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miRNAs Modulate Chemotherapeutic Sensitivity in a model of Acute Myeloid Leukemia

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A substantial number of chemo-refractory Hematological malignancies involve CNS localization, causing impairments in cognitive function as well as enhanced co-morbidities associated with tumour infiltration into the brain parenchyma. Identifying therapeutic strategies that reduces CNS infiltration would greatly improve leukemic patient outcomes, as those with Hematological malignance absent of CNS localization are responsive to various chemotherapeutic agents such as rituximab. Noncoding RNAs play an important role in regulating the cellular pathways that modulate responses to chemotherapeutic agents. Therefore, we performed a microRNA (miRNA) gain-of function screen to identify miRNA(s) that function as drivers of chemotherapeutic resistance. Using HL-60 cells, a drug-sensitive acute myeloid leukemia (AML) cell line, we identified certain miRNAs from a pool of >400 of miRNAs as robust drivers of resistance to the chemotherapeutic agents cytarabine (Ara-c) and daunorubicin (DNR). Forced expression of these miRNAs in HL-60 cells decreased DNR- and Ara-c-induced cell death. Furthermore, HL-60 cells expressing high levels of these miRNAs proliferated at slower rates than those without the miRNA. Out of the miRNAs tested, miRNAs that drive chemotherapeutic resistant also induced a quiescence-like phenotype, as determined by CFSE staining experiments, by assessing direct miRNA targets such as CCDN2, the modulation of which results in an increased frequency of cells in G1. This in vitro data is supported by the finding that high levels of these miRNAs in AML clinical samples correlated with poorer overall survival (OS). Therefore, we argue that miRNAs can functions as a diagnostic marker in AML patients, and specifically as a predictor of chemotherapeutic response. These findings are the basis for ongoing studies elucidating the role of miRNAs within Hematological malignancies involving CNS localization.

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