Classifying High-Grade Serous Ovarian Carcinoma

High-grade serous ovarian cancer, the histological type with the worst prognosis, has recently been divided into four prognostic gene expression subtypes: mesenchymal, immunoreactive, proliferative, and differentiated. Murakami et al (Am J Pathol 2016, 1103–1113) aimed to establish a novel histopathological classification corresponding to the gene expression subtypes. Unsupervised hierarchical clustering identified four clusters correlating with histopathological subtypes, with significant overlap to the four molecular subtypes. Further, the poor prognostic mesenchymal gene expression subtype, corresponding to the mesenchymal transition histological type, was sensitive to the therapeutic agent taxane. This study emphasizes the potential of individualized medicine against ovarian cancer.

SHARPIN Inhibits Caspase 1 in Sepsis

Sepsis exhibits high mortality due to uncontrolled inflammatory response, with increased caspase 1 activation a therapeutic challenge. Nastase et al (Am J Pathol 2016, 1206–1220) identified a novel role for the inflammation regulator SHARPIN in the negative control of caspase 1 in lipopolysaccharide (LPS)-induced endotoxemia. Mice lacking caspase 1, caspase 11, or both in a Sharpin-deficient background were exposed to LPS and injected with caspase 1 inhibitor. Septic Sharpin-deficient mice were enriched in mature Il1β/18 and active caspase 1 in addition to having shortened survival whereas caspase 1 inhibition ameliorated these effects. The caspase 1-SHARPIN axis represents a potential target in the treatment of sepsis.

Circulating miRNAs Detect Acute Muscle Damage

Reliable identification of biomarkers for skeletal muscle damage is greatly needed in the clinical laboratory. With this in mind, Siracusa et al (Am J Pathol 2016, 1313–1327) characterized circulating miRNAs in plasma in response to acute notoxin-induced muscle damage in rats. RT-qPCR profiling uncovered several muscle-specific miRNAs that were highly increased in plasma in response to notoxin injection into several muscles. miRNA levels peaked 12 hours after injury and were present in the vesicular and non-vesicular fractions. Interestingly, damage to slow- or fast-type muscle had a very limited impact on the miRNA response. Circulating muscle-specific miRNAs, specifically 378a-3p and 434-3p, are promising biomarkers of acute muscle damage in rats.

GT198 Expression Defines Mutant Breast Tumor Stroma

Mutations in GT198—a steroid hormone receptor coactivator and crucial factor in DNA repair—occur in breast and ovarian cancer families as well as in ovarian tumor stromal cells. Since GT198 mutations induce tumor-specific cytoplasmic GT198 expression, Yang et al (Am J Pathol 2016, 1340–1350) hypothesized that mutant tumor stroma with cytoplasmic GT198 may identify precursor breast cancer lesions. Human breast tumor stromal cells carried GT198 somatic mutations and expressed cytoplasmic GT198 protein. Multiple lineages were involved: myoepithelial cells, adipocytes, perivascular cells, capillary pericytes, and stromal fibroblasts. GT198 expression is a specific marker to define mutant reactive breast cancer stroma.

IL-19 Regulates Plaque and Cholesterol Homeostasis

Atherosclerosis regression and atherosclerotic plaque reversal are important clinical goals. Using LDLR−/− mice fed a Western diet, Gabunia et al (Am J Pathol 2016, 1361–1374) examined whether the Th2 cytokine IL-19 could attenuate progression of preformed atherosclerotic plaque. IL-19−−treated mice exhibited similar atherosclerosis burden to baseline mice whereas control mice showed increases in plaque. IL-19−−treated mice also displayed key features of atherosclerosis regression, such as reduced macrophage content and enriched markers of M2 macrophages. Further, IL-19 promoted the activation of key pathways leading to M2 macrophage polarization and reduced cytokine-induced inflammation in vivo. IL-19 functions as a link between inflammation and macrophage cholesterol metabolism.