This Month in AJP

Stellate Cells as Agents of Pancreatic Fibrosis

Liver stellate cells, formerly known as Ito or fat-storage cells, are the major agents of liver fibrosis leading to cirrhosis. Similar cells have been described in the pancreas and the kidney (glomerular mesangial cells). Pancreatic stellate cells (PSC) can be activated to express α-smooth muscle actin and replicate. Both in liver and pancreas, stellate cells appear to function as wound healing myofibroblasts after injury, secreting various cytokines and growth factors as well as collagens. Fibrosis is controlled by both collagen deposition and matrix degradation involving metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), both of which are regulated in part by TGFβ. Shek et al (Am J Pathol 2002, 160:1787–1798) show that PSC express mRNAs for pro-collagen 1, MMPs, and TIMPs. The cells contain TGFβ receptors types I and II and secrete active TGFβ1 into the medium. The data demonstrate that PSC express collagens and mediators of matrix remodeling which are under TGFβ1 autocrine control, suggesting that PSC are key mediators of fibrogenic responses in the pancreas.

Angiopoietin-1 Protects against Diabetic Retinopathy

Angiopoietin-1 enhances endothelial cell survival without inducing cell proliferation. It stabilizes endothelial cell interactions with surrounding cells and antagonizes vascular endothelial growth factor (VEGF) effects on vessel permeability. In diabetic retinopathy in human and rodents there is increased expression of the adhesion molecule 1CAM-1 and leukocyte adherence, leading to endothelial cell injury and capillary occlusion. Joussen et al (Am J Pathol 2002, 160:1683–1693) show that intravitreal administration of angiopoietin-1 to diabetic rats decreases retinal VEGF and 1CAM-1 (both mRNA and protein) and reduces endothelial cell injury. The authors obtained similar results by systemic administration of an adenovirus that expressed angiopoietin-1. Inhibition of retinopathy was associated with reduction in eNOS, nitric oxide, and other mediators of VEGF activity and leukocyte adhesion. The work shows that angiopoietin-1, a naturally occurring protein, is highly protective against diabetic retinopathy.

TSG-14, a TNF Target Gene that Regulates TNF Biological Effects

Inflammatory responses, depending on their intensity and causes, can be beneficial or harmful to the host. Tumor necrosis factor (TNF), a key regulatory cytokine in inflammation, has been extensively studied as to its mechanisms of action and target genes. Among these genes is TSG-14, which is induced by TNF, 1L-1β, and LPS, and belongs to the long pentraxin family of proteins. In contrast to other acute phase proteins, TSG-14 is not expressed in the liver but is detected mostly in skeletal and myocardial muscle endothelial cells and stimulated macrophages. Previous studies showed that mice overexpressing TSG-14 have increased resistance to LPS and higher survival rate in experimental peritonitis. These animals produce high levels of TNF after LPS injection. Souza et al (Am J Pathol 2002, 160:1755–1765) show that TSG-14 transgenic mice have reduced survival after ischemia/reperfusion injury created by temporary occlusion of the superior mesenteric artery. TNF is an important mediator of the response since injection of soluble TNF receptor prevented lethality after ischemia/reperfusion. The data indicate that TSG-14 can regulate TNF biological activities, both to prevent or promote injury.

Parkin Is a Component of Lewy Bodies in Parkinson’s Disease

Lewy body formation is a characteristic feature of Parkinson’s disease (PD). Parkin mutations are present in autosomal recessive early-onset parkinsonism which is similar to sporadic PD. Lewy bodies are detected in sporadic and α-synuclein mutated PD but generally not in parkin-associated PD. Parkin is a member of a family of zinc-binding proteins which have ubiquitin ligase activity that promotes proteasome 1 degradation of proteins. Schlossmacher et al (Am J Pathol 2002, 160:1655–1667) report that anti-parkin antibodies labeled Lewy bodies in sporadic, parkin-linked, and inherited α-synuclein PD, as well as in dementia with Lewy bodies. α-synuclein and parkin co-localized in brain stem and cortical Lewy bodies. Presynaptic fractions rich in α-synuclein also contained parkin and its binding partner, Ubc H7. The work shows that parkin is present in subcellular compartments of normal brain and co-localizes with α-synuclein in PD’s Lewy bodies, suggesting that parkin may be required for Lewy body formation.
Targeting Epstein-Barr Virus Sequences in Post-Transplant Lymphomas

One of the complications of organ and bone marrow transplantation is the development of B cell lymphomas associated with Epstein-Barr virus (EBV). High doses of immunosuppressants such as cyclosporine increase the risk of post-transplant lymphoproliferative disorders (PTLD) while reduction in dose or withdrawal of immunosuppressive agents generally leads to tumor regression. Cytotoxic lymphocytes (CTL) responding to irradiated EBV-transformed B lymphocytes have also been used to induce regression or prevent PTLD in bone marrow transplant recipients, without development of graft versus host disease. In these studies a single EBV laboratory strain (B95–8) was used to transform CTLs. Tao et al (Am J Pathol 2002, 160:1839–1845) asked whether this viral strain shares epitopes with EBV genomes present in PTLD that can be recognized by EBV-specific CTLs. They characterized the viral strain and the sequence of commonly recognized CTL epitopes in 25 PTLD specimens and reported that 24 of 25 specimens contained EBV subtype A. However, CTLs to B95–8 peptides targeted the sequences of the EBV strain present in PTLD tumors. Thus, these cells may be effective agents for immune therapy of post-transplant lymphomas.

FISHing for GOLDFISH: A New Technique to Detect HER-2/neu Amplification

Detection of HER-2/neu overexpression and amplification is widely used for the management of patients with breast tumors and to evaluate the response to therapy. Gene amplification can be detected by a variety of methods including fluorescence in situ hybridization (FISH). A limitation of FISH methodology is that tissue and cell morphology is not visualized. Moreover, fading and bleaching of the fluorescence signal present difficulties for archiving and documentation. Tubbs et al (Am J Pathol 2002, 160:1589–1595) developed a method for detection of Her-2/neu amplification using bright-field microscopy without oil immersion. The technique, which they named as GOLDFISH (for gold-facilitated in situ hybridization), was validated by analyzing 100 invasive breast carcinomas for which Her-2/neu gene copy number and RNA and protein expression assays were available. Autometallographic gold-based in situ hybridization correlated well with FISH analysis and offered the additional advantage of morphological visualization on the same slide.