This Month in AJP

Modeling Polycystic Kidney Disease

Transmembrane protein 207 (TMEM207) promotes tumor invasion and is overexpressed in aggressive gastric signet-ring cell carcinomas. To study the pathobiological roles of TMEM207, Kito et al (Am J Pathol 2017, 187:1916–1922) generated transgenic mouse strains ectopically expressing Tmem207 under the proximal promoter of the murine intestinal trefoil factor (Mift) gene. One mouse strain surprisingly showed high frequency of spontaneous kidney, liver, and pancreatic cysts with histopathological features mimicking human polycystic kidney disease (PKD). The majority of transgenic mice exhibited pathological characteristics of PKD within one year. The transgene construct insertion is in Mift at chromosome 6 and the transgenic mice have decreased expression of Mift and polycystin-1. These unique transgenic mice with mutated Mift and Tmem207 overexpression may prove useful in understanding PKD pathogenesis.

Understanding Carpal-Tarsal Bone Disorders

Mutations in v-maf musculoaponeurotic fibrosarcoma oncogene ortholog B (MAFB) and matrix metalloproteinases (MMP2 and MMP14) lead to bone dysplasia; however, the underlying skeletal physiology is unclear. Lazarus et al (Am J Pathol 2017, 187:1923–1934) hypothesized that MAFB, MMP-2, and MMP-14 have critical roles in carpal/tarsal and epiphyseal bone development. Examination of neonatal mouse forepaws revealed sequential bone ossification with two distinct patterns of calcification (via subarticular and physeal ossification) and different morphological features. MafB, Mmp-2, and Mmp-14 are expressed in peripheral carpal chondrocytes and highly expressed during carpal excavation and in newly formed bone. The underlying abnormality of carpotarsal osteosclerosis disorders may be disruptive bone remodeling rather than an osteolytic pathology, suggesting alternative treatment plans.

Understanding HIV Cardiomyopathy

Human immunodeficiency virus (HIV) cardiomyopathy is associated with increased expression of the gap junction protein connexin 43 (Cx43). Using postmortem human heart tissues obtained from HIV-infected and control uninfected individuals, Prevedel et al (Am J Pathol 2017, 187:1960–1970) studied Cx43 expression and distribution. Cx43 expression and localization is dysregulated in the hearts of HIV patients. Cx43 is overexpressed at both the transcript and protein levels. Cx43 is present at both intercalated disk and, abnormally, lateral cardiomyocyte membrane regions. Areas of dysregulated Cx43 expression exhibit calcium overload, increased collagen deposition, and sarcofilamental atrophy. The damage caused by Cx43 dysregulation in the heart may lead to cardiomyopathy in HIV-infected individuals.

Reversing Sepsis in Chronic Alcoholics

Chronic alcohol consumption may cause serious health problems including severe chronic liver inflammation and sepsis. Using an established chronic alcohol-consuming mouse model (CAC-mice), Kobayashi et al (Am J Pathol 2017, 187:1998–2007) studied the effect of short-term abstinence on the host antibacterial resistance. CAC-mice and CAC-mice with short-term abstinence from alcohol (aaCAC-mice) were orally infected with Enterococcus faecalis. Although severe sepsis was observed in CAC-mice exposed to the pathogen, it was absent in aaCAC-mice. Monocyte-derived M2b and M1 macrophages were respectively responsible for the antibacterial status of CAC- and aaCAC-mice. Reducing the frequency of hepatic M2b monocyte-derived macrophages may improve resistance to gut bacteria–induced sepsis in chronic alcoholics.

Preventing Fistula Maturation Failure

Fistula maturation failure is a concern for patients being treated with hemodialysis for end-stage renal disease. Tong et al (Am J Pathol 2017, 187:2095–2101) explored smooth muscle cell (SMC) responsiveness to the endothelium-derived vasodilator nitric oxide (NO) in maturation failure. SMCs from explants of vein tissue obtained at the time of fistula creation from 19 patients with end-stage renal disease were studied. Patients with fistula maturation success showed higher NO-induced inhibition of SMC migration than those with maturation failure. Oxidation of sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) was associated with dysregulation of NO responsiveness. SERCA oxidation was reversed by overexpressing SERCA or down-regulating Nox4-based NADPH oxidase, the reactive oxygen species–generating enzyme that oxidizes SERCA. Restoring nitric oxide responsiveness may prevent fistula maturation failure.