In this issue

Pseudohypoparathyroidism, $G_S\alpha$, and imprinting

(See article on pages 1167–1174)

Pseudohypoparathyroidism (PHP) is the general term for a group of related disorders in which there are clinical and biochemical features of hypoparathyroidism, such as hypocalcemia and hyperphosphatemia, despite high circulating levels of parathyroid hormone (PTH). In individuals affected by the type IA variant of PHP (PHPIA), there are heterozygous mutations in the α subunit of the stimulatory G protein ($G_S\alpha$), and patients show resistance not only to PTH, but also to other hormones dependent on $G_S\alpha$ signaling from activated receptor to adenyl cyclase. The gene for $G_S\alpha$, known as *GNAS1*, is known to be imprinted paternally; i.e., PHPIA only occurs if a defective *GNAS1* allele is inherited from an affected female. Another form of PHP, known as PHPIB, is usually sporadic but is sometimes familial. Individuals with PHPIB manifest PTH resistance in the kidney, but show no other endocrine abnormalities, and $G_S\alpha$ function in peripheral blood cells is normal in PHPIB patients. Nevertheless, in four families with PHPIB, the *GNAS1* gene was found to be linked to the disorder, though coding region mutations in *GNAS1* were excluded in the four linked families and the vast majority of PHPIB patients. These interesting observations, together with the finding that in mouse renal proximal tubule (the site of PTH action) $G_S\alpha$ is produced only from maternal allele transcripts, prompted Liu et al. to pursue detailed studies of *GNAS1* imprinting in PHPIB patients. *GNAS1* is a complex gene encoding multiple different transcripts and protein products, as a result of the use of four alternative promoters and first exons. The most downstream of the four promoters produces transcripts encoding $G_S\alpha$. Liu et al. report that a region upstream of the $G_S\alpha$ promoter and associated with the promoter for *GNAS1* exon 1A, which generates transcripts of unknown function, is normally methylated on the maternal allele and unmethylated on the paternal allele. Remarkably, the exon 1A region was found to be unmethylated on both alleles in all 13 PHPIB patients studied. Moreover, while the exon 1A alternative promoter is normally only active on the paternal allele, in PHPIB patients, the exon 1A promoter was active on both paternal and maternal alleles. The authors hypothesize that loss of imprinting in the exon 1A region in PHPIB patients results in decreased $G_S\alpha$ expression in renal proximal tubules. Attention will now be focused on defining mutations at or near the *GNAS1* locus that lead to the loss of imprinting in the upstream region, as well as on mechanisms that regulate imprinting and expression at the *GNAS1* locus in renal proximal tubule and other cells.

Nurture versus nature: IL-13 as an endogenous mediator of COPD

(See article on pages 1081–1093)

Chronic obstructive pulmonary disease (COPD) affects 16 million people in the US alone and is one of the four leading causes of death worldwide. While COPD occurs predominantly in cigarette smokers, only 10–15% of active smokers develop the disease. Almost 40 years ago, it was proposed that endogenous, rather than exogenous, factors might play an important role in the development of COPD (the so-called "Dutch Hypothesis"). Noting that many COPD patients exhibit asthmalike symptoms, investigators pondered whether common mechanisms might contribute to the pathogenesis of both disorders. Now, Zheng and coworkers demonstrate that IL-13, a Th2 cytokine recently linked to asthma, can induce COPD in an in vivo murine model. Using an externally regulable, lung-targeted transgenic model, IL-13 expression caused a lung-destructive phenotype that mirrored human COPD with mucus metaplasia, inflammation, and emphysema. Using this powerful model system, their efforts then focused on delineating the roles of various proteinases that have been previously associated with alveolar destruction in emphysema. In a tour de force, the authors demonstrate not only that IL-13 stimulates the expression of a wide range of tissue-destructive matrix metalloproteinases and cysteine proteinases, but that synthetic inhibitors directed at each class of enzymes can alone, or in combination, exert powerful protective effects in vivo. The authors suggest that IL-13 may prove to be an important endogenous risk factor for COPD, and that matrix metalloproteinase as well as cysteine proteinase could play key roles in mediating the associated tissue-destructive effects in vivo.

Lysosomal cathepsin B mediates apoptotic cell death

(See article on pages 1127–1137)

Mitochondria are previously established, but unexpected players, in TNF-α–induced apoptosis. Following the assembly of a TNF-TNF receptor complex, caspase cascades are activated which converge at the mitochondrial level, provoking the translocation of cytochrome *c* to the cytoplasm. In turn, cytochrome *c* binds the CED-4 homologue, Apaf-1, which recruits caspase 9 to generate the "aptosome," a critical activator of the final effector caspases. In a variant of this model, Guicciardi and coworkers now demonstrate that a second intracellular organelle, the lysosome, may also participate in apoptotic cell death by acting as a reservoir for the cysteine proteinase cathepsin B. Cathepsin B, a member of the cysteine proteinase family, is normally confined to the lysosomal system where its major intracellular role has long been assumed to be confined to the proteolytic degradation of internalized proteins. In this new model, TNF-α initiates the caspase-8–dependent release of lysosomal cathepsin B to the cytosol where the cysteine proteinase then collaborates with other unidentified species to promote cytochrome *c* release from mitochondria. In support of their construct, hepatocytes isolated from cathepsin B–deleted mice were shown to display a significant resistance to TNF-α–induced apoptosis in vitro. Perhaps even more strikingly, cathepsin B–deleted animals survived a TNF-α treatment protocol that was uniformly lethal to similarly treated control littermates. While many of the details of this new cell-death cascade remain to be characterized, the findings suggest that cathepsin B might represent a new therapeutic target for reducing inflammation-induced hepatocellular damage.