This Month in AJP

**Lung Allograft Rejection: Role of Chemokines in Lymphocyte Recruitment**

Migration of lymphocytes into the pulmonary parenchyma is an essential component of the mechanisms involved in lung graft rejection. Agostini et al (Am J Pathol 2001, 158:1703–1711) examined the expression of CXCL10 (IP-10), a chemokine induced by interferon α, and its receptor CXCR3. Immunohistochemical analysis of areas of acute cellular rejection and acute obliterative bronchiolitis contained T cells that expressed CXCR3. CXCL10 was highly expressed in graft-infiltrating macrophages and some epithelial cells. T cells obtained by bronchoalveolar lavage of lung transplant patients with rejection episodes expressed CXCR3 and exhibited a strong migratory response to CXCL10 in vitro. Alveolar macrophages secreted CXCL10 and induced chemotaxis in T cell lines containing CXCR3. The involvement of the CXCL10/CXCR3 system in the recruitment of lymphocytes at sites of rejection after lung transplantation may provide a rationale for testing agents that can block this system. Such agents may prevent lung allograft rejection.

**A Rat Model for Inherited Intrahepatic Dilatation of the Biliary Tree and Polycystic Kidney (Caroli’s Disease)**

Caroli’s disease is the name of a condition in which there is non-obstructive cystic dilation of the biliary tree associated with renal cystic disease. Sanzen et al (Am J Pathol 2001, 158:1605–1612) analyzed the biliary tree of polycystic kidney rats (PCK rat, established from a Crj:CD Sprague-Dawley spontaneous mutant) and found that at 19 days of gestation, the liver of these animals contained intrahepatic bile ducts with multiple dilatations. These defects increased and persisted and were accompanied by portal fibrosis as well as histological features of ductal plate malformation. In PCK rats, biliary epithelial cells had greater proliferative activity and less apoptosis up to 1 week of age, in comparison with wild-type Crj:CD rats. Although the exact definition of the term “Caroli’s disease” is a topic of debate, the PCK rat may serve as a good model in which to study the pathogenesis of inherited non-obstructive dilatations of the intrahepatic biliary tree accompanied by polycystic renal disease.

**Allelic Loss in the Progression of Pancreatic Carcinogenesis**

The presumed precursor lesions of pancreatic ductal adenocarcinoma are classified according to their degree of dysplasia and designated as Pancreatic Intraepithelial Neoplasia (PanIN) 1 through 3. Lüttges et al (Am J Pathol 2001, 158:1677–1683) tested whether specific molecular genetic alterations correlate with this classification. They determined the frequencies of allelic loss at chromosomal arms 9p, 17p, and 18q in 81 microdissected duct lesions of various PanIN grades, using a combination of whole genome amplification and microsatellite analysis. They also examined p53 and Dpc4 protein expression patterns by immunohistochemical analysis. No allelic losses were detected in PanIN-1. However, allelic losses were found in PanIN-2; particularly in lesions with moderate grade dysplasia (low grade 20%, 33%, and 17% loss at 9p, 17p, and 18q, respectively; moderate grade 46%, 77%, and 58%). PanIN-3 and invasive carcinomas exhibited losses at very high frequency. Abnormal p53 and Dpc4 protein expression, which was only rarely detected in PanIN-2, occurred frequently in PanIN-3 lesions and invasive carcinomas. Allelic loss analysis may be useful in distinguishing between low and moderate grade PanIN-2 lesions. The results of these combined genetic and protein expression analyses suggest that allelic loss may be the first hit in the biallelic inactivation of the p53 and DPC4 tumor suppressor genes during pancreatic carcinogenesis.

**Discovery of Molecular Markers for Renal Epithelial Tumors by Analysis of Gene Expression Profiles**

Young et al (Am J Pathol 2001, 158:1639–1651) used cDNA microarrays to compare expression profiles of clear cell renal cell carcinomas and those of chromophobe renal cell carcinoma and oncocytomas. Chromophobe RCC and oncocytomas had similar gene expression profiles that included many genes involved in oxidative phosphorylation and genes that are normally expressed in the distal nephron. In contrast, clear cell RCCs had lower expression of mitochondrial and distal nephron genes and increased expression of vimentin. Immunohistochemical analysis showed that vimentin was a good marker for clear cell RCC, whereas parvalbumin was detected primarily in chromophobe RCC/oncocytomas. Analysis of gene expression patterns in renal tumors can help characterize tumor subtypes and identify diagnostic markers.
Survivin Mediates the Anti-Apoptotic Effect of VEGF during Angiogenesis

During angiogenesis, endothelial cell survival is protected by the expression of several genes, particularly by vascular endothelial growth factor (VEGF). Using an antisense nucleotide to the apoptosis inhibitor survivin, Mesri et al (Am J Pathol 2001, 158:1757–1765) found that blockage of survivin expression suppressed the anti-apoptotic effect of VEGF, enhanced caspase-3 activity and the generation of an active caspase-3 subunit, and increased the cleavage of the caspase-3 substrate polyADP ribose polymerase (PARP). Survivin blockage had no effect on bcl-2 expression in endothelium or on endothelial cell survival in the absence of VEGF. Other anti-sense nucleotides tested (against PECAM-1, LFA-3, or ICAM-1) did not interfere with VEGF anti-apoptotic activity. Modulation of the survivin pathway might be used to increase endothelial cell survival in compensatory angiogenesis or to promote endothelial cell apoptosis in tumor angiogenesis.

Identification of Specific Chromosomal Abnormalities as Early Markers in Carcinoid Development

Carcinoid tumors are rare neuroendocrine tumors that occur in the lung or digestive tract. Tumors occurring in the gastrointestinal tract are subclassified as foregut, midgut, and hindgut carcinoids. To better understand the genetic basis of different carcinoid tumors, Kytölä et al (Am J Pathol 2001, 158:1803–1808) characterized numerical chromosome imbalances in midgut carcinoids and compared the results to previous findings in lung carcinoids. Numerical imbalances were detected in 16 of 18 tumors. The most commonly detected aberrations were losses of 18q22-qter (67%), 11q22-q23 (33%), and 16q21-qter 9 (22%), and gain of 4p14-qter (22%). Losses of 18q and 11q were detected in both primary tumors and metastases, whereas loss of 16q and gain of 4 were only detected in metastases. Loss of 18q and 11q appear to be early events, and loss of 16q and gain of 4p are late events in tumor progression of midgut carcinoids. Compared to previously published data on lung carcinoids, loss of 11q was detectable in both lung and midgut carcinoids, whereas loss of 18q and 16q and gain of 4 were not present in lung tumors. Inactivation of a putative tumor suppressor gene in 18q22-qter may be a frequent, specific, and early event in the development of midgut carcinoids.

Mechanism of Cast Formation in Cast Nephropathy

Cast nephropathy (myeloma kidney) is a potentially reversible cause of chronic renal failure. In this condition, immunoglobulin light chains bind to a common site on Tamm-Horsfall protein (THP), which is produced by cells of the thick ascending limb of the loop of Henle. Aggregation of these proteins produces casts that obstruct tubule fluid flow, resulting in renal failure. Ying et al (Am J Pathol 2001, 158:1859–1866) used the yeast two-hybrid system to determine the site of interaction of light chains with THP and found that the third complementarity-determining region (CDR3) of both κ and λ light chains interacted with THP. These finding were confirmed in a series of competition studies using a CDR3 synthetic peptide, purified THP, and light chains. Variations in the CDR3 sequence of the light chain affected binding. These studies identify the earliest step in cast formation and may lead to the development of specific strategies to block the process.