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This Month in *AJP*

Transforming Growth Factor-β1 (TGF-β1) Contributes to Kidney Disease

Fibrosis in the kidney leads to progressive renal failure. This fibrosis, as well as nephron degeneration, can result from high levels of TGF-β1 in the kidney tubules. To clarify the mechanisms regulating TGF-β1–mediated renal fibrosis, Koesters et al (Am J Pathol 2010, 177:632–643) overexpressed TGF-β1 in renal tubules of mice. Nephron degeneration in this system was mediated by tubular dedifferentiation and autophagic decomposition of the tubular cells, resulting in atubular glomeruli. However, there was no evidence of epithelial to mesenchymal transition (transition of tubular epithelial cells to fibroblasts and myofibroblasts), a process that is thought to be prominent in fibrosis. Taken together, these data suggest that TGF-β1 may play a novel role in autophagy of renal cells, thus contributing to renal fibrosis.

T-Cell Lymphoma Microenvironment

Peripheral T-cell lymphomas (PTCLs) are rare but have poor prognosis. Subtype differentiation of peripheral T-cell lymphomas, such as autoimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphomas not otherwise specified (PTCL/NOS), is critical for the application of specific therapeutic strategies. Tripodo et al (Am J Pathol 2010, 177:792–802) therefore examined the immunological microenvironment of PTCLs to find diagnostic criteria to differentiate AITLs and PTCL/NOS. They found that T helper 17 (Th17) cells and mast cells directly contributed to the proinflammatory microenvironment of AITLs but not PTCL/NOS. From their data, they propose that AITL cells may directly recruit mast cells, which then secrete factors that result in the proinflammatory, Th17-generating microenvironment that leads to autoimmunity in these patients.

Novel Cause for Genetic Tooth Decay

Rickets is associated with severe bone deformities, including dental ailments due to impaired dentin mineralization. Familial hypophosphatemic rickets is often caused by a mutation in the endopeptidase *PHEX* (phosphate regulating gene with homologies to endopeptidases on the X chromosome). Boukpessi et al (Am J Pathol 2010, 177:803–812) hypothesized that PHEX impairment resulted in the release of the C-terminal ASARM (acidic serine and aspartate rich motif) peptide, which is known to inhibit dentin mineralization. They observed abnormal cleavage of MEPE (matrix extracellular phosphoglycoprotein), the parent protein of ASARM, in hypophosphatemic patients. These effects were attenuated by a diet of 1-hydroxylated-vitamin D and phosphate during growth. The presence of the ASARM peptide may thus contribute to impaired dentin mineralization in rickets, in a manner compensated for by vitamin D and phosphate.

Preventing HIV-Associated Nephropathy

HIV-associated nephropathy is characterized by cell proliferation in both glomerular and tubular lesions. To determine whether mammalian target of rapamycin (mTOR), which plays a key role in cell growth, was involved in this proliferative phenotype, Kumar et al (Am J Pathol 2010, 177:813–821) examined mTOR activation in a mouse model of HIV-associated nephropathy. Both mTOR and its downstream targets were phosphorylated at higher levels in these mice as compared with controls, indicating enhanced activation of the mTOR signaling pathway. In addition, both mTOR activation and renal disease could be attenuated by treatment with rapamycin, which inhibits the mTOR pathway. This report therefore supports mTOR as a therapeutic target for HIV-associated nephropathy.

Morphine Inhibits Tumor Angiogenesis

Morphine is commonly used to treat cancer pain, but the effects of morphine use on tumor growth remain controversial. Using a clinically relevant morphine dose in a mouse model of Lewis lung carcinoma, Koodie et al (Am J Pathol 2010, 177:984–997) examined the effect of morphine use on tumor angiogenesis. They found that chronic morphine use decreased levels of tumor angiogenesis in a manner dependent on the opioid receptor. This effect was mediated by suppression of hypoxia-induced signaling, leading to a reduction in the levels of proangiogenic factors. Therefore, morphine may not only serve as an analgesic for cancer patients but may also inhibit tumor angiogenesis and growth.