S1P signaling pathway

- Sphingosine kinase 1 promotes M2 macrophage infiltration and enhances glioma cell migration via the JAK2/STAT3 pathway
- Resveratrol-driven macrophage polarization: unveiling mechanisms and therapeutic potential
- Sphk1/S1P pathway promotes blood-brain barrier breakdown after intracerebral hemorrhage through inducing Nlrp3-mediated endothelial cell pyroptosis
- Sphingosine-1-phosphate receptor 3 promotes neuronal apoptosis via the TNF-alpha/caspase-3 signaling pathway after acute intracerebral hemorrhage
- Role of Luteolin as Potential New Therapeutic Option for Patients with Glioblastoma through Regulation of Sphingolipid Rheostat
- The Role of Sphingosine-1-Phosphate Receptor 2 in Mouse Retina Light Responses
- Sphingosine-1-phosphate Signalling in Aneurysmal Subarachnoid Haemorrhage: Basic Science to Clinical Translation
- Dexmedetomidine (Dex) exerts protective effects on rat neuronal cells injured by cerebral ischemia/reperfusion via regulating the Sphk1/S1P signaling pathway

S1P is generated from the phosphorylation of sphingosine, and it acts through specific receptors to regulate various cellular processes, including cell migration, survival, proliferation, and angiogenesis. S1P also has effects on the immune system, and it is involved in the regulation of blood flow, inflammation, and tissue homeostasis. Dysregulation of S1P signaling has been implicated in a number of diseases, including cancer, autoimmune disorders, and cardiovascular disease.

Dexmedetomidine could protect cerebral I/R-induced neuronal cell injury by suppressing the Sphk1/S1P signaling pathway [1].

Sphingosine-1-phosphate (S1P) is generated intracellularly and, when transported to the extracellular compartment, predominantly signals through S1P receptors. The S1P signaling pathway has been implicated in the pathophysiology of neurological injury following aneurysmal subarachnoid hemorrhage (aSAH).

In a review, Gaastra et al. bring together all the available data regarding the role of S1P in neurological injury following aSAH. There is an agreement in the literature that S1P increases in the cerebrospinal fluid following aSAH and leads to cerebral artery vasospasm. On the other hand, the role of S1P in the parenchyma is less clear-cut, with different studies arguing for beneficial and deleterious effects. A parsimonious interpretation of this apparently conflicting data is presented. They discuss the potential of S1P receptor modulators, in clinical use for multiple sclerosis, to be repurposed for aSAH. Finally, they highlight the gaps in the knowledge of S1P signaling in humans, the clinical challenges of targeting the S1P pathway after aSAH, and other research priorities [2].

Bioactive sphingolipids-ceramide, sphingosine, and their respective 1-phosphates (C1P and S1P)-are signaling molecules serving as intracellular second messengers. Moreover, S1P acts through G protein-coupled receptors in the plasma membrane. Accumulating evidence points to sphingolipids' engagement in brain aging and in neurodegenerative disorders such as Alzheimer's, Parkinson's, and

Huntington's diseases and amyotrophic lateral sclerosis. Metabolic alterations observed in the course of neurodegeneration favor ceramide-dependent pro-apoptotic signaling, while the levels of the neuroprotective S1P are reduced. These trends are observed early in the diseases' development, suggesting causal relationship. Mechanistic evidence has shown links between altered ceramide/S1P rheostat and the production, secretion, and aggregation of amyloid β/α-synuclein as well as signaling pathways of critical importance for the pathomechanism of protein conformation diseases. Sphingolipids influence multiple aspects of Akt/protein kinase B signaling, a pathway that regulates metabolism, stress response, and Bcl-2 family proteins. The cross-talk between sphingolipids and transcription factors including NF-κB, FOXOs, and AP-1 may be also important for immune regulation and cell survival/death. Sphingolipids regulate exosomes and other secretion mechanisms that can contribute to either the spread of neurotoxic proteins between brain cells, or their clearance. Recent discoveries also suggest the importance of intracellular and exosomal pools of small regulatory RNAs in the creation of disturbed signaling environment in the diseased brain. The identified interactions of bioactive sphingolipids urge for their evaluation as potential therapeutic targets. Moreover, the early disturbances in sphingolipid metabolism may deliver easily accessible biomarkers of neurodegenerative disorders [3)].

Emerging evidence implicates sphingosine-1-phosphate (S1P) signaling in the pathobiology of glioblastoma and angiogenesis, but its role in glioblastoma-endothelial crosstalk remains largely unknown. In a study of Hadi et al., in 2018 from the Department of Medical Biotechnology and Translational Medicine, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico Milan, Laboratory of General Physiology, Department of Biology and Biotechnology “Lazzaro Spallanzani”, University of Pavia, Italy, sought to determine whether the crosstalk between glioblastoma cells and brain endothelial cells regulates sphingosine-1-phosphate signaling in the tumor microenvironment. Using human glioblastoma and brain endothelial cell lines, as well as primary brain endothelial cells derived from human glioblastoma, they report that glioblastoma-co-culture promotes the expression, activity, and plasma membrane enrichment of sphingosine kinase 2 in brain endothelial cells, leading to increased cellular level of sphingosine-1-phosphate, and significant potentiation of its secretion. In turn, extracellular sphingosine-1-phosphate stimulates glioblastoma cell proliferation, and brain endothelial cells migration and angiogenesis. They also showed that, after co-culture, glioblastoma cells exhibit enhanced expression of S1P1 and S1P3, the sphingosine-1-phosphate receptors that are of paramount importance for cell growth and invasivity. Collectively, the results envision glioblastoma-endothelial crosstalk as a multi-compartmental strategy to enforce pro-tumoral sphingosine-1-phosphate signaling in the glioblastoma microenvironment [4)].

Following transient global cerebral ischaemia (tGCI), only the CA1 subregion of the hippocampus undergoes apoptosis. In this study, we evaluated S1P levels and S1P processing enzyme expression in different hippocampal areas following tGCI in rats. We found that S1P was upregulated earlier in CA3 than in CA1. This was associated with upregulation of SphK1 in both regions; however, SphK2 was downregulated quickly in CA3. S1P lyase was also downregulated in CA3, but not in CA1. Spinster 2, the S1P exporter, was upregulated early in both regions, but was quickly downregulated in CA3. Together, these effects explain the variable levels of S1P in the CA1 and CA3 areas and indicate that S1P levels play a role in the preferential resistance of the CA3 subregion to tGCI-induced ischaemia. FTY720 did not improve neuronal survival in the CA1 subregion, indicating that these effects were due to intracellular S1P accumulation. In conclusion, the findings suggest that intracellular S1P levels affect neuronal cell fate following tGCI [5)].

Sorafenib inhibited the phosphorylation of STAT3 induced by IL-6 and sphingosine-1-phosphate (S1P), a identified regulator for STAT3, in neuroblastoma. Moreover, sorafenib downregulated phosphorylation of MAPK (p44/42) in neuroblastoma cells, consistent with inhibition of their upstream regulators MEK1/2 [6].

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