Inhibiting Glucosylceramide Synthase Sensitizes CML T315I Mutant to Bcr-Abl Inhibitor and Cooperatively Induces Glycogen Synthase Kinase-3-regulated Apoptosis

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Inactivation of glycogen synthase kinase (GSK)-3 has been implicated in cancer progression. We previously showed abundance of inactive GSK-3 in human chronic myeloid leukemia (CML) cell line. CML is a hematopoietic malignancy caused by an oncogenic Bcr-Abl tyrosine kinase. In Bcr-Abl signaling, the role of GSK-3 is not well defined. Here we report that enforced expression of constitutively active GSK-3 reduced proliferation and increased Bcr-Abl-inhibition-induced apoptosis by nearly 1-fold. Bcr-Abl inhibition activated GSK-3 and GSK-3-dependent apoptosis. Inactivation of GSK-3 by Bcr-Abl activity is therefore confirmed. To re-activate GSK-3, we inhibited glucosylceramide synthase (GCS) to accumulate endogenous ceramide, a tumor-suppressor sphingolipid and a potent GSK-3 activator. We found silence of GCS and GCS inhibitor increased Bcr-Abl-inhibition-induced apoptosis by 4-fold and 10% respectively. Furthermore, GCS inhibitor sensitized the most clinical problematic drug-resistant CML T315I mutants to Bcr-Abl inhibitor GNF-2- or imatinib-induced apoptosis by more than 5-fold. Combining GCS and Bcr-Abl inhibitors eliminated transplanted-CML-T315I-mutants in vivo and dose-dependently sensitized primary cells from CML T315I patients to Bcr-Abl inhibitor-induced proliferation inhibition and apoptosis. The synergistic efficacy was Bcr-Abl-restricted and acted through GSK-3-mediated apoptosis. This study suggests a feasible novel anti-CML strategy by accumulating endogenous ceramide to re-activate GSK-3 and abrogate drug resistance.

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