A microarray-based, integrated approach to identify novel regulators of cancer drug response and apoptosis

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DNA microarrays are powerful tools for the analysis of gene expression on a genomic scale. The importance of individual regulatory events for the process under study can however not be deduced unequivocally without additional experiments. We devised a strategy to identify central regulators of cancer drug responses by combining the results of microarray experiments with efficient methods for phenotypic testing of candidate genes. We exposed murine FL5.12 pro-B cells to cisplatin, camptothecin, methotrexate or paclitaxel, respectively and analysed the patterns of gene expression with cDNA microarrays. Drug-specific regulatory events as well as intersections between different apoptotic pathways, including previously studied responses to staurosporine and interleukin-3 (IL-3) deprivation, were identified. Genes shared by at least three pathways were chosen for further analysis. Ectopic expression of three such genes, TEAP, GP49B, and Lipin1 was found to have an anti-proliferative effect on pro-B cells. Interestingly, we identified hemoglobin alpha as a strong pro-apoptotic regulator. While hemoglobin-expressing cells were growing normally in the presence of IL-3, they displayed accelerated apoptosis with similar kinetics as Bax overexpressing cells upon IL-3 removal. The pro-apoptotic effect of hemoglobin was suppressed by Bcl-2 and was characterized by enhanced stimulation of caspase activity.
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