The Role of S1P in Multiple Myeloma Progression

Jessica Yang, Grade 12, St. Clement's School,
Sun Life Gene Medical Science Institute Cancer Research Program Student, Toronto, Ontario, Canada

Abstract
Multiple Myeloma (MM) is a blood cancer of the bone marrow that develops when malignant plasma cells overproduce abnormal proteins. MM can lead to long-term problems like anemia, impaired immunity, and organ damage. Disease progression and drug resistance are significant barriers preventing MM from being curable. Studies have highlighted sphingosine-1-phosphate's (S1P) role in regulating cancer cell proliferation and angiogenesis. Increased levels of this bioactive sphingolipid and the abnormal activation of its receptors (S1PRs) have been found to promote MM development and reduce cells' sensitivity to anti-myeloma drugs. Recent preclinical research has found that targeting the S1P signalling pathway with S1P receptor antagonists such as fingolimod, and with inhibitors of sphingosine kinases (SphK1 and SphK2), may suppress MM growth and induce apoptosis. However, mechanisms affecting S1P's role in MM and its integration into existing treatments remain insufficiently understood. This review will discuss the structure and function of S1P, the role of S1P signalling in MM progression, and its implications on drug resistance.

Keywords: Sphingosine-1-phosphate (S1P); Sphingosine-1-phosphate receptors (S1PR); Sphingosine kinase 1 (SphK1); Sphingosine kinase 2 (SphK2); Multiple myeloma (MM)

Introduction

S1P is a molecule that functions both as an extracellular ligand and an intracellular messenger. It plays a key role in regulating important cellular processes and functions such as cell growth, proliferation, and angiogenesis (Strub et al., 2010). The concentration of S1P has a positive correlation with cancer progression in that S1P concentrations in cancer tissues are almost always significantly higher compared to concentrations in surrounding non-cancerous tissues (Nagahashi et al., 2018).

S1P is crucial in MM progression because it promotes MM cell survival and increases drug resistance. In fact, S1P binds to S1PR1, S1PR2, and S1PR3 receptors on the surface of myeloma cells. This in turn increases production of anti-apoptotic proteins that impede apoptosis (Li et al., 2008). In addition, S1P activates α4β1 integrin, enhancing the migration and adhesion of myeloma cells, and ultimately enabling the overall process of homing (Garcia-Bernal et al., 2013).

Targeting the S1P signaling pathway with sphingosine kinase (SK) inhibitors or S1P receptor antagonists like fingolimod is a potential strategy for impeding MM development (Fu et al., 2017).

S1P Structure and Function

Structure

A lysophospholipid that binds to a family of five specific G protein-coupled receptors, S1P molecules consist of a sphingoid base backbone and an attached phosphate group (Gupta et al., 2012). S1P is amphipathic with a hydrophobic long alkyl chain and a hydrophilic head group (Wojciak et al.,

2009). Further, S1P is derived from the sphingoid base sphingosine by phosphorylation (Gupta et al., 2012).

