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ALTERATIONS IN SPHINGOLIPID METABOLISM ATTRIBUTE TO RESISTANCE TO CORNERSTONE ACUTE MYELOID LEUKEMIA THERAPY

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A growing body of evidence demonstrates that modifications in sphingolipid (SL) metabolism are key in cancer cell growth and response to chemotherapy. For example, the generation of ceramide is of specific relevance due to its role in orchestrating apoptosis in response to cytotoxic chemotherapies. However, relatively little is known regarding the impact of SL's on chemotherapy resistance, which is of important because the destruction of ceramide favors cancer growth. In the present study, we used cell culture selection pressure with cytarabine (Ara-c) and daunorubicin (dnr), cornerstone therapy for acute myeloid leukemia (AML), to generate drug resistant cells to mimic acquired resistance that is seen *in vivo*. HL-60, a human AML cell line, was utilized as drug-naïve control and characterized alongside HL-60/Ara-c (selected for growth in 500 nM Ara-c) and HL-60/dnr (selected for growth in 400 nM dnr) cells. Ara-c- and dnr-resistant cells demonstrated elevated glucosylceramide synthase (GCS, the enzyme that catalyzes ceramide glycosylation, forming glucosylceramide), acid ceramidase (AC, catalyzes ceramide hydrolysis to yield sphingosine), and sphingosine kinase 1 (SPHK1, catalyzes formation of mitogenic sphingosine 1-phosphate from sphingosine) activities compared to wild-type cells. Consistent with global enhancement of SL enzyme activity, immunoblot analysis showed that HL-60/Ara-c and HL-60/dnr cells overexpressed GCS, AC, and SPHK1. Juxtaposed with ceramide's role as sentinel of cancer cell growth, HL-60/dnr cells exhibited diminished expression of ceramide synthases 1, 4, and 6 enzyme family members that catalyze formation of apoptosis- and autophagy-inducing C16:0 and C18:0 ceramide molecular species. Interestingly, HL-60/dnr cells were sensitive to pharmacological inhibitors of GCS, AC, and SPHK1, data that highlight the important relationship between chemotherapy resistance and key SL branch-point enzymes that regulate ceramide fate. In conclusion, these data show that the enzymes of SL metabolism play a role in acquired resistance to chemotherapy and suggest that SL enzymes represent exploitable therapeutic targets.

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