Comment on Dany et al, page 1944

Fighting fat in AML

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In this issue of Blood, Dany et al demonstrate a critical role of the ceramide-regulated signaling pathway in inducing mitophagy to cause cell death and overcome drug resistance of acute myeloid leukemia (AML) cells carrying internal tandem duplication (ITD) of the Fms-like tyrosine kinase 3 (FLT3) gene.1 Inhibition of FLT3-ITD signaling through altering ceramide-involved lipid metabolism provides a new strategy for treating FLT3-ITD–positive AML and overcoming drug resistance by pharmacologically blocking FLT-3-ITD downstream signaling to enhance ceramide-mediated mitophagy.

AML is a group of heterogeneous hematopoietic malignancies caused by various oncogenic genetic lesions, of which FLT3-ITD is one of most common genetic alterations found in ~30% of AML patients carrying the gain-of-function FLT3-ITD mutations.2 FLT3-ITD–associated AML has a poor prognosis,3,4 and FLT3 tyrosine kinase inhibitors (TKIs) have been developed to treat AML by inhibiting FLT3-ITD kinase activity.5 However, the resistance to TKIs occurs due to the development of FLT3 kinase domain mutations. Several TKIs are currently used in treating AML patients, but clinical efficacy has not been convincing.6 Alternative therapeutic strategies need to be created to target FLT3-ITD downstream signaling, and a success in this approach relies on a better understanding of FLT3-ITD signaling mechanisms for identifying new targetable signaling molecules that regulate FLT3-ITD oncogenic activity. This study shows a functional link between FLT3-ITD signaling and lipid metabolism.

Lipid metabolism has been shown to be involved in cancer development. In particular, sphingolipid-related functions are shown to regulate proliferation, differentiation, senescence, and death of cancer cells.7 Ceramide is a major family member of sphingolipids and plays a key role in the response of cancer cells to chemotherapy,8 implying that the ceramide-mediated pathway could be targeted to kill cancer cells. Ceramide is known to regulate autophagy and induce lethal mitophagy.9 However, a mechanistic link between FLT3-ITD signaling and ceramide metabolism for the regulation of mitophagy-dependent cell death in AML has not been established.

In this study, Dany et al reported that FLT3-ITD suppresses C18-ceramide generation by ceramide synthase 1 (CerS1) in AML cells, and small interfering RNA (siRNA) knockdown of FLT3-ITD or the inhibition of FLT3-ITD by a FLT3 inhibitor (such as crenolanib) induces cell death. The role of ceramide in crenolanib-induced cell death was confirmed by inhibiting CerS1 activity to reduce ceramide production, leading to resistance to TKI-induced cell death. These results indicate that alteration of ceramide synthesis provides a strategy for regulating FLT3-ITD signaling by bypassing a direct effect of a TKI on FLT3-ITD kinase.

Subsequently, the cell death mechanism mediated by ceramide is linked to the regulation of autophagy initially and mitophagy at the terminal stage of apoptosis. Specifically, siRNA knockdown of autophagy protein light-chain 3 B (LC3B) protects AML cell death induced by crenolanib, and conversely, AML cells with LC3B overexpression are more sensitive to crenolanib-induced cell death, showing a functional link between FLT3-ITD signaling and autophagy. In addition, upon crenolanib treatment, CerS1 and ceramide colocalize to mitochondria, and mitochondrial ceramide binds to LC3B to recruit autophagosomes. Finally, dynamin-related protein 1 (Drp1) known to regulate mitophagy, induces mitochondrial fission and lethal mitophagy of AML cells, because siRNA knockdown or pharmacologic inhibition of Drp1 protects AML cells from crenolanib-induced cell death. Mechanistically, activation of Drp1 is induced by its dephosphorylation at S637, which is mediated by crenolanib-stimulated decrease of kinase activity of protein kinase A (PKA). It will be worth testing whether PKA is an additional target in combination with alteration of ceramide synthesis for AML therapy. Importantly, the in vivo experiment using immunocompromised nonobese diabetic–severe combined immunodeficiency (NOD/SCID) mice (NOD-SCID/IL-2gamma-null [NSG] mice) engrafted with crenolanib-resistant human AML cells shows that LCL–461, a mitochondria-targeted ceramide analog, induces lethal mitophagy and improves the pathological appearance of the AML mice.

The study conducted by Dany et al is comprehensive, but the majority of the experiments were done using AML cell lines. Although bone marrow (BM) blasts obtained from FLT3-ITD–positive AML patients were used selectively in a few experiments, human relevance of the study can be further increased by testing the following ideas using NSG mice engrafted with human AML BM blasts sensitive or resistant to crenolanib therapy: (1) does crenolanib suppress CerS1-ceramide generation in vivo? (2) does LCL–461 improve survival of the NSG mice? and (3) does LCL–461 synergize with crenolanib to attenuate AML development in mice?

Without any doubt, the current study provides a new strategy for overcoming crenolanib resistance in AML treatment, which is illustrated clearly in Figure 2J in the article by Dany et al. The findings in this study also call for the development of new therapeutic drugs that regulate the ceramide pathway in AML. Furthermore, future work is needed to test whether targeting FLT3-ITD–regulated ceramide pathway has an effect on AML-initiating cells that are likely responsible for disease progression and failure of eradication of AML cells by chemotherapy. On the other hand, besides ceramide that mediates antiproliferative responses, another sphingolipid family member is sphingosine 1-phosphate (SIP) and plays a stimulatory role in regulating proliferative responses.8 It is worth studying further the functional relationship between ceramide and SIP in FLT3-ITD signaling in order to develop more effective therapeutic strategies for treating AML and overcoming drug resistance.

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