This Month in AJP

LINE-1 Is a Hallmark of Many Cancers

Long interspersed element-1 (LINE-1) can contribute to genetic changes in cancers, with somatic LINE-1 insertions seen in selected cancers. Rodić et al (Am J Pathol 2014, 184:1280–1286) studied the expression of LINE-1 open reading frame 1 protein (ORF1p) in various cancers. LINE-1 protein expression was a common feature of many types of high-grade malignancy, was rarely detected in early stages of tumorigenesis, and was absent from normal somatic tissues. LINE-1 ORF1p protein is a surprisingly broad yet highly tumor-specific antigen, with as many as half of human cancers expressing ORF1p. The correlation between LINE-1 expression and TP53 mutation as well as histological hallmarks of aggressive neoplasms suggests that LINE-1 expression may be an acquired feature that is restricted to high-grade lesions at more advanced phases of tumorigenesis.

Varied Genetic Profiles of Head and Neck Squamous Cell Carcinoma

Dissimilarities in prognosis and molecular profiles of head and neck squamous cell carcinoma (HNSCC) with and without HPV infection have attracted much attention. Using targeted next generation sequencing, Zhang et al (Am J Pathol 2014, 184:1323–1330) interrogated single nucleotide variants (SNVs) and detected SNVs in 25 cancer-related genes from HNSCC tissue specimens with and without HPV infection. Five genes (PDGFRα, PIK3CA, KIT, and APC) showed similar variant patterns regardless of HPV infection. In HPV-positive specimens, tyrosine kinase receptor and associated pathway genes (EGFR, FGFR3, PDGFRα, MET, KDR, CSFRI, and KIT) predominated whereas tumor suppressor-related genes (AKTI, TP53, ABL1, and FLT3) prevailed in HPV-negative specimens. These results emphasize the importance of improved HNSCC patient selection using comprehensive variant analyses for the most effective targeted therapies.

Fibroblast Progenitor Cells in Idiopathic Pulmonary Fibrosis

Despite intensive investigation, the origin of the fibroblasts mediating fibrotic organ destruction in idiopathic pulmonary fibrosis (IPF) remains unknown. Xia et al (Am J Pathol 2014, 184:1369–1383) identified and molecularly characterized a subpopulation of cells with the properties of mesenchymal progenitors in the lungs of IPF patients. In contrast to progenitors isolated from nonfibrotic lungs, IPF mesenchymal progenitor cells produced daughter cells manifesting the full spectrum of IPF hallmarks, including the ability to form fibrotic lesions in zebrafish embryos and mouse lungs, and a corresponding transcriptional profile. IPF mesenchymal progenitor cells and their progeny also comprised the fibrotic reticulum. These newly identified fibrogenic mesenchymal progenitors represent a therapeutic paradigm shift focused on targeting fibrogenic mesenchymal progenitor cells before they mediate organ failure.

Food Restriction during Postmyocardial Infarction

The functional role of autophagy in heart disease and whether it up- or down-regulates cellular function remain poorly understood. Using a mouse model of myocardial infarction, Watanabe et al (Am J Pathol 2014, 184:1384–1394) investigated the effect of food restriction (FR), which potently induces autophagy, on postinfarction cardiac remodeling and dysfunction. FR implemented during the subacute stage after a large myocardial infarction significantly mitigated the adverse left ventricular remodeling and subsequent heart failure seen at the chronic stage. The therapeutic efficiency was strongest in mice receiving 60% of their normal food intake. Chloroquine, which inhibits autophagy, completely canceled the therapeutic effect of FR. This negative effect was associated with reduced activation of AMPK and ULK1, and phosphorylated ULK1 was significantly increased in hearts from the FR group. Thus, a dietary protocol started during the subacute stage of myocardial infarction may provide a preventative strategy against progression of postinfarction left ventricular remodeling and heart failure.

CD146 in Colitis and Colitis-Associated Carcinogenesis

Enhanced expression of the CD146 has been reported on endothelial cells from patients with inflammatory bowel disease (IBD). Xing et al (Am J Pathol 2014, 184:1604–1616) examined the role of CD146 in murine models of IBD and colitis-associated colorectal carcinogenesis (CAC) progression. Overexpression of endothelial CD146 promoted inflammatory responses in IBD, further potentiating CAC. Eliminating endothelial CD146 by conditional knockout or by blocking antibody significantly alleviated the disease severity in two murine models of colitis and decreased tumor incidence in a murine model of CAC. Mechanistically, the cytokine TNF-α up-regulated endothelial CD146 expression through NF-κB transactivation, which promoted both angiogenesis and proinflammatory leukocyte extravasation, contributing to inflammation. This first evidence that CD146 plays a dual-role on endothelium suggests its use in the treatment of IBD and prevention of CAC.