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Sphingosine-1-phosphate signaling: unraveling its role as a drug target against infectious diseases

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Sphingosine-1-phosphate (S1P) signaling is reported in variety of cell types, including immune, endothelial and cancerous cells. It is emerging as a crucial regulator of cellular processes, such as apoptosis, cell proliferation, migration, differentiation and so on. This signaling pathway is initiated by the intracellular production and secretion of S1P through a cascade of enzymatic reactions. Binding of S1P to different S1P receptors (S1PRs) activates different downstream signaling pathways that regulate the cellular functions differentially depending upon the cell type. An accumulating body of evidence suggests that S1P metabolism and signaling is often impaired during infectious diseases; thus, its manipulation might be helpful in the treatment of such diseases. In this review, we summarize recent advances in our understanding of the S1P signaling pathway and its candidature as a novel drug target against infectious diseases.

Introduction

Lipids have been implicated as important biomolecules that contribute to cellular signaling in addition to their contribution to the structural organization of the cell and regulation of membrane properties [1–3]. Recent advances in the field of lipidome research have unraveled obscure classes of bioactive lipid that are dysregulated during pathophysiological conditions and microbial infections [4–6]. Among them, the role of sphingosine-1-phosphate (S1P) has been well recognized. S1P is a lysophospholipid that is produced by the ATP-dependent phosphorylation of sphingosine by two kinases: sphingosine kinase 1 and 2 (SphK1 and SphK2) [7]. Both kinases are localized in different cellular compartments. SphK1 is localized mainly in the cytosol and is recruited in the plasma membrane upon activation [7], whereas SphK2 is mainly localized in nucleus [8]. The degradation of S1P is carried out by S1P lyase (SPL) and S1P phosphatases (S1PP) [9]. S1PP catalyzes the hydrolysis of phosphate from S1P to sphingosine, which can be rephosphorylated to S1P (Fig. 1a) [10]. However, SPL irreversibly degrades S1P into phosphoethanolamine and hexadecenal [11]. Secretion of S1P across the membrane is regulated by S1P transporters. Spinster homolog 2 (SPNS2) is a member of the major facilitator superfamily of transmembrane proteins that function as transporters of S1P and S1P analogs [12]. In addition to SPNS2, there are also various reports of the involvement of ATP-binding cassette (ABC) transporters in the release of S1P. In particular, the role of ABCA1 and ABCC1 was suggested in the export of S1P, because inhibition of the ABCA1 transporter and ABCC1 in endothelia cells blocked the release of S1P [13].

S1P regulates diverse cellular processes, including cell proliferation, survival, differentiation and immune cell trafficking, by activating different signaling pathways upon binding S1P receptors (S1PRs), which are members of the G-protein-coupled receptor family [14–16]. S1P can either function as a second messenger or can be transported to the extracellular milieu, where it can act in an autocrine or paracrine fashion by binding to different S1PRs, leading to different effector functions (Fig. 1b). Currently, five types of receptor (S1PR1–5) have been identified. S1PR1, S1PR2 and S1PR4 are expressed on macrophages and monocytes [17,18];

