IN THE SPOTLIGHT

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

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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. 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; ref. 2). S1P is a pleiotropic lipid mediator regulating a myriad of cellular functions in various cell types, including proliferation, migration, matrix adhesion, cell–cell contact, and inflammation. Notably, in the immune and vascular systems, S1P signaling modulates immune cell trafficking and vascular integrity via the regulation of inflammatory processes (3). S1P is a ligand for five high-affinity G protein–coupled receptors, namely S1PR1–5 (3). Among the five S1P receptors, S1PR3 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 (4). 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, and the emergence of leukemic stem cells (LSC) in acute myeloid leukemia (AML). LSCs exhibit properties of self-renewal and chemoresistance similar to their normal counterpart, and modulation of inflammatory signaling pathways can eliminate LSCs and, in some cases, induce differentiation of AML blasts (5). Thus, targeting inflammatory signaling shows great therapeutic potential for the treatment of myeloid malignancies, particularly by preventing LSC emergence and its maintenance. Inflammatory factors, such as TNFα, IL1β, IL6, IL8, IFNα, IFNγ, and endogenous Toll-like receptor ligands (e.g., damage-associated molecular patterns) are increasingly secreted as a result of the altered microenvironment during leukemogenesis, giving rise to compromised normal HSC function and bone marrow failure (5). Among these inflammatory factors, TNFα has a seemingly contradictory role in hematopoiesis, as normal HSC maintenance requires baseline TNFα signaling, while excessive TNFα signaling is associated with bone marrow failure and MDS (6). Of note, a mouse study has recently shown that TNFα differentially stimulates the activity of NFκB, which is a key transcriptional factor to regulate the inflammatory activation, between HSCs and granulocyte-macrophage progenitors (GMP; ref. 6). As a result, HSCs upregulate a distinct set of NFκB target genes, including S1PR3, upon TNFα exposure, leading to their enhanced survival and myeloid differentiation, while GMPs undergo apoptosis. Notably, these HSC-specific TNFα targets are also upregulated in MDS stem cells and AML LSCs (6), suggesting that this mechanism is also utilized in these malignant stem cells. 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–NFκB axis via stabilizing the critical scaffolding protein RIPK1 (7). 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...
Figure 1. Suggested roles of S1PR3 in the regulation of human HSCs and LSCs. A, Healthy, steady-state human HSCs. With no inflammation, HSCs do not express S1PR3. Cer, ceramide; SM, sphingomyelin; Sph, sphingosine. B, Healthy HSCs during inflammation and LSCs. S1PR3 is expressed and activated in healthy HSCs upon inflammation via TNFα exposure. TNFα can also promote production of S1P, the ligand of S1PR3. S1P production involves a series of sphingolipid conversions from sphingomyelin to ceramide, then to sphingosine, and finally to S1P via phosphorylation by SPHKs. S1PR3 expression potentiates the TNFα–NF-κB axis possibly via S1P-mediated stabilization of the critical scaffolding protein RIPK1, or yet unknown mechanisms, leading to HSC differentiation into myeloid lineage. In contrast, a subset of LSCs in AML constitutively express S1PR3 on their surface, possibly due to an inflammatory microenvironment. These S1PR3-expressing LSCs are less functional because S1PR3 restricts self-renewal of LSCs at least, in part, via potentiation of TNFα-induced differentiation. C, Effect of FTY720 on S1P signaling. FTY720 is phosphorylated by SPHK, and p-FTY720 acts to disrupt LSC self-renewal likely via induction of myeloid differentiation. Whether FTY720 acts as an agonist or a functional antagonist in this context remains to be determined. Colored arrows indicate signaling pathways shown by Xie and colleagues.

lineage, and that its surface expression is specifically induced in HSCs, but not GMPs, upon TNFα exposure (Fig. 1A and B). They further demonstrated that S1PR3 overexpression in human HSCs strongly induced inflammatory gene sets, including those upregulated via the TNFα–NF-κB axis, leading to enhanced HSC survival, and promoted myeloid and megakaryocytic differentiation at the expense of erythroid differentiation (Fig. 1B), which is reminiscent of the TNFα-induced differentiation skewing observed in the mouse study (6).

Next, they proceeded to investigate the role of S1PR3 in the development of AML. By analyzing gene expression profiles in patients with AML, they reported a strong correlation between S1PR3 expression and myeloid differentiation in AML cells that marks a distinct activated inflammatory state. Interestingly, they demonstrated that S1PR3 expression was associated with a subset of cells with low LSC activity, and overexpression of S1PR3 in AML disrupts LSC function via 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 (7). 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-κB 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.

Published first December 1, 2020.

REFERENCES


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Blood Cancer Discov 2021;2:3-5. Published OnlineFirst December 1, 2020.

Access the most recent version of this article at:
doi: 10.1158/2643-3230.BCD-20-0200

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