This Month in AJP

Modeling Jacobsen Syndrome with Haploinsufficiency

E26 transformation specific 1 (ETS1) and friend leukemia integration 1 (FLI1) genes are implicated in Jacobsen syndrome (JS), but with unclear function. Using mice heterozygous for mutant alleles of Ets1 and Fli1, alone or in combination, Carpinelli et al (Am J Pathol 2015, 185:1867–1876) modeled their role in JS. Both Fli1+/− and Ets1+/− Fli1+/− mice displayed mild thrombocytopenia and craniofacial abnormalities such as small middle ear cavity, short nasal bone, and malformed interface between the nasal bone process and cartilaginous nasal septum. They also exhibited hearing impairment, otitis media, fusions of ossicles to the middle ear wall, and deformed stapes. The functions of Ets1 and Fli1 were partially redundant, suggesting that some of the defects associated with JS are due to hemizygosity for ETS1 and FLI1.

Glypican-5 Promotes Diabetic Nephropathy

A variant in the gene encoding the cell-surface heparan sulfate proteoglycan glypican-5 (GPC5) is associated with diabetes mellitus nephropathy (DN), a major complication of type 2 diabetes mellitus. Okamoto et al (Am J Pathol 2015, 185:1889–1898) examined the functional role of GPC5 in DN in human and mouse specimens. Human diabetic kidneys showed higher expression of GPC5, which was proportional to the severity of disease. Challenge of diabetic mice with exogenous broblast growth factor 2 (Fgfr2) induced progressive proteinuria, via increased Fgf receptors (Fgr3 and -4) during high-glucose conditions, but had no effect in Gpc5 knockdown mice. The accumulation of extraglomerular Fgf2 during the progression of DN was Gpc5 dependent. Urinary GPC5 levels may thus be a useful biomarker in monitoring nephrotic deterioration in DN.

Understanding RUNX2-Mediated Vascular Calcification

Runt-related transcription factor 2 (Runx2) is critical for arterial medial calcification (AMC), a hallmark of aging, diabetes, and chronic kidney disease. Because global deletion of Runx2 in mice is perinatal lethal, Lin et al (Am J Pathol 2015, 185:1958–1969) generated smooth muscle cell (SMC)—specific Runx2 conditional knockout (KO) mice to examine the function of Runx2 in osteogenic differentiation and mineral deposition. Conditional KO mice were viable with normal bone mineralization and ossification. The SMC-specific Runx2 ablation significantly reduced vitamin D–induced AMC in abdominal aortas and common iliac arteries as compared with control mice. In contrast, SMCs were the major source of Runx2 signaling in Runx2+/− mice and were required for the vitamin D–induced changes. Pathways controlling RUNX2 expression represent potential targets for managing AMC in high-risk patients.

Connecting Cell Fusion and Oncogenesis

Whether cell fusion alone can initiate cancer remains unresolved. Zhou et al (Am J Pathol 2015, 185:2049–2060) examined the oncogenic molecular events occurring early after fusion of normal (non-neoplastic) rat intestinal crypt epithelial (IEC-6) cells. Diploid IEC-6 cells were differentially labeled with dyes, mixed, allowed to undergo fusion, and then sorted to identify fused cells. Clonal analysis revealed that cell fusion provoked aneuploidy, DNA damage, phenotypic heterogeneity, and transformation, and the capacity to form tumors was confirmed in vivo. These properties were established immediately or within a few cell divisions after the fusion event. One cell fusion event can initiate malignancy and drive tumor evolution.

Exploring Transcriptional Activity of MYC

The nucleophosphoprotein nucleophosmin (NPM) and the transcription factor MYC coregulate cell via unknown regulatory mechanisms remain. Using SK-BR3 breast cancer cells, Kim et al (Am J Pathol 2015, 185:2061–2068) explored the role of the cell-cycle nucleolar protein GLTSCR2 in regulating NPM-dependent transcriptional activity of MYC. GLTSCR2 weakly bound to NPM in the nucleolus with binding affinity improved when GLTSCR2 was induced to translocate to the nucleoplasm. Enhancing the interaction between GLTSCR2 and NPM competitively inhibited the formation of the NPM–MYC binary complex. The resultant decrease in recruitment of the NPM–MYC complex to MYC-target genes suppressed the transcriptional and transformational activities of MYC. Regulation of the oncogenic activity of MYC by GLTSCR2 may suppress the growth of cancer cells caused by MYC hyperactivation.