© 2001 Nature Publishing Group http://genetics.nature.com

match with sequences in the Genbank/EMBL database, was selected. Further analysis of the genes and expressed sequence tags identified with either approach was performed using a real-time polymerase chain reaction. We used a minimum of 120 samples in the expression profile for each gene or EST, which included a panel of normal tissues and matching samples (cancer and normal adjacent from the same individual) for breast, endometrium, cervix, uterus, colon and stomach, among other tissues. Eleven genes or ESTs showed upregulation in 45–100% of the breast cancer samples when compared with the normal adjacent tissue. Three of them showed high specificity for breast tissue. Full-length cloning and antibody production for these genes are in progress. Further evaluation will allow us to determine their potential use in early detection, differential diagnosis, disease monitoring and surveillance of breast cancer.

Samatar, Ahmed [20]

Identification of TGF-βII as a transcriptional target of Akt

Ahmed Samatar[1], Suxing Liu[1], Luquan Wang[1], Marnie McMguirk[1], Murali Ramachandra[2] & Chandra Kumar[1]

[1]*Schering-Plough Research Institute, Kenilworth, New Jersey 07033, USA*
[2]*Canji, Inc.*

Akt/PKB is a serine–threonine kinase that plays a critical role in cell survival signaling by phosphorylating and inactivating components of the cell death machinery. Akt has been shown to phosphorylate a subfamily of forkhead transcription factors and prevent their nuclear localization, leading to repression of genes involved in apoptosis, such as *Fas* ligand. Other genes involved in forkhead-mediated apoptosis have yet to be identified. Using bioinformatics approaches, we have identified genes containing forkhead factor binding sites in their promoter sequences. One gene identified by this search is that coding transforming growth factor βII (TGF-βII). We show that activated Akt can downregulate TGF-βII promoter activity and that this repression is mediated by the three forkhead factor binding sites present in its promoter region. TGF-βII (but not TGF-βI) messenger RNA levels are significantly downregulated in pancreatic and breast cancer cell lines expressing activated Akt (through either gene amplification or inactivation of the *PTEN/MMAC1* tumor suppressor gene). Tumor cell lines expressing activated Akt and an intact TGF-βII signaling pathway are responsive to TGF-β-mediated growth inhibition. Our studies demonstrate that repression of TGF-βII promoter in tumors expressing activated Akt is a new mechanism to abrogate the growth inhibition or apoptotic effects (or both) of TGF-β.

Samimi, Goli [21]

Gene expression profiling of oxaliplatin-resistant cell lines

Goli Samimi, Jim Breaux, Misako Mishima, Charles Berry, Stephen Howell & Gerrit Los

Cancer Center and Department of Biomedical Sciences, University of California San Diego, San Diego, California, USA

We compared the gene expression patterns of oxaliplatin-resistant cell lines with the patterns of their sensitive counterparts in an attempt to discover universal mechanisms that characterize resistant cells. Isogenic oxaliplatin-resistant variants of four ovarian carcinoma cell lines and one squamous cell carcinoma line were selected by repeated exposures of increasing concentrations of oxaliplatin (resistance levels ranged from 4-fold to 20-fold). We harvested RNA from all five pairs and assayed gene expression through hybridization to Affymetrix HuGeneFL arrays. Using global, unsupervised, two-way hierarchical clustering we observed that resistant cell lines clustered with their corresponding parental cell lines, indicating that the number of changes in gene expression leading to resistance are probably few and that these changes are diluted in the global gene expression profile of the entire cell. In addition, Venn diagram analysis revealed that very few genes were commonly up- or downregulated across all cell lines. However, employing a recently developed supervised clustering method that uses principal component analysis to extract groups of genes with maximal variance across cell lines, we found a small cluster of genes that were consistently differentially expressed in most but not all resistant cell lines. Although this group of genes contains some interesting members, it is unlikely that these genes are the sole determinants of oxaliplatin resistance. Finally, comparison of the numbers of differentially expressed genes from each pair that were associated with specific MeSH terms supported our conclusion that no common mechanism of resistance could be detected within the five resistant pairs.

Sanchez-Carbayo, Marta [22]

Expression profiling of osteosarcoma-transfected cells with *MDR1* and *NEO*

Marta Sanchez-Carbayo[1], Thomas Belbin[2], Geoffrey Childs[2], Katia Scotlandi[3], Nicola Baldini[3] & Carlos Cordon-Cardo[1]

[1]*Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10021, USA*
[2]*Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA*
[3]*Instituti Ortopedici Rizzoli, 40136 Bologna, Italy*

Using complementary DNA microarrays we compared the expression patterns of the osteosarcoma cell line U2OS and three derived subclones obtained by transfection of *MDR1, NEO* and *MDR1/NEO* and selected with doxorubicin and neomycin. The expression arrays included 8,976 sequence-verified clones comprising both known genes and expressed sequence tags. We performed Northern blots to confirm the expression changes obtained for certain genes. *MDR1* expression was associated with changes in the expression of genes related to different processes, including regulation of certain cell adhesion genes such as *zyxin;* drug transport proteins such as *MRP1;* metabolic enzymes such as monoamine oxidase A; apoptotic signaling genes such as *I-TRAF;* and tumor suppressor genes such as *KISS-1*. The presence of *MDR1* and downregulation of *MRP1* were also confirmed by immunohistochemistry. Cells transfected with *MDR1* alone or co-transfected displayed more related expression profiles than cells transfected only with the *NEO* gene, as confirmed by hierarchical clustering. This study provides further characterization of genetic events associated with *MDR1* expression, in addition to identifying new targets and potential pathways involved in the molecular mechanism of multidrug resistance.

© 2001 Nature Publishing Group http://genetics.nature.com