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Review

Biological function of SPNS2: From zebrafish to human

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ABSTRACT

Sphingosine-1-phosphate (S1P), a bioactive metabolite of sphingolipid, has an important role in lymphocyte trafficking, immune responses, vascular and embryonic development, cancer, bone homeostasis, etc. S1P is produced intracellularly and then secreted into the circulation to engage in the above physiological or pathological processes by regulating the proliferation, differentiation and survival of target cells; however, the underlying mechanisms of S1P secretion and function remain poorly understood. Recently, Spinster 2 (SPNS2), a newly identified transporter of S1P, was shown to act as a mediator of intracellular S1P release and play an important role in the regulation of S1P. In this review, we focus on the primary biological characteristics and functions of SPNS2 and provide novel insights into the development of therapies for S1P-related disorders.

1. Introduction

Sphingosine-1-phosphate (S1P), a conserved, active sphingolipid metabolite, is widely distributed in various cell types, including hematopoietic cells (erythrocytes, platelets), astrocytes, vascular endothelial cells (ECs), and lymphatic ECs (Ogretmen, 2018; Mendoza et al., 2017). In the cell, S1P formation is induced by sphingosine phosphorylation via sphingosine kinases (SPHKs, such as SPHK1 and SPHK2) (Aoki et al., 2016); SPHK1 is localized at the plasma membrane, and SPHK2 is localized in the mitochondria, ER and nucleus. Intracellular S1P, known as a second messenger, exerts its biological functions mainly by targeting downstream effectors (Alvarez et al., 2010). When needed, S1P is released into plasma, lymph and secretory fluids and subsequently interacts with its specific G protein-coupled receptors (S1PR1-5), after which it becomes further activated and is involved in diverse cellular processes and diseases (Tedford et al., 2017; Nishi et al., 2014).

Under physiological conditions, the concentration of S1P in circulatory fluids (plasma and lymph) is high (μM); however, in most tissues, especially lymphoid tissue, S1P is detected at low (nM) levels, which is attributed to high S1P-degrading activity (Fukuhara et al., 2012; Schwab and Cyster, 2007). Maintaining balance among S1P synthesis, degradation, and release is indispensable for the functions of cells and tissues. There are two major intracellular pathways that mediate S1P degradation: one mechanism of action is the removal of the phosphate group to regenerate sphingosine via lipid phosphate phosphatases (LPPs)/S1P phosphatases (SPPs)-induced dephosphorylation, and the other mechanism of action is its degradation to ethanolamine phosphate and hexadecenal by S1P lyase (SPL) (Nishi et al., 2014). As the final step in the establishment of S1P concentration, S1P release is an important factor for the homeostasis of S1P that is localized to the inner leaflet of the plasma membrane rather than inside secretory vesicles, and S1P is exported mainly in a transporter-dependent manner (Kobayashi et al., 2009).

Spinster 2 (SPNS2), a multipass transmembrane protein, is a crucial S1P transporter involved in S1P secretion and function; however, its precise regulatory mechanism is still unclear. In this review, the origin, distribution, structure, mechanism, and functions of SPNS2 will be highlighted.

2. Development of SPNS2

SPNS2 is a member of the Spinster (SPNS) family that includes SPNS in Drosophila and SPNS1-3 in vertebrates (Nishi et al., 2014). The SPNS gene was first defined in Drosophila in 1997 (Suzuki et al., 1997); its expression was observed in the ovary (follicle cells) and the nervous system (surface glial cells) (Nakano et al., 2001). Mutation of the SPNS gene in females leads to enhanced rejection of courting males and, consequently, to low mating success (Nakano et al., 2001). In addition, both the viability, life span, and oviposition rate in SPNS mutants were shown to decrease (Nakano et al., 2001). These behavioral phenotypes of SPNS mutants are at least partly attributed to degeneration of the ovaries and nervous system by downregulating programmed cell death (PCD) expression in nurse cells and neurons, respectively, which will

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Table 1
Development of SPNS2.

Species	Disease	Function	Pathway	Year
Zebrafish	Embryogenesis	Myocardial precursor migration	S1P-miles apart /S1PR2	2009 (Kawahara et al., 2009)
Zebrafish	Vascular development	Embryonic vascular patterning	S1P-S1PR1	2013 (Mendelson et al., 2013)
Mice	Immune response	Lymphocyte trafficking	–	2012 (Hisano et al., 2012; Nijnik et al., 2012)
Mice/Human (In vitro)	Prostate cancer	Osteoblast proliferation and survival	S1P-S1PR1	2014 (Brizuela et al., 2014)
Mice	Hearing loss	Endocochlear potential	–	2014 (Chen et al., 2014)
Mice	Colitis-associated cancer	–	–	2014 (Degagne et al., 2014)
Mice	Inflammatory and autoimmune diseases	Lymphopenia	–	2015 (Donoviel et al., 2015)
Mice	Lung cancer	Lymphocyte composition and phenotype	S1P-S1PR1/5	2017 (van der Weyden et al., 2017)
Human	Immune response	Transport of FTY720 (S1P analogs)	S1PR1	2011 (Hisano et al., 2011)
Human (In vitro)	Vascular development	Capillary-like structure formation	S1PR1/S1PR3	2015 (Laurenzana et al., 2015)
Human (In vitro)	Prostate cancer	Transcription,translation proliferation, apoptosis, metabolism	–	2015 (Lu et al., 2015)
Human	Liver fibrosis	mRNA levels of α-SMA and serum ALT levels	–	2016 (Donoviel et al., 2015)

