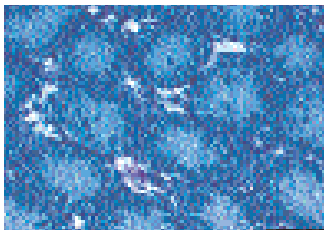
In this issue

By John Ashkenas, Science Editor

Ion transporter mutations cause testis and inner ear defects

(See article on pages 441–450.)

Pace and coworkers have targeted the mouse gene for the Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1), 1 of 2 such inwardly directed ion transporters that occur in a wide variety of tissues. These transporters apparently help regulate cell volume, and they shuttle K^+ ions into epithelial cells, permitting K^+ to be concentrated in secreted fluids. The NKCC1-deficient animals are notable both for their generally mild phenotype and for the specific effects seen on functions of the inner ear (hearing and balance) and of the testis. The former phenotypes are not surprising, since the endolymph of the ear is enriched for K^+, and mutations in other genes that disturb ionic homeostasis in the ear interfere with K^+ currents, which are required for signaling by sensory cells in the auditory and vestibular systems. The fluid of the seminiferous tubule also contains high concentrations of K^+, and mutant mice are delayed in their formation of the lumen of this structure. Testes of these males are nearly devoid of mature sperm. Because both the Sertoli cells that line this tubule and germ cells themselves express NKCC1, it is not clear whether the defect is intrinsic to spermatocytes or secondary to changes in the seminiferous tubule. No defect in ion excretion is evident in these mutant mice, but another recently described *NKCC1* mutant line showed a more severe phenotype that included hypotension. The divergent findings may reflect background genotype differences, which could be of use in defining additional mechanisms that ion transport in the kidney.



A novel role for dynein in RNA regulation

(See article on pages 505–512.)

The 3′ untranslated regions (UTRs) of many mRNA species are comparably, or even better, conserved across species than are the corresponding coding sequences, but the functions of the 3′ UTR such sequences are mysterious in most cases. Epstein et al. previously showed that the distal 60 nucleotides of the parathyroid hormone mRNA interact specifically with as-yet unidentified proteins of the parathyroid, and they argued that those interactions modulate the stability of this mRNA in response to altered blood calcium levels. Now they have used this 3′ UTR as a probe to identify additional mRNA-binding proteins, and they show that 1 of the subunits of the microtubule motor dynein interacts with this same 60-nucleotide region. Whether this dynein subunit, LC8, affects mRNA stability is uncertain, but the authors show that it is not among the previously characterized binding proteins. The novel RNA-protein interaction causes the mRNA to associate with purified microtubules in an ATP-dependent manner, suggesting that it could help regulate the subcellular distribution of this message. Since mRNA association with the cytoskeleton correlates with translation, this interaction might also affect the translatability of the mRNA.

Integrin signaling required for bone resorption

(See article on pages 433–440.)

McHugh and collaborators previously disrupted the gene for the mouse β3 integrin, establishing a faithful model of the human bleeding disorder Glanzmann's thrombasthenia. This condition arises when either subunit of the αIIbβ3 integrin is lacking. Studies of thrombasthenic platelets have provided some of the earliest and clearest evidence that integrins not only bind extracellular matrix (ECM) proteins, but also convey information about adhesive interactions to cytoplasmic signaling proteins and the actin cytoskeleton. Here, the same group exploits these knockout animals to pursue the role of a related integrin, αvβ3, which they now show serves as a signal in osteoclasts. Revisiting findings made using inhibitors of αvβ3, McHugh et al. show that as β3-deficient mice age, bones grow abnormally dense and circulating calcium levels are low, suggesting that osteoclast-mediated bone resorption is inadequate. Osteoclasts in these animals differentiate proficiently from bone marrow macrophages, and they accumulate to unusually high numbers, but they fail to interact properly with bone ECM. During adhesion, β3-deficient osteoclasts fail to spread or to reorganize their actin cytoskeleton; when cultured on a calcified substratum, they degrade the material inefficiently, excavating only shallow tracks in it. In vivo, these cells do not respond to bone matrix, as normal osteoclasts do, by developing a ruffled membrane—the specialized membrane structure that allows them to create an acidic microenvironment conducive to degrading bone matrix. Thus, as with αIIbβ3, αvβ3-dependent signaling seems to promote changes in the cytoskeleton underlying the plasma membrane. Whether thrombasthenic patients with defects in the β3 subunit are also osteosclerotic or hypocalcemic does not seem to have been studied.