This Month in AJP

Reversing Age-Related Myocardial Fibrosis

Aging myocardium is associated with progressive and significant deposition of extracellular matrix proteins such as collagen. Using a mouse model, Rosin et al (Am J Pathol 2015, 185:643–650) studied the underlying mechanisms that regulate collagen homeostasis in age-related myocardial fibrosis. Collagen cross-linking was inhibited by blocking the key regulator lysyl oxidase (LOX). LOX inhibition in aging mice not only reduced fibrosis but also reversed it. LOX inhibition significantly reduced the amount of cross-linked collagen and modulated collagen synthesis, resident macrophage population, and the previously-implicated transforming growth factor β pathway. Fibrosis may be reversible, and modulating collagen homeostasis may reduce myocardial fibrosis in cardiovascular disorders.

A Unified Model to Study Influenza

No single animal model allows for the comprehensive study of influenza virus transmission and cellular immunity. Wiersma et al (Am J Pathol 2015, 185:643–650) explored the use of isogenic strain 2 guinea pigs as a unified model to study viral pathogenesis. Guinea pigs were infected with A/H1N1 influenza virus by intranasal (IN) or intratracheal (IT) route. In all animals, virus titers peaked in nasal secretions at day 2 postinoculation. IN inoculation resulted in higher virus excretion and higher virus titers than in IT inoculation. After IN inoculation, infectious virus was recovered only from the nasal epithelium, compared with the additional recovery from the trachea, lung, and cerebrum after IT inoculation. Consistently, histopathological changes were largely limited to nasal epithelium of animals infected IN but were more widespread in the respiratory tract of animals infected IT. Isogenic guinea pigs represent a promising model to study both influenza immunity and virus transmission.

Modeling Smoke-Induced Airway Disease

Limitations of chronic obstructive pulmonary disease (COPD) small animal models impede identification of new therapeutic targets and biomarkers for the disease. Polverino et al (Am J Pathol 2015, 185:741–755) assessed the use of female cynomolgus macaques as nonhuman primate (NHP) large animal models of COPD. NHPs were exposed to air or cigarette smoke (CS) followed by monitoring for airway disease. Lungs of CS-exposed NHPs developed robust pathological and functional changes in the airways that were similar to those occurring in COPD patients. Although CS-exposed NHPs did not develop emphysema over the duration of the study, they exhibited pathologies that precede development of emphysema. NHPs provide the benefits of longitudinal sampling as well as greater genetic and physiological similarities with humans, rendering NHPs useful for assessing novel biomarkers or therapeutics for COPD.

Linking Type 2 Diabetes and Alzheimer Disease

Both Alzheimer disease (AD) and type 2 diabetes (T2D) exhibit local amyloid deposits in their pathogenesis. Because structures with amyloid-seeding ability may induce both homologous and heterologous fibril growth, Oskarsson et al (Am J Pathol 2015, 185:834–846) studied the molecular interaction between different synthetic amyloid forms [islet amyloid polypeptide (IAPP), proIAPP, or amyloid-beta (Aβ)] to induce amyloid formation in the pancreas of IAPP-humanized mice. I.V. injection of preformed fibrils accelerated IAPP amyloid in the islet of Langerhans. Sensitive morphological analysis of pancreases from T2D patients and brains from AD patients revealed colocalization of IAPP and Aβ peptide in Aβ cerebral plaques, but no Aβ was detected in islet amyloid deposits in the endocrine pancreas. Such heterologous seeding between IAPP and Aβ may represent a molecular link between T2D and AD.

A Gene Signature for Prostatic Disease

Not all patients with benign prostatic hyperplasia (BPH) benefit from inhibitors against 5-alpha reductase (SRD5A2), which is critical for prostatic development and growth. Ge et al (Am J Pathol 2015, 185:870–882) hypothesized that the unresponsiveness stems from reduced SRD5A2 gene expression and protein production due to SRD5A2 methylation. Methylation of SRD5A2 was found to be regulated by DNA methyltransferase 1 (DNMT1), which in turn was regulated by TNF-α, NF-κB, and IL-6. Increased expression of DMNT1, methylation of the SRD5A2 promoter, and reduced expression of SRD5A2 protein were strongly associated with increased inflammatory mediators with aging. Experimentally induced inflammation in prostate primary epithelial cells hypermethylated the SRD5A2 promoter and silenced SRD5A2, whereas inhibiting an inflammatory mediator reactivated SRD5A2 expression. Understanding the epigenetic factors that regulate the expression of prostatic SRD5A2 lays the groundwork for strategies to personalize care and management of BPH.