MicroRNAs in Cancer Pharmacology and Therapeutics: Exploiting a Natural Synergy between 'omic' and Hypothesis-Driven Research

John N. Weinstein

In 2008 in this journal, we reported the first broad-based study of the impact of microRNAs on drug activity in cancer cells. Because microRNAs had previously been shown to influence such processes as development, carcinogenesis, cell survival, and apoptosis, it seemed likely that they would also modulate sensitivity and resistance to anticancer drugs. To test that hypothesis, we first analyzed drug–microRNA correlations in data sets we had previously obtained by molecular profiling of the NCI-60, a cancer cell line panel used by the National Cancer Institute to screen compounds for anticancer activity (1). Because the NCI-60 had already been profiled at the DNA, mRNA, and protein levels more extensively than any other set of cells (2), we had the advantage of placing our findings for microRNAs in the context of those multiple additional characterizations. Approximately 30 microRNAs showed highly significant correlations with various anticancer agents by quite stringent statistical criteria.

As reported in the MCT article, we then followed up with focused pharmacologic studies of 3 microRNAs previously implicated in cancer biology (let-7i, mir-16, and mir-21) in 3 diverse cell lines from the NCI-60 set. In our experimental system, the expression of individual microRNAs was increased by transfecting the cells with their precursors (which are active) or suppressed by transfecting the cells with antisense oligomers. Overall, we assessed the growth-inhibitory potencies of 14 compounds selected for structural and functional diversity. Altering the levels of let-7i, mir-16, and mir-21 affected the potencies of a number of the anticancer agents by up to fourfold. The effect was most prominent with mir-21; 10 of 28 cell-compound pairs showed significant shifts in growth-inhibitory activity. Varying mir-21 levels changed potencies in opposite directions depending on the class of the agent, indicating differences in mechanism of toxic and protective effects. Overall, the results supported a substantial role for microRNAs in anticancer drug response and suggested novel potential approaches for improving the results of chemotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

Partially funded by the Michael & Susan Dell Foundation (honoring Lorraine Dell) and the H.A. and Mary K. Chapman Foundation.

Received September 21, 2011; accepted September 22, 2011; published November 9, 2011.

References

Molecular Cancer Therapeutics

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