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Changes in a new animal model of Ménière's disease

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Ménière's disease (MD) is a vexing malady of the inner ear function associated with recurrent vertigo, variable hearing loss, and tinnitus. Endolymphatic hydropathy is believed to be the underlying cause of these symptoms; existing models use a surgical approach to induce the condition through blockage of fluid outflow. Egami *et al* have developed a new model of MD in the guinea pig by combining electrocauterization of the endolymphatic sac with administration of desmopressin. This agonist stimulates the vasopressin type 2 receptor, inducing endolymphatic hydrops mediated by aquaporin-channel activation. The hydrops distinctly involves the cochlea and saccule while sparing the utricle and semicircular canals, similar to what is seen in the more severe form of the human disease. In addition, the guinea pigs treated with desmopressin suffered from prominent spontaneous nystagmus and balance disorders, which are rarely seen in existing surgical models of MD. The classic pathological findings of inner-ear hydropathy were also observed and quantified. The addition of desmopressin dramatically accelerates onset of severe hydropathy as a result of greatly increased fluid influx. This occurs over roughly an hour, whereas hydropathy after surgery alone takes a few weeks to present because its only cause is

endolymphatic retention. As compared with previous models, this model more fully recapitulates the features of human disease, and the study's results suggest that the rate of onset of endolymphatic hydrops may be an important factor in the pathogenesis of MD.

Distal nephron injury in urinary tract obstruction

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Congenital urinary tract obstruction is the single most important cause of chronic kidney disease in children. Previous work in humans and primates has demonstrated that fetal obstruction causes medullary injury, including interstitial expansion, α -smooth muscle actin deposition, and

collecting-duct epithelial dysfunction. There is great interest in understanding how medullary and collecting-duct injury contributes to kidney injury following obstruction. Mouse models of unilateral ureteric obstruction (UUO) are widely used because of their ease of use and the availability of many transgenic models. These are generally postnatal models, and their evaluation has focused on late damage to the proximal convoluted tubule.

Hiatt *et al* investigated the early changes associated with mouse UUO models to determine whether they were similar to those in congenital urinary tract obstruction, with the aim of better understanding how early changes contribute to its pathogenesis. They found that, even though the ureters were obstructed postnatally, the changes were indeed similar to those seen in congenital obstruction. Dilation of tubules occurs in a retrograde fashion, from distal to proximal. There was remodeling and dedifferentiation of the collecting duct and distal nephron epithelium, presumably because the repair and inhibition of further damage are enhanced by dedifferentiation. In addition, there was rapid accumulation of myofibroblasts and fibrosis in the interstitium. The authors propose that fibrosis may serve to stiffen tubules to decrease injury. Because the postnatal UUO model does a surprisingly good job of recapitulating the important features of congenital urinary tract obstruction, it could serve as a useful model for studying its pathogenesis.

Targeting *Lnk* accelerates bone-fracture healing

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Delay or failure of fracture healing results in considerable morbidity and disability. Because lack of adequate blood supply is considered a major factor, angiogenesis is a therapeutic target. Bone marrow endothelial progenitor cells are thought

to promote angiogenesis during bone healing. Therefore, it is reasonable to propose that bone marrow stem cells promote bone healing by increasing angiogenesis. Lnk, an intracellular adaptor signaling protein, is a negative regulator of the stem cell factor–c-Kit signaling pathway. Lnk-deficient mice exhibit better osteogenic and hematopoietic reconstitution, which suggests that inhibiting Lnk might enhance bone healing by increasing bone marrow function. Kawakami *et al* investigated this hypothesis in a mouse fracture model.

Because Lnk does not have enzymatic activity, it is difficult to inhibit. The authors elected to deplete it using small interfering RNA (siRNA). Interestingly, they chose to attach Lnk-specific siRNA to atelocollagen because it is taken up by both dividing and nondividing cells and is resistant to nucleases. They found that atelocollagen complexed with Lnk siRNA effectively depleted Lnk both *in vitro* and *in vivo*. Depletion of Lnk resulted in increased stem cell numbers as well as improvement in angiogenesis and osteogenesis. The bones of mice that were fractured and subsequently treated with Lnk siRNA showed an increase in mineralization and stiffness. Although the long-term effects of Lnk siRNA were not explored in this study, these results suggest that depleting Lnk via bone marrow stem cell preparations used to treat severe fractures could accelerate and improve bone healing in humans.

