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Sphingosine-1-phosphate in chronic intestinal inflammation and cancer

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A B S T R A C T

Sphingosine-1-phosphate (S1P), a pleiotropic bioactive lipid mediator, and the kinase that produces it have now emerged as key regulators of numerous cellular processes involved in inflammation and cancer. Here, we review the importance of S1P in colitis and colitis-associated cancer (CAC) and discuss our recent work demonstrating that S1P produced by upregulation of SphK1 during colitis and associated cancer is essential for production of the multifunctional NF-κB-regulated cytokine IL-6, persistent activation of the transcription factor Stat3, and consequent upregulation of the S1P receptor, S1PR1. The effectiveness of the prodrug FTY720 (known as fingolimod), approved for the treatment of multiple sclerosis, has become the gold standard for S1P-centric drugs, and will be used to illustrate the therapeutic value of modulating SphK1 and S1P receptor functions. We will discuss our recent results showing that FTY720/fingolimod administration interferes with the SphK1/S1P/S1PR1 axis and suppresses the NF-κB/IL-6/Stat3 malicious amplification loop and CAC. These preclinical studies suggest that FTY720/fingolimod may be useful in treating colon cancer in individuals with ulcerative colitis.

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Introduction

It is now more than two decades since it was discovered that S1P is a signaling molecule that regulates cell growth and the suggestion that it may play a role in cancer (Olivera and Spiegel, 1993; Zhang et al., 1991). A large subsequent body of work has demonstrated that S1P regulates many processes important for inflammation and cancer, including cell proliferation, survival, migration, invasion, cytokine and chemokine production, angiogenesis and lymphangiogenesis (Nagahashi et al., 2012, 2010; Pyne and Pyne, 2010; Spiegel and Milstien, 2011). S1P is generated intracellularly by two sphingosine kinase isoenzymes, SphK1 and SphK2. Numerous agonists and stimuli, such as growth factors, hormones, and pro-inflammatory cytokines activate SphK1 by inducing its phosphorylation and translocation from the cytosol to the plasma membrane where its substrate sphingosine is localized (Alvarez et al., 2007; Maceyka et al., 2012). This translocation enables localized production of S1P that in turn activates a family of five G protein coupled receptors (S1PR1-5), a process known as "inside-out signaling" by S1P (Takabe et al., 2008). S1P is exported out of the cells by ATP binding cassette transporters, ABCA1 (Sato et al., 2007), ABCC1, ABCG2 (Mitra et al., 2006; Takabe et al., 2010) and Spns2 (Hisano et al., 2011; Kawahara et al., 2009; Nagahashi et al., 2012). In contrast, much less is known about the roles of S1P produced by SphK2, which is present in several subcellular compartments including mitochondria and nucleus (Hait et al., 2009; Strub et al., 2011).

Intracellular S1P levels are tightly maintained by the balance between synthesis and degradation. S1P can be dephosphorylated by the action of two specific endoplasmic reticulum localized S1P phosphatases back to sphingosine, which is reutilized for synthesis of ceramide and complex sphingolipids. As the end product of metabolism of all cellular sphingolipids, S1P is also irreversibly degraded by S1P lyase to hexadecenal and phosphoethanolamine (Fyrst and Saba, 2010). By degrading tissue S1P, S1P lyase plays a major role in generation of a S1P concentration gradient between the circulation and tissues (Cyster and Schwab, 2012) – S1P levels in blood and lymph are high, whereas levels are orders of magnitude lower in tissues and interstitial fluids (Cyster and Schwab, 2012). Immune cells, such as lymphocytes, hematopoietic progenitor cells, and dendritic cells utilize this S1P gradient to regulate their trafficking. Interestingly, the successful development of FTY720/fingolimod for treatment of multiple sclerosis (MS) and the elucidation of its mechanism of action has provided insight into the importance of the S1P/S1PR1 axis for the immune system.

In addition to the canonical extracellular actions of S1P that are now well known, it has long been suspected that S1P also has receptor independent intracellular actions that remained mysterious until the last few years. This situation has changed with discovery of several intracellular targets of S1P (Alvarez et al., 2010; Hait et al., 2009). The first example is TRAF2, an adaptor protein containing a RING domain that is implicated in the regulatory ubiquitination of RIP1, a critical event in activation of NF-κB in response to TNF-α. We showed that S1P produced by SphK1 binds to TRAF2 and is a cofactor required for its E3 ligase activity and consequently, Lys-63-linked polyubiquitination of RIP1 and NF-κB activation (Alvarez et al., 2010), explaining the importance of SphK1 and S1P in cytoprotection, inflammation, and immune responses (Spiegel and Milstien, 2011). Intriguingly, S1P, produced in the nucleus by SphK2, is an endogenous inhibitor of histone deacetylases (HDACs) (Hait et al., 2009). Nuclear SphK2 was shown to be a component of HDAC containing repressor complexes that are present at the promoters of specific genes, producing S1P that binds to and inhibits both HDAC1 and HDAC2, and regulates gene transcription, including the cyclin dependent kinase inhibitor *p21*. These results link sphingolipid metabolism in the nucleus to epigenetic regulation (Hait et al., 2009).

FTY720, the basic properties

FTY720 was first synthesized in 1992 in an attempt to simplify the complex structure of myriocin (ISP-1), a fungal metabolite with immunosuppressive properties isolated from *Isaria sinclairii* culture broth. A phenylene moiety was introduced in the side chain and this compound, designated FTY720 (2-amino-2-[2-(4octylphenyl)ethyl]propane-1,3-diol) was found to have even more potent immunosuppressive activity than myriocin (Chiba et al., 1998). Although it was initially thought that FTY720 itself was biologically active, it was later noted that FTY720 is structurally homologous to sphingosine, and then shown that it is phosphorylated in vivo to FTY720-P, a mimetic of S1P and an agonist of all of