A Novel Function of Sphingolipid Signaling via S1PR3 in Hematopoietic and Leukemic Stem Cells

Chong Yang1, Masayuki Yamashita2, and Toshio Suda1,3

Summary: In this issue of Blood Cancer Discovery, Xie and colleagues describe a novel function of sphingosine-1-phosphate receptor 3 (S1PR3) to regulate myeloid differentiation and activate inflammatory programs in both normal and leukemic hematopoiesis. The study by Xie and colleagues characterized a novel function of sphingolipid signaling via sphingosine-1-phosphate receptor 3 (S1PR3) to mediate inflammatory programs in normal and leukemic hematopoiesis. Sphingolipids are essential structural components in the mammalian cell membranes, and their metabolism involves the interconversion of sphingomyelin, ceramide, sphingosine, and sphingosine-1-phosphate (S1P). Among the five S1P receptors, S1P3 activities were found mostly paralleling those of S1PR1 but may differentially regulate cellular processes with distinct signaling pathways. In the hematopoietic system, S1PR3 has been shown to support CXCR4-mediated hematopoietic stem/progenitor cell residence and trafficking in their bone marrow niche. However, the more specific role of S1PR3 remains elusive in the context of hematopoiesis.

Moreover, prolonged exposure to inflammatory insults underlies leukemogenesis, involving the emergence and selection of mutant hematopoietic stem cells (HSC) in preleukemic phase, such as myelodysplastic syndrome (MDS) and myeloproliferative neoplasms. Importantly, more evidence shows that the perturbation of cell survival and myeloid differentiation is caused not only by cytokine exposure and inflammatory signaling pathways, but also by various cellular metabolites, including sphingolipids, and they often interplay with one another. Indeed, TNFα reportedly induces S1P through upregulation of sphingosine kinases (SPHK), and S1P in turn potentiates the TNFα–NF-κB axis via stabilizing the critical scaffolding protein RIPK1. However, the functions of S1P signaling via S1P receptors in normal and leukemic hematopoiesis in the context of inflammation remain understudied.

Here, to explore novel lineage regulators and their machineries mediated by inflammatory programs in human HSCs and AML, Xie and colleagues identified that among the five S1P receptors, S1PR3 is specifically expressed in myeloid...
self-renewal including those upregulated via the TNFα in human HSCs strongly induced inflammatory gene sets, B). They further demonstrated that S1PR3 overexpression α in HSCs, but not GMPs, upon TNFα lineage, and that its surface expression is specifically induced by potentiation of the myeloid differentiation program driven by the TNFα–NF-κB axis (Fig. 1B), thus establishing S1PR3 as a biomarker to distinguish a subset of less functional LSCs in patients with AML and also as a functional molecule that mediates TNFα-induced LSC differentiation.

To provide clinical relevance by therapeutically targeting S1P signaling pathways, Xie and colleagues subsequently reported an association between sphingolipid genes and AML patient prognosis through the analysis of gene expression profiling of LSC +/- AML patient samples. These findings may harbor therapeutic significance in the modulation of S1P signaling to disrupt LSC functions in human AML. Importantly, xenograft assay showed that treatment with the S1P prodrug fingolimod (FTY720), which is known to modulate S1P receptors, including S1PR3, resulted in decreased leukemia burden by disrupting LSC functions perhaps, in part, due to increased myeloid differentiation (Fig. 1C).

Notably, fingolimod is an immunomodulating drug and has previously shown efficacy for the treatment of multiple sclerosis. It is a structural analogue of sphingosine and able to undergo phosphorylation in vivo by SPHK to produce fingolimod phosphate (p-FTY720) that binds to four S1P receptors (S1PR1 and S1PR3-5) with high affinity. Upon ligation, fingolimod initially acts as an agonist, but then may cause the internalization and degradation of S1P receptors. In multiple sclerosis therapy, the latter antagonistic mechanism underlies fingolimod-mediated block of lymphocyte egress from the lymph nodes, preventing their invasion into the central nervous system (8). The utility of fingolimod in multiple sclerosis opens a therapeutic avenue for its potential administration in patients with AML, although its mechanism of action described in this study is contrasted with that indicated in an S1PR3-driven AML mouse model (9). Since it remains controversial whether FTY720 acts as an agonist or a functional antagonist to target LSC/AML, the treatment regimen should be carefully chosen so that S1P receptors will not be internalized. The study also provided evidence to encourage further investigation of other sphingolipid signaling-modulating drugs to target LSCs in AML, such as SPHK inhibitors, as well as agents targeting the TNFα–NF-kB axis. While pharmaceutical agents to specifically modulate S1PR3 are currently limited, targeting sphingolipid metabolic and signaling pathways provides novel insight into the development of improved agents to treat AML.

**Authors’ Disclosures**

No disclosures were reported.

**REFERENCES**

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