provide novel insight into neurodegenerative diseases and aging, as SPNS gene orthologs have been confirmed in humans (Nakano et al., 2001). SPNS localized with late endosomes/lysosomes has been confirmed to encode a putative lysosomal efflux permease, whose absence was found to contribute to mTOR reactivation after starvation and then induce autophagic lysosome reformation (Rong et al., 2011). Although this discovery provides a potential target for autophagic lysosome-induced metabolic disease, the underlying mechanism by which SPNS regulates autophagic lysosomes and whether SPNS homologs in vertebrates also participate in this process need to be further studied, despite the identification of SPNS-1 (Sasaki et al., 2017). Because autophagic-lysosomal pathway defection is associated with neurodegeneration (Jenwitheesuk et al., 2014), Hebbar et al. further uncovered the underlying mechanism of the SPNS-mediated lysosomal autophagy pathway in the regulation of neurodegenerative diseases. These researchers used SPNS mutants to create a lysosomal storage disorder (LSD)-like neurodegeneration model in Drosophila and determined that adult SPNS mutants showed aggravated accumulation of brain ceramide and sphingosine, which caused damage in the early stages of neurodegeneration, suggesting that targeting the SPNS-mediated perturbation of lipid metabolism will provide a new strategy for the treatment of neurodegenerative diseases (Hebbar et al., 2017) and that more attention should be given to whether and how SPNS orthologs influence human neurodegenerative disease. Furthermore, genetically reducing Drosophila SPNS expression also has a critical role in suppressing Duchenne muscular dystrophy, a lethal genetic disease, as the reduction of SPNS function has been confirmed to be similar to the genetic elevation of S1P (Pantoja et al., 2013). Recently, the beneficial role of S1P in Duchenne muscular dystrophy in mice was confirmed by inhibiting the activation of histone deacetylase, which reduces the expression of inflammatory genes and increases that of metabolic genes by targeting miR-29 and miR-1, eventually promoting the use of fatty acids as an energy source to maintain energy metabolism in muscle cells (Nguyen-Tran et al., 2014). However, whether SPNS or its homologs, via altered regulation of S1P levels, can improve dystrophic muscle phenotypes and whether their function at least in part relies on the acetylation of specific histone residues still need to be further explored.

In vertebrates, SPNS2 has high sequence conservation among humans, mice and zebrafish (72% homology between zebrafish and human or mouse; 95% homology between human and mouse) (Hisano et al., 2012). In 2009, the role of SPNS2 in embryogenesis was identified by Kawahara et al. (2009). In this study, a zebrafish SPNS2 mutant, ko157, displaying two hearts was shown to be defective in regulating myocardial precursor migration via the S1P-miles apart/S1PR2 pathway and could be rescued via restoration of S1P expression (Kawahara et al., 2009). Based on this finding, in 2014, Mendelson et al. showed that SPNS2 plays an important role in the regulation of S1P-mediated embryonic vascular development by cooperating with S1PR1 in zebrafish (Mendelson et al., 2013). Loss of SPNS2 in mice, however, resulted in no abnormalities in their cardiovascular system, which indicates that the physiological function of SPNS2 in cardiogenesis is different between zebrafish and mammals (Nijnik et al., 2012). Since 2011, the role of SPNS2 in the immune system has received more attention and has been confirmed in vitro and in vivo. In vitro, human SPNS2 functions as a transporter of the S1P analog FTY720, a novel immunomodulating agent that is phosphorylated within cells and transported out of cells to bind S1PR1 and block lymphocyte egress into the circulating blood (Hisano et al., 2011). In vivo, SPNS2 mutant mice exhibit impaired progression of humoral immune responses to immunization due to disrupted S1P-dependent lymphocyte trafficking, thus contributing to the advancement in immunosuppressive therapy in 2012 (Hisano et al., 2012; Nijnik et al., 2012). Recently, the roles of SPNS2 in cancer, including lung cancer (van der Weyden et al., 2017), prostate cancer (Brizuela et al., 2014; Lu et al., 2015) and colitis-associated cancer (Degagne et al., 2014); hearing loss (Chen et al., 2014); vessel-like formation (Laurenzana et al., 2015); inflammatory and autoimmune diseases (Donoviel et al., 2015); and liver fibrosis (Sato et al., 2016) have also been reported (Table 1).

3. Structure and mechanism of SPNS2

Most mechanisms of molecular transport across lipid bilayers mainly depend on three major types of transporters, which include channels, primary active transporters and secondary active transporters; the latter is also commonly called solute carriers. SPNS2, a protein with 504 amino acid residues and 12 transmembrane domains, is a member of the major facilitator superfamily (MFS) according to amino acid sequence homology (Perland et al., 2017). MFS is the largest secondary transporter family, and its members are responsible for transporting a broad spectrum of substrates such as amino acids, sugars, intermediary metabolites, ions and other small molecules across membranes, playing important roles in maintaining homeostasis in the body (Yan, 2015). The mechanism of transport by MFS members relies on gradients of solutes or ions and does not seem to require energy consumption (Ranaweera et al., 2015). A recent study showed that SPNS2 transports S1P in a concentration gradient-dependent manner, which appears to be the same mechanism used by members of MFS