration                          | FTY720 (fingolimod)        | (Blaho & Hla, 2014; Debien et al., 2013; Mayol et al., 2011; Scott et al., 2016) |

Note. Abbreviations: Akt = protein kinase B; eNOS = endothelial nitric oxide synthase; ERK = extracellular receptor kinase; ERM = Ezrin–Radixin–Moesin; Nox2 = NADPH oxidase; PI3K = PI3-kinase; PLC = phospholipase C; PTEN = phosphatase and tensin homologue; Rac = Rac family small GTPase; Ras = Ras family small GTPase; Rho = Rho family of small GTPases.

*Shown to have activity on multiple receptors.
following sections will highlight findings with implications for innate immune cells (Figure 2).

1.3 | S1PR1

S1PR1 is one of the most widely studied receptors of S1P (Blaho & Hla, 2014; Garris et al., 2014; N. Pyne & Pyne, 2017). Recent evidence suggests that signalling through S1PR1 occurs via the binding of G\textsubscript{i} and \(\beta\)-arrestin together to allow for binding of Src leading to receptor internalisation mediated by clathrin and dynamin-2 and activation of downstream pathways (N. Pyne & Pyne, 2017).

In innate immunity, S1PR1 is ubiquitously expressed and has been found to mediate functions in most innate immune cells. Macrophages express S1PR1, and migration toward S1P was shown to be dependent on expression of S1PR1 in studies that utilised an S1PR1/3 antagonist, VPC23019, and S1PR1 deficient mice (Weichand et al., 2013). Other work utilised S1PR1 specific agonist, SEW2871, and S1PR1 antagonist, VPC44116, to show that stimulation of S1PR1 can induce an anti-inflammatory phenotype (Hughes et al., 2008). Additionally, recent work in myeloid specific S1PR1 deficient mice showed enhanced protection of macrophages from apoptosis both in vitro and in vivo (Gonzalez, Qian, Tahir, Yu, & Trigatti, 2017). S1PR1 has also been linked to neutrophil migration. In a rat model of hyperalgesia, S1PR1 was found to be necessary for neutrophil recruitment (Finley et al., 2013). In a model of Candida albicans water-soluble fraction induced vasculitis, treatment with ONO-W061, a S1PR1 agonist,
decreased neutrophil recruitment (Miyabe et al., 2017). In mast cells, S1PR1 is reported to induce migration similar to what has been observed in lymphocytes (Oskeritzian et al., 2010). In eosinophils, S1PR1 inhibition by FTY720 or SEW2871, an S1PR1 agonist, leads to reduced recruitment of eosinophils during hapten application-induced cutaneous responses in mice and reduced chemotaxis in vitro (Sugita et al., 2010). Additionally, S1PR1 has been implicated in plasmacytoid dendritic cell signalling, by degrading interferon alpha receptor 1 to inhibit aberrant interferon alpha production during viral infection (Teijaro et al., 2016). The role of S1PR1 in innate cell migration can also be observed in a model of systemic Yersinia pestis, where it was found that S1PR1 specific agonist, SEW2871, and S1PR1 conditional deletion in mononuclear phagocytes reduced trafficking of infected dendritic cells and monocytes and prevented disease progression (St John et al., 2014). S1PR1 was also found to contribute to natural killer cell trafficking, but its role is purported to be minor due to a dependence on CD69 regulation (Jenne et al., 2009; Shiow et al., 2006). S1PR1 exerts its influence in many different pathways and is a major regulator of immunity in both adaptive and innate immune response. Although many findings have been geared toward defining its role in autoimmune responses, they also support the idea that S1PR1 plays a role in immune responses to infectious diseases by affecting recruitment and trafficking of innate immune cells, macrophage polarisation, and plasmacytoid dendritic cell functions.

1.4 S1PR2

Unlike S1PR1, S1PR2 has been reported to be able to signal through several different G-alpha subunits, Gα, G12/13, and Gq. Each of these subunits can activate an array of downstream pathways, depending on the stimulus and cell type (M. Adada, Canals, Hannun, & Obeid, 2013). One recognised role of S1PR2 is to oppose the activity of S1PR1 by repelling rather than attracting cells in response to S1P. It has been suggested that induction of G12/13 opposes the actions of Gα by inhibiting Rac and Akt (Green et al., 2011; Sanchez et al., 2007; Takashima et al., 2008).

