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

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Commentary on:
Paul E. Blower, Ji-Hyun Chung, Joseph S. Verducci, Shili Lin, Jong-Kook Park, Zunyan Dai, Chang-Gong Liu, Thomas D. Schmittgen, William C. Reinhold, Carlo M. Croce, John N. Weinstein, and Wolfgang Sadee. **MicroRNAs modulate the chemosensitivity of tumor cells.** Mol Cancer Ther 2008;7:1–9.

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 had 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.

Concepts and findings in the study have been followed up by numerous investigators. The almost 100 papers citing it have included prominent publications in *MCT* (3) and other AACR journals (4). The study was published in *MCT*'s "Spotlight on Molecular Profiling" series (5), which was established by the Editors in 2005 to highlight publications that feature comprehensive molecular characterization of cancer cells and their pharmacology. The series presaged current projects like The Cancer Genome Atlas enterprise that are doing the same for clinical cancers. In doing so, the series highlighted a natural synergy between -omic and hypothesis-driven research. Hearty congratulations to *MCT* on its tenth anniversary of insight, foresight, and seminal contributions to cancer pharmacology and therapeutics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Blower PE, Verducci JS, Lin S, Zhou J, Chung JH, Dai Z, et al. MicroRNA expression profiles for the NCI-60 cancer cell panel. Mol Cancer Ther 2007;6:1483–91.
2. Weinstein JN, Myers TG, O'Connor PM, Friend SH, Fornace AJ Jr, Kohn KW, et al. An information intensive approach to the molecular pharmacology of cancer. Science 1997;275:343–9.
3. Liu H, D'Andrade P, Fulmer-Smentek S, Lorenzi P, Kohn KW, Weinstein JN, et al. mRNA and microRNA expression profiles of the NCI-60 integrated with drug activities. Mol Cancer Ther 2010;9:1080–91.
4. Yang N, Kaur S, Volinia S, Greshock J, Lassus H, Hasegawa K, et al. MicroRNA microarray identifies Let-7i as a novel biomarker and therapeutic target in human epithelial ovarian cancer. Cancer Res 2008;68:10307–14.
5. Weinstein JN. Spotlight on molecular profiling: 'integromic' analysis of the NCI-60 cancer cell lines. Mol Cancer Ther 2006;5:2601–5.