Identification of Novel Targets for Cancer Therapeutics through Genome Expression Profiling

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In recent years, as exemplified by Gleevec, Herceptin, Avastin, and others, targeted therapeutics is revolutionizing cancer therapy. Systematic and comprehensive characterizations of genome-wide expression patterns might reveal new critical molecular factors that can be used in the targeted cancer therapeutics. We have constructed a database containing genome expression profiles in surgical specimens of human cancers. Mining of the database allowed us to identify several novel genes that are differentially expressed in cancerous tissues compared to corresponding normal tissues. For example, a cancer-upregulated gene (CUG2) was identified as an EST exhibiting significant differential expression in multiple human cancer types. CUG2 shows weak homology with a human transcriptional repressor, and is predominantly localized in the nucleus. Mouse fibroblast cells over-expressing CUG2 exhibits distinct cancer-specific phenotypes *in vitro* and generates tumors in nude mice which are comparable to those resulting from a well-known oncogene As another example, we identified a novel gene encoding a secreted protein that was dramatically upregulated in human pancreatic adenocarcinoma. Over-expression of the gene enhances cell proliferation, motility and invasiveness *in vitro* and promotes tumor growth *in vivo*. Treatment of cancer cells with the protein shows increases cell motility and invasiveness, whereas treatment with antibodies decreases those abilities. The protein activates important cellular signaling pathways at least *via* ERK and AKT. Currently, we are developing human monoclonal antibodies for cancer therapeutics by targeting the secreted protein. In addition, utilization of the database to identify potential diagnostic markers by examining cancer-specific expression of secreted proteins will be presented.