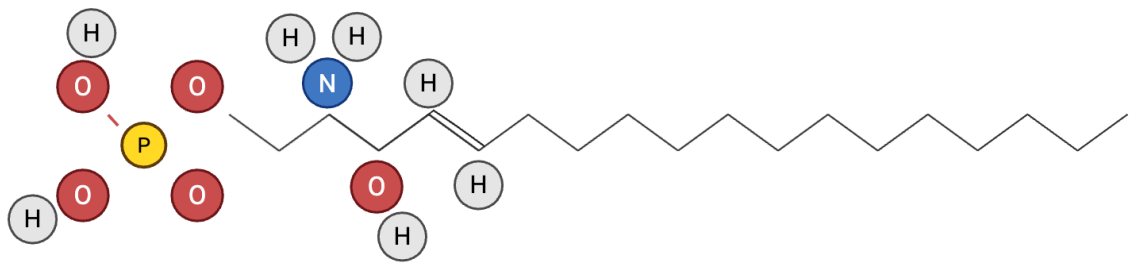

Figure 1: Chemical structure of S1P

Function

Upon binding to these five high-affinity G protein-coupled receptors, multiple downstream signals will take place, triggering intracellular signalling pathways (Rosen et al., 2013). S1P performs most of its physiological functions by binding to S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5. This then triggers many downstream intracellular signals, where the specific pathway depends on the receptor (Yuan et al., 2021). These resulting signals are significant in regulating key cellular processes, including cell migration, angiogenesis, adhesion, and inflammatory response (Xu et al., 2022). Conversely, abnormal S1P signalling is implicated in a range of conditions including cardiovascular, autoimmune, and neurodegenerative cancers and diseases (Xu et al., 2022).

S1P Signalling in Multiple Myeloma Progression

S1P activation in MM cell lines is implicated with the proliferation and survival of MM cells (Tanaka et al., 2022). On the other hand, specific S1P receptor antagonists, such as fingolimod, reduce the influence of S1P, suggesting that anti-S1P agents could be viable in MM treatment (Tanaka et al., 2022). Further, SK inhibitors have been identified to have anti-cancer potential against cell proliferation and survival (Xu et al., 2022). Individuals with MM have significantly higher levels of serum S1P compared to individuals without MM, suggesting that fingolimod or SK inhibitors could be novel approaches to treating MM (Tanaka et al., 2022).

Inhibition of SKs and S1PR1 suppresses MM cell growth and promotes apoptosis (Tanaka et al., 2022). Furthermore, this inhibition impairs endothelial cell migration, thereby potentially reducing MM progression in the bone marrow microenvironment (Tanaka et al., 2022).

These findings relate to the broader role of bone marrow microenvironment in MM progression because it facilitates abnormal plasma cell growth, which has several downstream effects like interference with bone cell homeostasis (Petrusca et al., 2022). An abnormal microenvironment fosters tumorigenesis by providing extracellular stimuli which drives tumor transformation. These stimuli also induce metabolic changes, disrupting important signalling pathways and the sphingolipid balance (Petrusca et al., 2022).

Studies have shown that the activation of S1PRS—specifically S1PR1—in MM cells, promotes survival. Another attribute of MM progression is increased angiogenesis (Giannakoulas et al., 2024).

In fact, the SphK1-S1P-S1PR1 pathway is heavily involved in angiogenesis regulation, where anti-S1P antibodies significantly reduce vessel growth (Petrusca et al., 2022). Thus, the targeting of sphingolipids or angiogenesis offers a potential avenue for treatment, with some studies testing anti-angiogenic therapies in MM (Petrusca et al., 2022).

Extracellular S1P acts in both autocrine and paracrine ways through interaction with S1PRs, giving it a vital role in many cellular processes (Petrusca et al., 2022). One of the most studied S1PR modulators in MM is fingolimod. Fingolimod has been found to inhibit growth of both drug-sensitive and drug-resistant MM cell lines (Yasui et al., 2005). In the same study, the growth of tumor cells from relapsed, refractory patients was inhibited (Yasui et al., 2005). Specifically, fingolimod was able to cause the death of MM cells through the activation of multiple caspases, altering the mitochondrial membrane potential, and triggering proapoptotic signals like the cleaving of PARP and BAX protein (Yasui et al., 2005).

Petrusca et al. (2022) categorize sphingolipid-based treatments in two types: interventions that induce MM cell death by indirectly affecting sphingolipid pathways and those that directly target sphingolipids. In addition, because MM is so complex, it is very likely that more than one agent therapy is needed to suppress cell growth (Petrusca et al., 2022). In conjunction with other chemotherapeutic treatments, bioactive sphingolipids, which play a crucial role in cell signalling, are a promising way to target MM.