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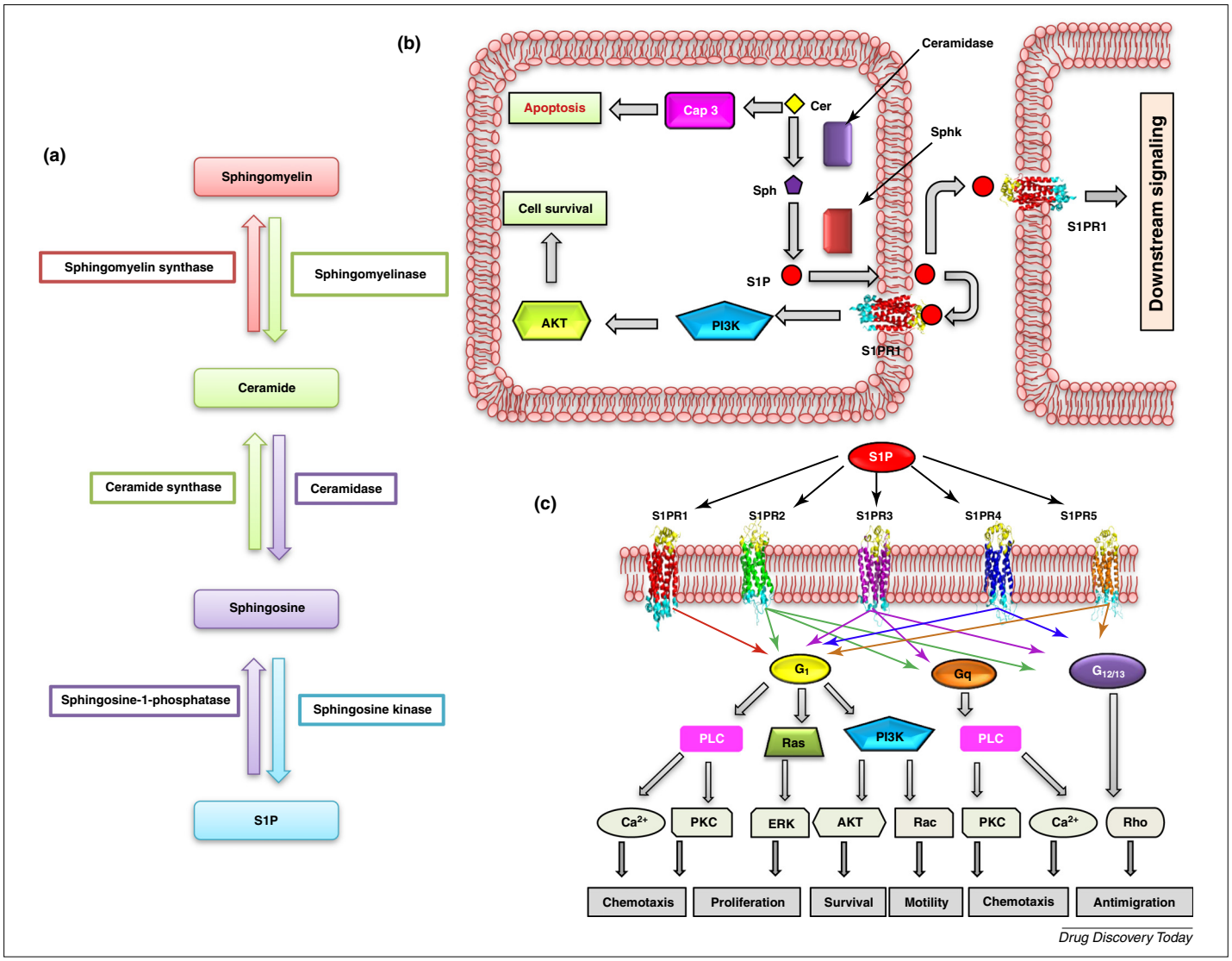

FIGURE 1

Sphingosine-1-phosphate signaling. **(a)** The multistep production of sphingosine-1-phosphate (S1P) is governed by several enzymes, including sphingomyelinase, ceramidase and sphingosine kinase (SphK). **(b)** Ceramidase converts ceramide (Cer) into sphingosine (Sph), which is later phosphorylated by SphK into S1P. Cer leads to the activation of caspase-3 (cap3), resulting in apoptosis, while S1P can also be transported to the extracellular milieu, where it acts in an autocrine or paracrine fashion by binding the S1P receptor (S1PR) and activating phosphoinositide 3-kinase (PI3K) and AKT, leading to cell survival. **(c)** Binding of S1P to its receptor initiates several downstream signaling pathways via coupling to respective G-proteins. Cartoon diagrams of SIPR1–5 were generated using PyMOL. All protein structures except S1PR1 were modeled using MODELLER 9.13S1PR2, S1PR3, S1PR4 and S1PR5 protein models were generated using the template structure of the S1PR1 (Protein Data Bank id: 3V2W). Transmembrane helices of different receptors are shown in different colors to differentiate them in the membrane. Abbreviations: ERK, extracellular signal-regulated kinase; PKC, protein kinase C; PLC, phospholipase C.

S1PR1 and S1PR3 are expressed on astrocytes, T cells and B cells [19–21]; S1PR4 is expressed on lymphocytes [15]; and S1PR5 is extensively expressed by brain endothelial cells [22]. Expression of S1PR5 has also been reported on dendritic cells (DCs) and natural killer cells [23,24]. These receptors are coupled to different small G-proteins, such as Gi, Gq, $G_{12/13}$ and Rho, which are known to activate diverse downstream signaling molecules, including phospholipase C (PLC), protein kinase C (PKC), extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) (Fig. 1c) [25].

The role of S1P–S1PR signaling has been extensively studied in cancers, autoimmune disorders, inflammation and neurological disorders, as reviewed elsewhere [26–28]. Additionally, in light of current reports [29–31], we discuss here the role of S1P signaling in infectious diseases. It has been observed that S1P signaling is impaired during infections. In most infectious diseases, the enzymes involved in S1P metabolism are targeted, although a few studies have reported that S1PRs are also targeted by infectious agents. In this review, we highlight recent milestones that provide an overview of S1P metabolism and signaling in infectious diseases, as well as the therapeutic potential of this molecule in the treatment of such diseases.

S1P signaling during infectious diseases

The role of S1P and its signaling pathway has been documented extensively in various diseases and disorders, including cancer, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and Alzheimer's disease [26–28]. With recent advances, it is

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