The Role of Genetic Instability in Tumor Growth: Challenge of a Concept

Genomic instability has become an important concept in studies of cancer pathogenesis based on the notion that genetic instability is an essential component of tumorigenesis. Genetic instability could be cause or consequence of tumorigenesis or actually both. L. Loeb has argued (see Am J Pathol 1999, 154:1621–1626, among other references) that the multiple mutations and selective growth advantage developing during tumorigenesis may be dependent on the ability of the cells to mutate. Mutations in genes that control genomic stability are considered to be critical in this process. Mutations in these genes establish a “mutator phenotype” that may account to the very large number of mutations detected in cancer cells. Tomlinson et al in their commentary (Am J Pathol 2002, 160:755–758) take issue with these views and argue instead that normal mutation rates in tumor cells may account for many millions of mutations arising both during tumorigenesis as well as before tumor growth. They propose that the high number of mutations in tumor cells derives from three factors: the accumulation of somatic mutations in normal stem cells, the large number of cell generations needed for tumor growth, and the high cell turnover that occurs during tumorigenesis. Tomlinson et al conclude not only that genetic instability is not necessary to explain existing data on tumor growth, but also that there is actually little support for the involvement of genetic instability in tumorigenesis.

Chromosomal Translocation in Follicular Lymphomas: Pitfalls of Existing Techniques and Future Directions for Improvement

The detection of the t(14;18) translocation is used for the diagnosis of follicular lymphomas and the detection of minimal residual disease. The reported detection ratios for this translocation using polymerase chain reaction (PCR) methodology have been quite variable. One of the reasons for these disparities is that breakpoints on chromosome 18 may occur outside the mbr and mcr loci, the regions covered by the conventional PCR techniques. Albinger-Hegyi et al (Am J Pathol 2002, 160:823–832) developed an improved long-distance PCR (LD-PCR) protocol and designed sets of primer pairs for the 25-kb-long stretch between the mbr and mcr loci. Using this method, the translocation was detected in 71% of frozen tissue biopsies compared to a frequency of 36% detected by conventional PCR techniques. Moreover, the new technique also improved the detection of the t(14;18) translocation in formalin-fixed, paraffin-embedded biopsies. In their commentary, Aster and Longtine (Am J Pathol 2002, 160:759–763) discuss these finding in detail and consider the questions of the “true” incidence of the t(14;18) translocation in follicular lymphoma, which test might be best to detect the translocation, and the potential uses of Bcl-2 detection by immunohistochemistry. Both Albinger-Hegyi et al and Aster and Longtine indicate that most breaks on chromosome 18, contrary to the original expectations, are independent of V(D)J recombinase activity and may originate by diverse mechanisms. The article and the commentary point out both the pitfalls of existing molecular methods as well as future directions to perfect these methods as they become increasingly important in pathology practice.

Pancreatic Acinar Cell Carcinomas and Pancreatoblastomas Have Similar Genetic Abnormalities That Differ from Those of Ductal Adenocarcinomas

Genetic alterations in pancreatic ductal adenocarcinomas, the most common pancreatic tumor, have been extensively studied and include the loss of Dpc-4 expression and p53 accumulation. Abraham et al (Am J Pathol 2002, 160:953–962) investigated the molecular abnormalities in pancreatic acinar cell carcinomas (ACC) which are rare tumors distinct from ductal adenocarcinomas but with clinical and morphological features that resemble pancreaticoblastomas. In contrast to ductal adenocarcinomas, losses of chromosome 11p and mutations in APC/β-catenin pathway occur frequently in pancreaticoblastomas. Abraham et al found no losses of Dpc-4 expression or p53 accumulation in ACC. Instead, they detected allelic loss on chromosome 11p in 50% of informative cases and alterations in the APC/β-catenin pathway in 23% of cases. The data demonstrate that ACC share similar genetic abnormalities with pancreaticoblastomas and that these tumors have different molecular profiles from ductal adenocarcinomas.