SphK1 and SphK2 are sphingosine kinase isoforms that phosphorylate sphingosine, forming S1P. Despite both enzymes catalyzing the phosphorylation of sphingosine, they have opposite effects on cancer cells; this difference is largely due to the differing locations in the cell in which S1P is produced (Maceyka et al., 2005). Located in the cytoplasm, SphK1 aids in the growth and survival of cancer cells. Conversely, SphK2 is localized primarily to the mitochondria, nucleus, and endoplasmic reticulum where it can promote apoptosis of cells and inhibit cell proliferation (Maceyka et al., 2005; Gupta et al., 2011). Indeed, SphK2 has been studied for its potential in treating cancer, as well as other health conditions and diseases (Diaz Escarcega et al., 2021). Both SphK1 and SphK2 have been identified as potential drug targets in studies for cancer treatment—and various other conditions involving excessive cell proliferation—as they are able to control the relative concentrations of sphingosine and S1P in the cell (Kharel et al., 2012).

S1P's Impact on Drug Resistance:

For MM, patients could be initially resistant or develop resistance to drugs during or after treatment (Abdi et al., 2013). Elevated S1P levels foster a cellular environment that allows cancer cells to resist the effects of chemotherapy and anti-myeloma drugs through a variety of mechanisms. Specifically, S1P signalling promotes drug resistance by increasing cell proliferation and survival while inhibiting apoptosis (Fu et al., 2017)

Mechanisms of Drug Resistance Through S1P Signalling:

Research links sphingolipids to resistance to drugs and radiation in various solid tumors (Petrusca et al., 2022). This resistance could occur due to the alteration of cancer cells' sphingolipid metabolism or from changes in surrounding microenvironmental cells, which then "secrete an altered bioactive lipid profile" (Petrusca et al., 2022, 6 Sphingolipids as Mediators of Drug-Resistance in MM section).

Promoting Cell Proliferation and Inhibiting Apoptosis:

Researchers found that S1P promoted cell proliferation (Fu et al., 2017). Furthermore, S1P signalling via S1PR1 induces anti-apoptotic pathways, which directly aids in the survival of cancer cell (Alkafaas et al., 2024).

In addition, elevated levels of enzymes that move sphingolipid metabolism away from ceramide production can suppress apoptosis, thereby promoting drug resistance (Petrusca et al., 2022).

Therapeutic Strategies Targeting the S1P Pathway:

The aforementioned research proves that targeting the S1P signalling pathway can be a potential therapeutic strategy to not only manage MM, but also to impede drug resistance. As categorized by Petrusca et al. (2022), these therapeutic strategies involve either directly targeting sphingolipids or indirectly affecting their pathways.

Targeting S1P Receptors:

Targeting S1P and S1PR1 is also a potential avenue to overcome cancer cell resistance (Alkafaas et al., 2024). Fingolimod can be used as it downregulates target gene expression and works against the cancer cells (Fu et al., 2017). It also induces apoptosis, which is important in overcoming drug resistance (Yasui et al., 2005). It is important to note that fingolimod can bind with high affinity to each of the S1PR except for S1PR2 (Groves et al., 2015).

