prometaphase chromosomes. Linkage to existing physical maps is provided by the requisite presence of a mapped sequence tagged site in all selected BACs and in many cases by the full or end sequencing of the mapped clone itself. Clones in the repository should allow all chromosomal breakpoints to be localized to within 2 Mb and provide entry points to existing physical maps of the intervening distance. With the completion of a rough draft of the human genome, sequences between mapped breakpoints can be immediately queried for potential candidate genes. We will provide an update on the number of BAC clones and chromosomes currently mapped and available to the biomedical community. One critical issue is the integration of databases for the cytogenetic and physical maps. The National Cancer Institute and National Center for Biotechnology Information are working together to develop a meaningful integration that provides (1) a direct connection between catalogued and newly discovered chromosomal breakpoints or regions of genomic imbalances and the BAC clone set; (2) direct display of recurring chromosomal breakpoints that coincide with BAC locations; (3) placement of mapped BACs on the human sequence; (4) tools to build contiguous clone sets; (5) integration of the BAC clone set with databases for comparative genomic hybridization and spectral karyotyping and (6) an interface for the identification of orthologous regions of chromosomal aberrations in human cancers and their respective mouse models.

Klein, Christoph [29]

Transcriptome and genome analysis of single disseminated tumor cells: approach to study minimal residual cancer

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Despite increasing molecular-genetic understanding of the development of malignant epithelial neoplasias, the front-line therapy for patients with carcinomas is still surgery. Because systemic adjuvant treatments such as chemotherapy or immunotherapy have had limited success and because the characteristics of systemically disseminated tumor cells can be very different from those of the primary tumor or end-stage metastasis, we have studied the evolution and progression of systemic cancer directly. We have developed techniques to detect, isolate and study genomes and transcriptomes of single micrometastatic cells present in bone marrow of carcinoma patients. The first results of our genetic analysis demonstrate that disseminated tumor cells are clonally related, indicating their selection from heterogeneous cell populations of the primary tumor. Gene expression analysis of single disseminated tumor cells revealed their engagement in specific functional activities, such as tissue invasion, proliferation and DNA damage repair. Detailed analyses of single disseminated cells will help determine which genotypes and phenotypes are selected during dissemination, which cells survive in the new environment and what governs the establishment of a metastasis. This knowledge will be useful in selectively targeting the precursor cells with adjuvant therapies long before metastatic disease is clinically evident and incurable.

Krahe, Ralf [30]

Gene expression profiling reveals fundamental biological differences in AML with trisomy 8 and normal cytogenetics

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Acute myeloid leukemia (AML) is a heterogeneous group of diseases. Patients exhibiting normal cytogenetics (AML-CN) constitute the single largest group, and trisomy 8 (AML+8) as the sole abnormality is the most frequent trisomy. How trisomy contributes to tumorigenesis is unknown. Because hematopoietic differentiation is predominantly regulated at the transcriptional level, we proposed that, whatever the underlying molecular leukemogenic event(s) associated with AML-CN and AML+8, the molecular changes at the DNA level should be reflected in specific changes at the RNA level. We used oligonucleotide-based DNA microarrays to study global gene expression in ten AML+8 patients with +8 as the sole chromosomal abnormality and ten AML-CN patients, as well as seven CD34+ cell samples purified from normal bone marrow of healthy individuals as a representative heterogeneous population of stem and progenitor cells. For the 6,606 genes studied, expression patterns of AML patients were clearly distinct from those of CD34+ cells of normal individuals. AML+8 was associated with an overexpression of genes on chromosome 8, suggesting a role for gene dosage effects in the etiology of AML+8. Systematic analysis by cellular function indicated upregulation of genes involved in cell adhesion in both AML groups. We observed other highly significant results in the comparison of AML+8 with AML-CN for genes involved in the regulation of apoptosis, suggesting a fundamental biological difference in programmed cell death. The observed differences in the dysregulation of specific functional subsets of genes between the two AML subclasses merit further functional studies of the individual components of the pathways.

Krupke, Debra M. [31]

Electronic access to data from mouse cancer models: The Mouse Tumor Biology database

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The Mouse Tumor Biology database (MTB) has been developed to provide electronic access to mouse tumor biology data. The primary focus of MTB is spontaneous and induced tumors in genetically defined mice (inbreds, hybrids, mutants and genetically engineered strains). By making such data readily available online, MTB provides the scientific community with a much-needed, easily accessible central resource for rapidly finding and evaluating the expanding volume of mouse tumor data. MTB provides cancer researchers with access to data on mouse models for cancer and includes information such as tumor names and classifications, pathology reports, histopathological images, genetics of the strain, genomic changes in the tumor, strain names, tumor frequency and latency, references and