Tumor Blood Vessels Contain Abnormal Pericytes

Morikawa et al (Am J Pathol 2002, 160:985–1000) studied pericytes in tumor vessels to determine their frequency, immunoreactivity to α-smooth muscle actin (αSMA) and desmin, and their general architecture and relationships to endothelial cells. Although some studies have failed to find pericytes in tumor blood vessels, Morikawa et al detected...
immunoreactive pericytes for αSMA and desmin in more than 97% of 100μm-thick sections of blood vessels from three different tumors, viewed by confocal microscopy. In all tumors, pericytes had an abnormal association with endothelial cells, had cytoplasmic processes that extended deep into tumor tissue and exhibited long sleeves, which covered endothelial sprouts in the tumors. In addition to pericytes the tumors contained myofibroblasts which were αSMA positive but were not associated with blood vessels. It remains to be established if pericytes may be involved in the growth and retraction of endothelial sprouts in tumors.

Pathogenesis of Myocardium Abnormalities Caused by Desmin Deficiency

Knockout mice lacking the intermediate filament protein desmin develop dilation of cardiac chambers and heart failure as a result of cardiomyocyte alterations, fibrosis, and calcification of the myocardium. Mavroidis and Capetanaki (Am J Pathol 2002, 160:943–952) conducted a study of gene expression by differential display analysis in cardiac tissue of mice lacking desmin. The major finding from this analysis was the large increase in the knockout mice of the expression of the extracellular matrix proteins osteopontin and decorin, both at the RNA and protein levels. Osteopontin was localized by immunohistochemistry in areas of cardiomyocyte death and in calcified deposits surrounded by decorin. In addition to osteopontin and desmin, there was increased expression of TGF-β1 and angiotensin converting enzyme. These findings may explain the mechanisms of fibrosis and dystrophic calcification that occur in the heart of knockout mice lacking desmin.

Urokinase and Tissue-Type Plasminogen Activators Have Opposite Roles in an Experimental Model of Arthritis

It is known that urokinase plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA) participate in inflammation and joint destruction processes associated with rheumatoid arthritis (RA). Nevertheless, there is little information about the precise role of each of these enzymes. Cook et al (Am J Pathol 2002, 160:917–926) studied the development of collagen-induced arthritis in mice deficient for u-PA or t-PA. The disease was much more severe in t-PA knockout mice than in u-PA deficient animals and was associated with higher cytokine levels in the synovium and increased fibrin deposition within the joints. IL-1β levels were high in t-PA knockouts and decreased in u-PA deficient mice which also had a reduced T cell proliferative response and produced less γ-interferon on antigen stimulation. The results demonstrate that t-PA has a protective effect on arthritis development while u-PA activity may have the opposite effect. Thus, enhancement of t-PA activity or u-PA inhibition in joints may constitute useful therapeutic strategies in RA.

Precise Dissection, Laser Catapulting, and Microarray Hybridization of Dorsal Aorta in Mouse Embryos

Laser microbeam dissection followed by laser capture or laser pressure catapulting (LPC) is currently used for analysis of RNA expression in defined tissue structures and tumor nodules. It has been expected that refinements of these methods would allow analyses of precisely defined tissue segments and slender structures such as those present during embryonic development. Scheidl et al (Am J Pathol 2002, 160:801–813) report the analysis of dorsal aorta segments containing 1000 cells from mouse embryos at 9.5 days of development. Using laser microbeam dissection and LPC, the authors obtained RNA expression profiles from these cells by RNA amplification and microarray hybridization. Among the genes highly expressed by these cells are 11 known markers for blood vessels including endoglin, tie-2, PDGFB, and integrin-β1. These profiles contrasted with those from mesenchymal cells located only one cell diameter away from the aortic lumen. The results show that laser dissection followed by tissue capture or catapulting is an excellent technique for the analysis of gene expression of precisely localized tissue segments.