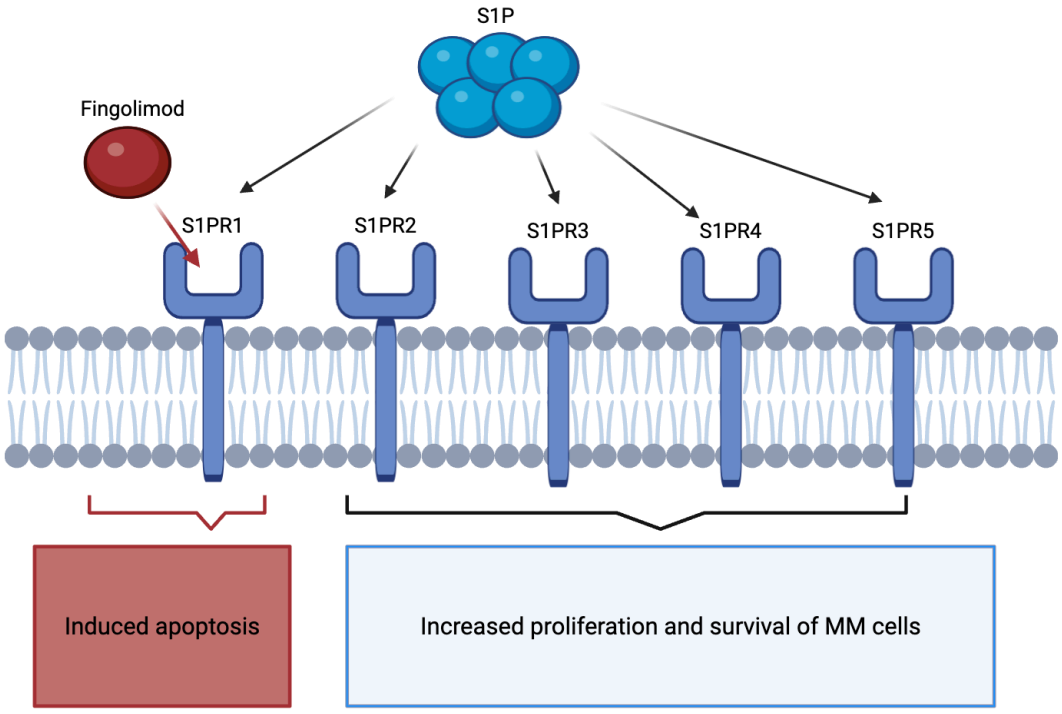

Figure 2: This diagram depicts fingolimod acting on the S1P signalling pathway. Fingolimod is a promising therapeutic strategy to overcoming drug resistance as it induces apoptosis.

Targeting S1P Production:

Building on this idea, another promising method to decrease drug resistance in cancer cells is the targeting of SphK1 and SphK2 using inhibitors, which would minimize the levels of S1P produced (Alkafaas et al., 2024). In previous studies, though, these inhibitors like trimethyl-sphingosine (TMS), Safingol, and dimethyl-sphingosine (DMS) could not solely target SphK1, though they TMS and DMS have selectivity for SphK2. Due to their limited selectiveness and robustness for SphK1, they were able to impact other protein kinases or lipids, leading to different off-target effects (Alkafaas et al., 2024).

Discussion and Conclusion:

The relationship between S1P signalling and MM is complex, with many mechanisms still not fully understood. Research demonstrates that S1P promotes MM development by increasing cell proliferation, survival, and angiogenesis. Furthermore, S1P fosters a bone marrow microenvironment that leads to increased tumorigenesis. These processes thus lead to both MM progression as well as increased drug resistance.

A potential therapeutic strategy explored in this paper is the targeting of S1P receptor antagonists, like fingolimod, and SphK1/SphK2 inhibitors that can impede MM cell growth, induce apoptosis, and reduce drug resistance. Specifically, fingolimod is a promising therapeutic agent because it has been shown to act against both drug-sensitive and drug-resistant MM cell lines. SphK1/SphK2 inhibitors, on the other hand, is important as these enzymes regulate the balance between S1P and sphingosine, thereby affecting whether cells undergo survival or apoptosis.

Therapies that either directly or indirectly target sphingolipid metabolism are potential ways to overcome MM (Petrusca et al., 2022). Pathways as targets is further supported by the fact that targeting S1P and S1PR1 could suppress pro-survival signalling and drug resistance (Alkafaas et al., 2024).

Future studies should be conducted to clarify the mechanisms of S1P signalling in MM and to identify SphK1 and SphK2 inhibitors that have minimal off-target implications. In addition, future research should examine how these strategies can be integrated with existing MM treatments, as this allows patient responses to be enhanced and helps combat drug resistance.

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