sequence tags that allows efficient selection of new potential tumor-associated genes. The resulting ranked list of candidates is analyzed in terms of its content in known genes, used as controls, and the new candidates are further tested for selective expression in normal and tumor tissues by real-time polymerase chain reaction with reverse transcription. The most highly tumor-specific candidates are then pursued to full-length cloning. We present the discovery of a series of new genes that are upregulated in colon cancer.

Visvanathan, Jaya [56]

Genomic aberrations in gastric adenocarcinoma

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Gastric adenocarcinoma (GA) presents a challenge in understanding the complex interactions of environmental factors with genotype in carcinogenesis. The National Cancer Centre has taken a multifaceted approach to this problem with comparative genomic hybridization of freshly resected GAs. Data from nine cases of intestinal and five cases of diffuse histological types showed the common aberrations to be loss of 4pq (four cases) and gains of 17pq (five cases) and 20pq (four cases). We also documented amplifications in 22q (six cases), 20q (five cases) and 1pq (two cases). High-level gains were present in 20q11.2q12 (three cases), 10q24.3q25.1 (one case) and 12q14 (one case). Two cases of diffuse GA showed no change. High-level amplifications in 10q24.3q25.1 and 12q14 have not been reported previously. High-level amplification of 12q14 could be associated with overexpression of *MDM2, CDK4* and *RAP1B.* Three cytochrome P450 hydroxylases map to 10q24. Loss of 4pq is a common abnormality in cases of GA; its biological significance may be related to loss of function of caspase 3, caspase 6 and PTPN13, which is frequently deleted in liver and ovarian cancers. High-level gain of 20q or 20pq was another striking finding of this preliminary study. Amplified genes of probable importance from this genomic region are those for DNA methyltransferase 3B, E2F transcription factor 1, EHT and matrix metalloproteinase 5. Gain of 17pq or 17q has been frequently reported in cases of GA, and candidate genes of relevance to gastric carcinogenesis are *HER-2/neu,* and those encoding survivin and gastrin.

Volik, Stanislav [57]

A 20q13.2 cancer amplicon: novel sequence analysis tools

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Progress in mammalian genome sequencing demands development of efficient, high-throughput methods for functional annotation of megabase-scale regions. We report the first complete sequence of a tumor amplicon that is associated with aggressive tumor behavior and occurs in a wide range of tumors. The overwhelming amount of data generated for this region by traditional analysis tools (such as GenScan, BLAST and RepeatMasker) required development of efficient annotation methods. For a comprehensive biological annotation of the amplicon we developed Genome Cryptographer. This tool integrates information on distribution and type of repetitive elements, results of database searches, comparative sequence data, expression data, array comparative genomic hybridization copy number data and information on CpG dinucleotide distribution. Genome Cryptographer revealed an uneven distribution of genes and repetitive elements in the 1-megabase region. The proximal amplicon peak as defined by array comparative genomic hybridization is composed of 60% repetitive sequence and encodes one protein-coding gene, *ZNF217.* A 14-kb duplicon was identified close to the 5′ end of *ZNF217;* it is 97% homologous to a 14-kb element on chromosome 22q13; contains one of three identified CpG islands, a conserved putative RNA gene and a single repetitive element; and is present at the murine *ZNF217* locus. The distal amplicon peak contains two genes, *CYP24* and *PFDN4.* Breakpoints for both amplicon peaks are located in regions of local repeat maxima. We have also developed software to create digital expression profiles of multi-megabase regions. This allowed us to confirm that *ZNF217* has the highest relative expression in tumors and to identify three additional putative cancer-related genes.

Watson, Mark [58]

Expression profiling of ductal carcinoma *in situ* by laser capture microdissection and high-density oligonucleotide arrays

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Gene expression profiling with nucleic acid arrays is a powerful method for the molecular classification of human neoplasms. Laser capture microdissection is an equally useful technique to isolate defined cell populations selectively from heterogeneous histological tissue sections. We demonstrate how a modest use of laser capture microdissection is sufficient to isolate nanogram quantities of high-quality RNA. Together with several internal standards and microcapillary electrophoresis of input RNA, we used two rounds of linear molecular amplification to generate sufficient quantities of labeled target for hybridization to high-density oligonucleotide expression arrays. Our results demonstrate that the technique is reproducible, generates only modest biasing of the original transcript population and offers sensitivity comparable to that achieved using standard methodology. Using this approach, we have compared the expression profiles of nonmalignant human breast epithelium and adjacent ductal carcinoma *in situ* lesions from breast cancer patients. Several genes, including those previously implicated in human breast cancer progression, demonstrate differential expression among the microdissected cell populations. This study demonstrates the feasibility of applying laser capture microdissection and nucleic acid expression array technology to histologically complex clinical specimens to classify human breast cancer molecularly and gain a better understanding of its molecular pathobiology.

Watts, George [59]

Microarray analysis of a human multiple myeloma cell line selected with melphalan or doxorubicin identifies a set of commonly affected genes

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Multiple myeloma is a monoclonal plasma cell neoplasm that is frequently treated with melphalan and doxorubicin. The development of resistance to drugs such as melphalan and doxorubicin poses a hurdle to their successful clinical use.