Clonal Abnormalities in Histologically Normal Breast Tissue

Breast cancers and even in situ lesions contain genetic abnormalities that include loss of heterozygosity (LOH) and allele imbalances. LOH has also been detected in histologically normal breast epithelium from women with and without breast tumors. In women with breast cancer, LOH has been found in areas adjacent to or distant from the primary tumor. It is not known whether these lesions are early precursors of breast tumors, if they are indicators of high risk of tumor development, or if their presence is unrelated to any of these conditions. Larson et al. (Am J Pathol 2002, 161:283–290) microdissected 173 histologically normal ducts or terminal ducto-lobular units and analyzed the samples for the presence of LOH on 10 chromosome arms. The LOH analysis of normal tissue was compared to that of samples from 18 breast cancers. Because LOH detected in normal tissue rarely coincided with that of co-existing tumors, Larson et al. concluded that individual clones are unlikely to be precursors of the tumors. However, in a large fraction of women with breast cancer, histologically normal epithelium contained aberrant clones. These lesions may be indicators of genetic instability in the breast tissue and might be a source of recurrent cancers.

Identification of Stem Cells in Pulmonary Bronchioles

In the respiratory system, stem cells have been identified in the trachea, in submucosal gland ducts, and in neuroepithelial bodies of the bronchiolar epithelium. The epithelium of the terminal bronchiole responds rapidly to injury. Yet the localization and main features of bronchiolar cells responsible for renewal of the epithelium have not been described. Giangreco et al. (Am J Pathol 2002, 161:173–182) investigated whether stem cells participate in the repair of terminal bronchioles after pollutant injury. They identified a niche for stem cells located at the broncho-alveolar duct junction. These cells were the predominant proliferative population after injury and included label-retaining cells. Bronchiolar stem cells located in the broncho-alveolar duct junction are independent of the neuroepithelial body and play a key role in the renewal of the bronchiolar epithelium.

Molecular Classification of Oligodendroglial Tumors

Oligodendroglial tumors constitute 5 to 18% of primary human brain tumors. They include oligodendrogliomas and oligoastrocytomas and subsets of these tumors may have differential responses to therapy. Loss of heterozygosity (LOH) in chromosomes 1p and 19q are found in both oligodendrogliomas and oligoastrocytomas. Presence of LOH 1p and 19q are generally associated with better responses to therapy and longer overall survival. Recent data suggested that the frequency of LOH in oligodendroglial tumors may vary depending on tumor location. Mueller et al. (Am J Pathol 2002, 161:313–319) analyzed 203 gliomas to determine whether molecular subsets of oligoastrocytomas may correlate with tumor location. Common molecular alterations were found in oligodendrogliomas and oligoastrocytomas arising in extratemporal sites. Based on these studies the authors propose that oligodendroglial tumors can be separated into three subsets, distinguishable by molecular profiles.

TGF-β1 Expression May Contribute to Invasiveness of Hepatocellular Carcinoma Cells

Despite very large numbers of studies, the molecular pathogenesis of primary liver cancers is not well understood. Even less information is available about the potential mechanisms of invasiveness of hepatocellular carcinomas, an event of major clinical importance. Previous data suggested that invasiveness is associated with the expression of α3β1-integrin. Giannelli et al. (Am J Pathol 2002, 161:183–193) show that TGF-β1 expression stimulates α3β1-integrin mRNA transcription and induces an invasive phenotype in non-invasive cultured cells. α3β1-integrin is abundantly expressed in hepatocellular carcinomas and its serum concentration correlates to TGF-β1 levels. The data suggest that, through its stimulation of α3β1-integrin, TGF-β1 plays an important role in inducing invasiveness in hepatocellular carcinoma cells.

Vaccination May Delay the Onset of Prion Disease in Mice

Prions are infectious agents that lack nucleic acid, their pathogenicity being dependent on the conformation of the prion protein. Prion infections do not produce the immune response characteristic of infectious agents. It is believed that the immune system helps prion propagation and facilitates their access to the central nervous system. Several agents such as β-sheet breaker peptides and amphotericin B have been used to delay the incubation time of prion infected animals.
Sigurdsson et al (Am J Pathol 2002, 161:13–17) investigated whether vaccination with recombinant mouse prion protein, either before or after exposure to prions, would delay the onset of disease. Although the effect was small, delayed onset was obtained in both groups, particularly in animals immunized before prior exposure, and correlated with the titer of anti-prion protein. Although preliminary, these results suggest that vaccination against prion diseases should be further explored as a way of preventing prion diseases.

**Frequent Amplification of the Cell Cycle Protein SKP2 in Small Cell Lung Cancers**

SKP2 is a cell cycle protein that promotes the ubiquitination and proteolysis of the cell cycle inhibitor p27. Studies of small cell lung cancers (SCLC) have reported that the 5p11-p13 region is frequently amplified in SCLC and in cultured cells obtained from these tumors. Yokoi et al (Am J Pathol 2002, 161:207–216) hypothesized that these chromosomal regions may contain genes whose amplification is associated with tumorigenesis. They report that the SKP2 gene was amplified in 44% of primary SCLC and overexpressed in 83% of 12 tumors examined. Expression of SKP2 was inversely correlated with that of p27 and its inhibition by an antisense oligonucleotide blocked the growth of SCLC cells in culture. The data suggest that SKP2 is an important amplification target in SCLC.

**A Simple Profile of Markers of Angiogenesis**

The analysis of angiogenesis in clinical samples requires a sensitive and simple molecular assay that can be used both to monitor the extent of angiogenesis and to determine the efficacy of angiogenesis-suppressing agents. Shih et al (Am J Pathol 2002, 161:35–41) used real-time quantitative polymerase chain reaction (PCR) technology in combination with cDNA standards to determine mRNA copy numbers of potential markers of neovascularization. The authors used two models to validate their marker panel, a skin angiogenesis model using vascular endothelial growth factor (VEGF)-injected nude mice and transgenic TRAMP mice with prostate carcinomas. In both models, VEGF expression correlated with increased expression of mRNAs for angiopoietin-1 and -2, tyrosine kinase receptors Flt-1, KDR, and Tie-1 and the adhesion molecules VE-cadherin and PECAM-1. This method offers the possibility of assessing angiogenesis by quantitative measurements of seven markers of neovascularization by a simple PCR procedure.