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links to other related online resources. The MTB database is designed to facilitate the selection of experimental models for cancer research, the evaluation of mouse genetic models of human disease, the review of patterns of mutations in specific cancers and the identification of genes that are commonly mutated across a spectrum of cancers. Recent enhancements to MTB include a redesigned Web interface for more powerful querying and improved views that simplify and better organize data presentations. A significantly expanded archive of histopathological images also is available. The MTB prototype database is accessible at http://tumor.informatics.jax.org. User support is available by e-mail to mgi-help@informatics.jax.org.

Kuzumaki, Noboru [32]

Epigenetic silencing of the tumor-suppressing gelsolin gene involves histone deacetylation of its promoter region in human urinary bladder cancer

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Alterations in histone acetylation seem to play a central role in the repression of several important genes, such as tumor suppressor genes. Previously we reported that gelsolin expression was reduced in human urinary bladder cancers and that ectopically expressed gelsolin acted as a tumor suppressor[1]. We have examined the effects of trichostatin A (TSA), a specific histone deacetylase inhibitor, to examine the histone acetylation status of the gelsolin promoter region in bladder cancers. We measured gelsolin protein expression by western blotting in bladder cancer cell lines treated with various doses of TSA. We assessed promoter activities of the gelsolin gene by luciferase assays in both nontreated and TSA-treated bladder cancer cell lines. The acetylation status of histones linked to the gelsolin promoter was checked using chromatin immunoprecipitation and a dot blot assay. Gelsolin protein production was much reduced in cancer cell lines. Both re-expression and the promoter activity of gelsolin induced by TSA were dose- and time-dependent. An antibody that reacts with acetylated histones H3 and H4 immunoprecipitated chromatin containing the gelsolin promoter in the TSA-treated bladder cancer cells, but not in nontreated cells. These results suggest that TSA activated the gelsolin gene promoter through histone acetylation. In bladder cancer, the repression of the gelsolin gene is related to the deacetylation of histones to its promoter region. Together with the reported epigenetic changes in histone acetylation in breast cancers, acetylation-mediated gene silencing could be a common mechanism of gelsolin downregulation in several cancers.

1. Haga, K. *et al. Cancer Res.* **55**, 3228 (1995).

Lacher, Markus [33]

Wnt-Frizzled signaling in cell proliferation and survival

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We have used the differential display method as a coincidence analysis technique to isolate genes expressed in different rat tissues undergoing physiological apoptosis, such as involuting mammary gland or prostate after castration. One isolate, *DDC-4*, encodes a secreted Frizzled-Related Protein of 39.7 kD in an open reading frame of 1,044 nucleotides. This protein family is thought to antagonize the signaling of Frizzled transmembrane receptors. Inappropriate expression of *DDC-4* in lactating mammary glands of transgenic mice induces apoptosis during late pregnancy and early lactation. *DDC-4* presumably acts by blocking a survival pathway. Classical Wnt-Frizzled signaling leads to the stabilization of cytosolic β-catenin and activation of Tcf/Lef transcription factors. Increased activity of this pathway owing to mutations in such genes as *tcf-4* or those for adenomatous polyposis coli or β-catenin results in the formation of tumors. In many colorectal carcinomas and tumor models Tcf/Lef-responsive genes are upregulated. Based on the hypothesis that the genes targeted by Tcf/Lef might be at risk for producing tumors when activated by a second, alternative signaling pathway, we analyzed their promoter regions for further, putative, tumor-associated *cis*-acting elements. The kind of analysis performed is based on the assumption that biologically relevant elements are statistically overrepresented compared with random elements. Since such elements might unravel transcription factor–binding sites active in transformed but not in normal cells, they are candidates for artificial cancer-specific promoters, for which there is an urgent need in several gene-therapy projects.

Larson, Garry P. [34]

Identification of disease gene variants based on gene–gene interactions

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New methods are needed for the identification of pathogenic alleles of candidate genes that may increase cancer susceptibility. Such risk alleles are expected to be of low penetrance and may act alone or modify the effects of other genes. We have developed a method that enriches for pathogenetic disease variants contingent on gene–gene interactions. Candidate gene pairs are chosen based on previous evidence demonstrating genetic or biochemical interaction. Utilizing a cohort of sibling pairs affected with breast cancer, we tested this paradigm by identifying risk variants of cell cycle control gene *CDKN1A* by means of interactions with *TP53* and *BRCA1*. This approach, which we call disease association by locus stratification, first stratified affected pairs based on sharing of both alleles at a microsatellite marker linked to *CDKN1A*. The second stratification was based on microsatellite marker sharing at *TP53* or *BRCA1*. We identified subsets of affected pairs sharing both alleles at both loci as screening targets. Utilizing this approach, we were able to enrich for two noncoding disease haplotypes of *CDKN1A* by virtue of *BRCA1* interactions. We defined each haplotype by single-nucleotide polymorphisms at two positions potentially important in *CDKN1A* transcriptional activation by both p53 and BRCA1p. Our results indicated that an approach based on allele sharing and gene–gene interactions will be valuable not only in identifying risk alleles but also in elucidating their mechanism of action.