In innate cells, S1PR2 is present on macrophages, monocytes, and granulocytes (Blaho & Hla, 2014). S1PR2 was found to mediate S1P dependent enhancement of phagocytosis of the fungal pathogen Cryptococcus neoformans by utilising both S1PR2 knockout alveolar macrophages and macrophages treated with S1PR2 antagonist JTE-013. S1PR2 knockout macrophages were found to have significantly lower expression levels of phagocytic receptors FcγR I, II, and III (McQuiston, Luberto, & Del Poeta, 2011). Another study found that S1PR2 knockout macrophages exhibited enhanced opsonin-independent phagocytosis of Escherichia coli due to S1PR2 signalling causing inhibition of RhoA-dependent cell contraction and IQGAP1-Rac1-dependent lamellipodial protrusion (Hou et al., 2015). The difference between these two observations lies in the different pathogens and pathways used for phagocytosis. In vitro, C. neoformans requires opsonisation in order for phagocytosis to take place; whereas phagocytosis of E. coli occurs independently of opsonin. The enhanced phagocytosis described by McQuiston was only observed in response to antibody opsonised phagocytosis, not complement mediated, showing that the effect of S1P-mediated enhancement via S1PR2 was specific to FcγR-mediated phagocytosis and did not affect other phagocytic pathways, making these two observations not mutually exclusive. S1PR2, via use of antagonist JTE-013, has also been linked to mast cell triggering and release of antimicrobial peptides during vaccinia virus infection (Wang et al., 2012). Additionally, a new pathway has been discovered in which intracellular S1P participates in S1PR2 activation to cause phosphorylation of Ezrin–Radixin–Moesin (ERM) proteins, which had been previously unreported (M. M. Adada et al., 2015). ERM proteins play an important role in phagocytic cell function, and this mechanism could possibly be involved in phagosome maturation (Erwig et al., 2006). These findings and others point to an important role for S1PR2 in innate immune cells by increasing antibody-mediated phagocytosis of fungi and inhibiting phagocytosis of bacteria in alveolar macrophages, affecting mast cell triggering during viral infection, and affecting ERM phosphorylation.

1.5 S1PR3

S1PR3, like S1PR2, has been reported to couple with G alpha subunits, Gq, G12/13, and Gα. In the past, S1PR3 has been studied in conjunction with the other receptors, but recent availability of genetic models (Kono et al., 2004) and S1PR3 allosteric agonist, CYM-5541 and antagonist SPM-242 (Jo et al., 2012) allow for more thorough study of this receptor. In innate immunity, S1PR3 was found to mediate S1P induced increase in mature dendritic cell migration and endocytosis (Maeda et al., 2007). More recently, it has been found to also be involved in dendritic cell maturation and promotion of a Th1 response and dendritic cell suppression of T-cell regulatory responses in an ischemic reperfusion injury murine model (Bajwa et al., 2012; Bajwa et al., 2016). S1PR3 has been shown to mediate chemotaxis of macrophages in vitro and has been linked to macrophage and monocyte recruitment to plaques in atherosclerosis models (Keul et al., 2011). A recent publication showed that S1PR3 drives bactericidal killing in macrophages by promoting reactive oxygen species generation by NOX2 and promoting phagosome maturation in a murine sepsis model (Hou et al., 2017). S1PR3 was found to be elevated in septic patients and was associated with increased bacterial clearance, better immune status, and preferable outcomes (Hou et al., 2017). In neutrophils, S1PR3 is upregulated when isolated from patients with pneumonia and the S1PR3 expressing neutrophils show enhanced chemotaxis in response to S1P (Rahaman, Costello, Belmonte, Gendy, & Walsh, 2006). Studies in S1PR3 knockout mice show reduced inflammation during bleomycin induced lung injury, this observed inflammation may be mediated in part by S1PR3 expressing neutrophils (Murakami et al., 2014). Similarly, S1PR3 is also found to be highly expressed on eosinophils during hapten application-induced cutaneous responses and may play a role in mediating recruitment (Sugita et al., 2010). Studies have also linked S1PR3 to other leukocyte functions. Expression of S1PR3 in endothelial cells drives leukocyte rolling by upregulating P-selectin in a Gαq phospholipase C-dependent fashion. S1P released by mast cells acts on S1PR3 to drive leukocyte rolling and recruitment to sites of inflammation (Nussbaum et al., 2015). Altogether, these studies present compelling evidence that S1PR3 plays a multifactorial role in immunity by affecting dendritic cell maturation, macrophage chemotaxis and killing, and neutrophil and eosinophil recruitment, while also promoting immune cell recruitment by driving leukocyte rolling on endothelial cells.
1.6 | S1PR4

