This Month in AJP

Using MALDI Imaging for Gastric Tumor Staging and Prognosis

mRNA expression profiles can identify genes involved in tumorigenesis; however, protein concentrations do not always correlate well with mRNA expression. Balluff et al (Am J Pathol 2011, 179:2720–2729) used matrix-assisted laser desorption/ionization (MALDI) imaging to determine protein profiles of gastric tumors. Of seven proteins positively correlated with poor prognosis, HNP-1 and S100-A6 helped delineate early (stage I) from later (stages II and III) disease, making prognostic evaluation more robust. The presence of CRIP1, the role of which is uncertain, was strongly correlated with decreased survival. This study is the first to demonstrate the utility of MALDI imaging in tumor profiling and prognosis and also to show that MALDI imaging requires much smaller amounts of tissue than are required for other analytic methods.

Combating Air Pollutant–Induced Asthma

Urban air pollutants are known to elicit asthma, but the immune factors that mediate immune cell infiltration are not well characterized. Kim et al (Am J Pathol 2011, 179:2730–2739) studied diesel exhaust particulate (DEP)-induced asthma in mice and observed that after DEP challenge, mice exhibited increased pulmonary inflammation, mucus production, reactive oxygen species (ROS, which drives chemokine production and inflammation), and inflammatory cell infiltration. The CXC chemokines macrophage inflammatory protein-2 (MIP-2) and keratinocyte-derived chemokine (KC) were present in lavage samples and lung tissue in the early response. Their essential involvement was confirmed by oropharyngeal pretreatment with blocking antibodies specific for KC and MIP-2, which attenuated eosinophil and neutrophil infiltration. Thus, modulating the expression of these chemokines and using antioxidants to attenuate ROS formation and resultant damage may be therapeutic to asthma patients.

Understanding LDL-Induced Damage in Diabetic Retinopathy

Elevated concentrations of low-density lipoproteins (LDL) are associated with diabetic retinopathy, but increased plasma levels of LDL are not observed. Rather, LDL may extravasate through a disrupted blood-retinal barrier where it becomes glycated and oxidized. Zou et al (Am J Pathol 2011, 179:2835–2844) examined this hypothesis in vitro and found that cultured human retinal pericytes treated with heavily oxidized and glycated LDL (HOG-LDL) underwent apoptosis. This apoptosis was accompanied by tyrosine nitration and deactivation of prostacyclin synthase (PGIS). Antioxidant treatment restored PGIS activity and inhibited apoptosis. In the Akita diabetic mouse model, diabetic onset enhanced the production of oxidized and glycated LDL in mouse retinas, resulting in PGIS nitration and pericyte apoptosis. However, administration of the superoxide scavenger tempol attenuated the accumulation of HOG-LDL, decreased PGIS nitration, and spared retinal cells from apoptosis. Thus, the use of antioxidant therapies might prevent such damaging sequelae of diabetes.

Starvation Compromises Gut Innate Immunity

Lack of enteral feeding is associated with increased intestinal permeability and translocation of bacteria, as well as high morbidity and mortality. Hodin et al (Am J Pathol 2011, 179:2885–2893) examined the influence of food deprivation on the function of Paneth cells, which serve a role in innate intestinal immunity. In a mouse starvation model, expression of antimicrobial products (ie, lysozyme, cryptdin, and RegIIIγ) was significantly decreased in ileal tissue. Late degenerative autophagolysosomes and aberrant Paneth cell granules were also evident. Furthermore, increased bacterial translocation to mesenteric lymph nodes coincided with Paneth cell abnormalities. Such changes may contribute to loss of epithelial barrier function and cause the apparent bacterial translocation in enteral starvation, supporting the restricted use of total parenteral nutrition in critically ill patients.

Targeting ADAMTS1 in Breast Tumors

ADAMTS1 remodels tissue by degrading extracellular matrix proteins, explaining its association with several metastatic carcinomas. But is ADAMTS1 required for metastasis? Ricciardelli et al (Am J Pathol, 179:3075–3085) modified a murine model of basal breast cancer by knocking out (KO) AdamiT1 (ADAMTS1 expression is characteristic of breast cancer cell lines and human breast cancers with high bone metastatic potential). Tumor mass (but not incidence) was greatly reduced, owing to increased apoptotic rates in tumor cells, and metastatic burden was significantly reduced as well. Cytotoxic T cells were strongly activated in KO mice, which may have contributed to keeping tumors in check. These data suggest that ADAMTS1 is essential for breast cancer metastatic progression, as tumor cells appear unable to exit their original site in the absence of ADAMTS1. Importantly, targeting ADAMTS1 may prove to be beneficial in breast cancer if therapeutics can be used early enough to prevent metastasis.