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Lau, Ching [35]

Identification of a new fusion of *ETV6/TEL* and *NTRK3/TRKC* in a primitive neuroectodermal tumor

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ETV6/TEL, a member of the ETS family of transcription factors, has been involved in a variety of gene fusions in various neoplasms. One of its fusion partners is *NTRK3/TRKC*, which encodes the receptor for neurotrophin-3. Although *NTRK3* is expressed broadly in neural tissues during the growth and development of the central nervous system, its fusion with *TEL* has never been reported in central nervous system tumors. We report here a new *TEL–NTRK3* fusion in a primitive neuroectodermal tumor (PNET). The patient was five months old when she underwent a resection of a left frontal tumor that was diagnosed as a benign desmoplastic infantile ganglioglioma. Three months later she had another resection for the recurrent tumor, which was diagnosed as a highly malignant PNET. G-banding karyotype analysis showed 46, XX in both tumors, but spectral karyotyping revealed a single near-tetraploid cell in the first tumor with a t(12; 15)(p13; q25) translocation and the same translocation in all metaphases in the PNET. Subsequent fluorescence *in situ* hybridization analysis using a *TEL* probe revealed the translocation of the *TEL* gene to the der(15) chromosome. Based on a similar translocation previously described in infantile fibrosarcoma, congenital mesoblastic nephroma and acute myeloid leukemia involving the *TEL* and *NTRK3* genes, we used the polymerase chain reaction with reverse transcription, with primers flanking the coding sequences of *TEL* and *NTRK3*, to detect a chimeric message of 1.6 kilobases. We located the breakpoint at the end of exon 4 of *TEL* in frame with exon 12 of *NTRK3*. This results in a unique *TEL–NTRK3* fusion transcript with the helix–loop–helix dimerization domain of *TEL* fused to the protein tyrosine kinase domain of *NTRK3*. Since t(12; 15) is the only structural chromosome aberration in this case and a similar *TEL–NTRK3* fusion product has been used to transform NIH 3T3 cells, we propose that the *TEL–NTRK3* fusion may have contributed to the cellular transformation and progression of this tumor.

Lee, Ann [36]

Identification of genes differentially expressed in breast cancer cells treated with tamoxifen, using microarray-based expression profiling

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Adjuvant tamoxifen therapy is effective in reducing the risk of recurrence and death in patients with estrogen-receptor-positive breast cancer. However, the development of acquired resistance to tamoxifen limits its clinical effectiveness. To determine the effects of tamoxifen on breast cancer cells, long-term cultures of the breast cancer MCF-7 cell line, treated with tamoxifen, were established. Gene expression profiles of tamoxifen-treated and untreated MCF-7 cells were characterized using the Clontech Atlas human cancer 1.2 array, representing 1,176 genes. RNA was extracted from tamoxifen-sensitive cells 4 days and 6 weeks after commencement of treatment with tamoxifen, as well as from untreated MCF-7 cells at the same time points. Only gene expression differences greater than twofold were considered. At 4 days, 13 genes were found to be overexpressed and 2 genes were underexpressed in the tamoxifen-treated MCF-7 cells compared with the untreated MCF-7 cells. In the tamoxifen-treated MCF-7 cells harvested at 6 weeks, 16 genes were overexpressed and 5 genes were underexpressed compared with the treated cells harvested at 4 days. Wnt-5a, disheveled homologue 1, cyclin kinase inhibitor p19INK4D and the signaling lymphocytic activation molecule were overexpressed in both of the comparisons. Gene expression profiling is useful for the rapid identification of genes differentially expressed during tamoxifen treatment.

Leszczynski, Dariusz [37]

Proteomics: new way to to determine possible biological effects of mobile phone radiation

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Radiobiology Laboratory, STUK–Radiation and Nuclear Safety Authority, Helsinki, Finland

Despite years of research, the question of whether exposure to radiofrequency-modulated electromagnetic fields (RF-EMF) generated by mobile phones affects human health remains unsolved. We obtained a comprehensive overview of the possible extent of cellular response to RF-EMF irradiation by determining the total cellular changes in protein expression and in protein phosphorylation that occur in response to RF-EMF exposure under athermal conditions. As a model we used human endothelial cell line EA.hy926. Cells were exposed for one hour to a 900-MHz GSM signal. Immediately following exposure we harvested cells and extracted and separated proteins using two-dimensional electrophoresis. To determine changes in protein phosphorylation, ^{32}P was present in the cultures during the exposure period. Using Bio-Rad's PDQUEST 6.1.0 software we identified over 1,200 proteins in two-dimensional gels (10 × 20 cm). A large number of protein spots changed expression following irradiation. In control cells we detected over 180 phosphoproteins. RF-EMF exposure has generated a large number of newly phosphorylated proteins that were not present in controls. Among the proteins with altered phosphorylation levels were shock proteins, such as hsp27. Thus the expression and phosphorylation of a large number of proteins isolated from EA.hy926 cells seems to be altered by short RF-EMF exposure, suggesting that cells mount a vigorous response to RF-EMF stress. However, whether the observed stress can cause long-lasting physiological effects remains to be determined.

Lin, Lin [38]

Identification and characterization of a 19q12 amplicon in esophageal adenocarcinomas using two-dimensional genomic scanning and amplification mapping of sequence tagged sites

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Amplification of genomic DNA can confer a selective advantage in tumors by increasing the dosage of gene(s) involved in tumor development or progression.

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