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nature.com/pathology

New mouse model of prostate cancer To study how ETS transcription factors collaborate with loss of PTEN, Chen and colleagues, as described in a recent article in *Nature Medicine*, generated a transgenic mouse that expressed ERG, an ETS transcription factor known to be involved in human prostatic adenocarcinoma, exclusively in the prostate. Whereas ERG expression on its own failed to induce neoplastic proliferations, when ERG was expressed in the context of PTEN loss, 80% of mice developed prostatic adenocarcinoma. Further mechanistic experiments generated data that support a pioneer model in which ERG causes local chromatin changes that facilitate androgen receptor (AR) binding to nearby but not adjacent sites, amplifying AR transcriptional output and priming prostate epithelium to cooperate with oncogenic upstream signaling caused by loss of PTEN.

Nature Medicine, published online 30 June 2013; doi:10.1038/nm.3216

Where do myofibroblasts involved in fibrosis come from?

Because fibrosis is involved in the pathogenesis of many diseases, there has been considerable interest in designing antifibrotic therapies. However, it is still not clear which cells cause fibrosis or where these cells come from. As described in a recent article in *Nature Medicine*, LeBleu and co-workers addressed these issues using genetically engineered mouse models. Using a unilateral ureteral obstruction model of renal fibrosis, they found that myofibroblasts were the predominant source of type I collagen. They also discovered that there were two main sources of myofibroblasts: 50% resulted from proliferation of resident renal tissue fibroblasts and 35% were recruited from the bone marrow. Surprisingly, only minor contributions to the myofibroblast pool were made by epithelial-to-mesenchymal transition (5%) and endothelial-to-mesenchymal transition (15%), and pericytes did not contribute at all.

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The cancer genome of ccRCC The authors of a recent article in *Nature Genetics* examined approximately 100 cases of clear-cell renal cell carcinoma (ccRCC) using whole-genome/exome, gene expression, copy-number, and methylation studies to provide an integrated snapshot of the ccRCC cancer genome. As expected, *VHL* inactivation by missense, deletion, or promoter methylation was common, but a novel mutation resulting in defective VHL-mediated proteolysis was also noted—namely, novel hot-spot mutations in *TCEB1* leading to accumulation of hypoxia-inducible factor were seen in a smaller subset of cases. Other affected pathways included PI3K/AKT/mTOR signal transduction, DNA methylation, p53-related pathways, and processing of mRNA. This study highlights multiple mechanisms for abrogating tumor suppressors or activating proto-oncogenes that can be selected and help drive tumor genesis and progression. Knowledge of these alternatives will aid testing for markers important for the stratification of ccRCC patients for treatment and prognosis.

Nature Genetics 2013;45:860–867; doi:10.1038/ng.2699

Typhoid toxin unraveled Highly purified typhoid toxin was administered to mice in a study recently reported in a letter in *Nature*. Many symptoms of typhoid fever were observed, including lethargy, stupor, malaise, weight loss, and death, although fever was absent. This toxin had an unusual structure of two covalently linked A subunits noncovalently bound to a pentameric B subunit. The two A subunits, PtA and CdtB, are homologous to the A subunits of pertussis and cytolethal distending toxins, with the latter apparently underlying most of the symptoms. In human epithelial cells, the toxin was found to bind to podocalyxin-like protein 1 (PODXL), a member of the sialomucin protein family, at the apical surface. This toxin also bound other receptors, apparently mediated by at least four major groups of surface glycans, suggesting a mechanism for the wide variety of cells and tissues affected by this scourge of humanity.

Nature 2013;499:350–354; doi:10.1038/nature12377