INSM1 Regulates Neuroendocrine Differentiation in Lung Cancer

Although the expression of the insulinoma-associated protein 1 (INSM1) gene is specific for small cell lung cancer (SCLC), its biological functions in lung cancer are unclear. Fujino et al (Am J Pathol 2015, 185:3164–3177) therefore studied the expression of INS1, as well as other neuroendocrine proteins (ASCL1, BRN2) in SCLC and non-SCLC specimens and cell lines. In vivo and in vitro studies showed that INS1 was exclusively expressed in SCLC. INS1 regulated NE differentiation pathways involving ASCL1, BRN2, and the NE molecules CGA, SYP, and NCAM, inhibited tumor cell proliferation, and activated apoptotic activity. Notch1—Hes1 signaling suppressed INS1. Targeting INS1 may improve the treatment and prognosis of SCLC.

Understanding Cardiac-Specific JAK2 Function

The role of Janus kinase 2 (JAK2), the predominant JAK in the heart, in cardiac homeostasis remains unclear. To study JAK2 tissue-specific function, Gan et al (Am J Pathol 2015, 185:3202–3210) generated a viable cardiac-specific JAK2-knockout mouse. The knockout mice showed early mortality, which was substantially higher in males compared to females. A detailed analysis of cardiac performance and histology in surviving mice revealed hypertrophy, dilated cardiomyopathy, and severe left ventricular dysfunction in both sexes, with milder responses in females. The expression of key sarcoplasmic reticulum proteins involved in cardiac excitation—contraction coupling was also altered in surviving mice, in a sex-specific manner. Preserving JAK2 function may help in the management of cardiac failure.

ADAR1 Protects from Inflammation-Related Liver Damage

In vivo functional study of the multifunctional enzyme adenosine deaminase acting on RNA 1 (ADAR1) in adult mouse liver is precluded by the embryonic lethality of its global loss. Wang et al (Am J Pathol 2015, 185:3224–3237) therefore generated and analyzed a hepatocyte-specific ADAR1-knockout mouse model. Conditional knockout mice showed high mortality, severe growth defects, and extensive structural and functional damage in the liver due to activated interferon signaling—especially via type I interferons. This damage included increased cell death,stellate cell activation, hepatocyte fibrosis, fatty change, and inflammation. Re-expression of ADAR1 in cultured knockout hepatocytes abrogated proinflammatory cytokine expression. ADAR1 may have additional protective roles in inflammation-associated liver diseases.

Epigenetic Reprogramming and Pancreatic Recovery Following Injury

The anti-epileptic drug valproic acid (VPA) contributes to pancreatitis through yet unknown mechanisms. Since VPA inhibits histone deacetylases (HDACs), which modulate pancreas development, Eisses et al (Am J Pathol 2015, 185:3304–3315) hypothesized that VPA predisposes patients to pancreatitis by inhibiting HDACs and thereby impeding pancreatic recovery. Administration of VPA in a mouse model of pancreatitis inhibited the pancreatic HDAC activity associated with that damage. In turn, this inhibition delayed pancreatic recovery by reducing proliferation of acinar cells, promoting acinar-to-ductal metaplasia complexes (via β-catenin), and arresting acinar redifferentiation. Targeting epigenetic reprogramming may enhance pancreatic recovery following injury.

Extracellular ATP/P2X Axis Regulates Duchenne Muscular Dystrophy

P2 purinergic (P2X) receptor signaling has been implicated in the pathogenesis of Duchenne muscular dystrophy (DMD). Using the mdx mouse model, Gazzerro et al (Am J Pathol 2015, 185:3349–3360) explored the role of extracellular adenosine triphosphate (eATP), a byproduct of dying cells, and P2X receptors in DMD. Treatment of mdx mice with periodate-oxidized ATP (oATP) irreversibly antagonized P2X receptors ameliorated the progression of the dystrophy, reduced inflammation, and increased immunosuppressive regulatory T cells. Administration of oATP was also associated with decreased pro-fibrotic cytokines, enhanced muscle strength, and reduced necrosis. eATP contributes to immunopathologic damage of dystrophic muscle, suggesting pharmacological P2X antagonism as a promising therapeutic approach for DMD.