S1PR4, although less studied than other receptors, is abundant on immune cells (Olesch, Ringel, Brüne, & Weigert, 2017). S1PR4 signals through G-alpha subunits G11 and G12,13 (Gräler et al., 2003). It has been suggested that one of the major roles of S1PR4 is to activate Rho-kinase downstream of G12,13 and affect cytoskeletal rearrangement (Sit & Manser, 2011). Another proposed downstream pathway is that Rho-kinase activates phosphatase and tensin homologue which in turn opposes Akt signalling (as in the S1PR2 pathway) to promote apoptosis in myoblasts, this mechanism could also be present in other cell types but could have additional effects because Akt also regulates the cell cycle, metabolism, and autophagy (Cencetti et al., 2013; Manning & Toker, 2017).

S1PR4, like the other receptors, has been proposed to play an important role in innate immune cells. Recent published work showed that S1PR4 knockout in mice lead to a decrease in plasmacytoid dendritic cell differentiation (Dillmann, Mora, Olesch, Brüne, & Weigert, 2015). Additionally, agonist Cym50138 that targets S1PR4, but not other compounds that target S1PR1–3, blocked human plasmacytoid activation and restricted production of interferon alpha in response to CpG oligodeoxynucleotides or tick-borne encephalitis vaccine, whereas S1P4 antagonist Cym50358 prevented the S1P triggered decrease in interferon alpha (Dillmann et al., 2016). S1PR4 has also been linked to roles in neutrophil recruitment. In mice that are deficient in S1P lyase, S1P accumulates and causes neutrophilia, which is partially rescued when S1PR4 is knocked out (Allende et al., 2011). Neutrophils upregulate S1PR4 upon stimulation, and FTY720 abrogates neutrophil homing to lymph nodes, further suggesting that S1PR4 is important for neutrophil migration (Gorlino et al., 2014). Additionally, a recent meta-analysis of human genetic variants revealed an association between S1PR4 missense variant and lowered circulating neutrophil counts and confirmed this phenotype in S1PR4 knockout mice and zebrafish (Pankratz et al., 2016). Recent work showed that S1PR4 is the most highly expressed receptor on human alveolar macrophages and that expression of S1PR2 and S1PR4 was highly correlated (Barnawi et al., 2015). In a comparison between M1- and M2-activated macrophages isolated from mouse bone marrow, S1PR4 was found to be the only receptor with a significantly different expression profile when comparing the two conditions, and the observed downregulation on M1-polarised macrophages could be responsible for differing responses to S1P, such as differences in migration, and cytokine production (Müller, von Bernstorff, Heidecke, & Schulze, 2017). S1PR4 is widely expressed on immune cells, and current findings suggest a role in plasmacytoid dendritic cell differentiation and activation, neutrophil recruitment, and also point to roles in macrophages as well. Altogether, these findings warrant further investigation into the potential roles of S1PR4 in innate immune cells during infection.

2 | CONCLUSIONS AND FINAL THOUGHTS

Great advances have been made toward understanding the biology of S1P signalling. S1PRs are attractive targets for design of small molecules, and this allows for advanced study of their roles in a variety of biological processes. In the field of immunity, there have been many studies that point to the role of S1PR signalling in trafficking, differentiation, and activation of immune cell effector functions, but there remain many unanswered questions when it comes to defining the specific mechanisms of these effects and how these receptors may affect responses to infectious diseases in innate immune cells. These unknowns need to be addressed, especially as S1PR agonists and antagonists are being used and proposed as treatments for disorders. Recently in the post marketing setting, treatment with fingolimod has been linked to several cases of infection with the opportunistic fungal pathogen C. neoformans, which causes a severe fungal meningitis if left untreated (Achtnichts, Obreja, Conen, Fux, & Nedeltchev, 2015; Commissioner, O. n.d.; Grebenciucova, Reder, & Bernard, 2016; Huang, 2015; Ward, Jones, & Goldman, 2016). Previous research showed that S1P is important for maintaining C. neoformans in granulomas in the lung and in neutrophil killing (Farnoud, Bryan, Kechichian, Luberto, & Del Poeta, 2015; McQuiston, Luberto, & Del Poeta, 2010). The influence of S1PRs on innate immunity could be one of the reasons for this increased susceptibility. The innate immune system is the first line defence against pathogens, and understanding the implications of S1PR signalling in innate immunity is valuable when proposing the use of these inhibitors in patients.

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CONFLICTS OF INTEREST

Dr. Maurizio Del Poeta is a co-founder and Chief Scientific Officer (CSO) of MicroRid Technologies Inc. Arielle Marie Bryan has no conflict of interest.
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