Duggan, David J.

Microarray analysis discriminates BRCA2 mutation-positive from BRCA1 and sporadic breast cancer patient tumour biopsies

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Distinctive pathological and cytogenetic alterations distinguish familial BRCA1 and BRCA2 mutation-positive (+) from sporadic (non-familial) breast cancers. Using cDNA microarrays containing 6,500 sequence-verified human cDNAs, we have compared familial BRCA1 and BRCA2 (+) and sporadic breast cancer patient tumours with a common reference. Relational analyses of individual genes across all experiments has identified a small subset that is consistently up- or downregulated in most BRCA2s and unchanged in most BRCA1 tumours. Similarly, we have identified a set of genes consistently up- or downregulated in most BRCA1 tumours and unchanged in BRCA2 tumours. Analysis of the degree of similarity between expression profiles for the entire gene set across all tumours showed that the BRCA2 tumours form a unique cluster. Visualization of the extent of similarity was performed using multidimensional scaling analysis. Statistical analysis of these data has identified a subset of genes that distinguish the BRCA2 tumours from the BRCA1 and sporadic tumours. The genes identified include several known from previous studies to be implicated in hereditary breast cancer, as well as others previously unrecognized as transcriptionally altered in this disease. An example of a gene in this subset includes that encoding cyclin D1, which was consistently upregulated in BRCA2 tumours, whereas it was unchanged in the BRCA1 and sporadic tumours. Cyclin D1 expression had not previously been correlated with BRCA1/2 mutation status. It is known, however, that cyclin D1 overexpression is positively correlated with estrogen receptor (ER) status, and in our sample set all BRCA2s were ER positive, whereas all BRCA1s were ER negative. This work suggests that investigation of the transcriptional networks of breast cancers can identify genes that clearly distinguish BRCA2 (+) patient tumour biopsies, and indicates this approach will have significant value in 'molecular fingerprinting' of breast cancers. We are currently confirming the microarray results and investigating the biological and pathological significance of the other genes identified as key discriminators of BRCA2 tumours.

duManoir, Stan

High resolution CGH of head and neck tumours

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The feasibility of high resolution CGH has been recently demonstrated. We designed a DNA chip of arrayed BAC cloned for frequently involved chromosomal regions in head and neck tumours. Our pilot experiments demonstrate that in our hands the method efficiently detects tetrasomy or trisomy. We will show our initial results with DNA extracted from histological sections from a series of selected head and neck archival tumours. Clinical parameters including grade, histological status, survival time and disease-free period are available. Results will be compared with conventionnal CGH on chromosomes. In the near future, this technique could contribute to the genetic profiling of tumours in a pathology department.

Edgerton, Mary E.

A bioinformatics tool to mine sequences for microarray studies of mouse models of oncogenesis

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One of the challenges to the effective use of cDNA array analysis in mouse models of oncogenesis is the choice of a critical set of probes which are informative for human disease. Given the thousands of genes with a potential role in human oncogenesis and the hundreds of thousands of mouse sequences available for use as probes, assimilation of an overlapping set can be an overwhelming task. We have developed a bioinformatics tool that will mine a source of mouse sequences. It presents the output in a form that enables the user to access the information necessary to define a list of sequences that will enhance gene discovery and functional assessment in mouse models of oncogenesis. This web-based sequence mining tool lists publicly available sequences in order of importance to oncogenesis in humans and provides a focused set of informative links including information on clone source and, if known, gene function. The Mouse Oncochip Design Tool uses the Mouse Genome Database (MGD) developed and maintained by the Jackson Laboratories for mouse DNA sequences. There are over 380,000 sequences in this database. The user can choose a subset of sequences based on expression in a specified tissue source, chosen from over 300 types of tissues. The output list has been ordered to present the most likely candidates first, as defined by identification of a mouse gene associated with the sequence, identification of a human homologue for the mouse gene marker and inclusion of the human homologue in an oncogene set. The tool is web based and uses a Perl common gateway interface (CGI) to the browser and Standard Query Language (SQL) scripts embedded in Data Base Independent Perl (DBI Perl) to extract the necessary information from the Mouse Genome Database and the Human Oncogene set (which was compiled in the Division of Clinical Sciences at the National Cancer Institute). Links to the clone source and annotation for the mouse genes stored in the MGD, to GenBank and the Unigene cluster resource of the National Center for Biotechnology Information (NCBI), and to GeneCards (Weizmann Institute) are constructed dynamically by the code so that there is no need for updating. This resource is part of a bioinformatics toolkit for studies of mouse models of human cancer which uses microarray technology.