

## In This Issue

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A growth factor found in the nucleus of proliferating cells (See article on pages 567–575.) As its name suggests, hepatoma-derived growth factor (HDGF) was first identified in the supernatant of transformed cells in culture, but this protein is broadly expressed and promotes the proliferation of multiple cell types. Everett et al. have cloned a rat cDNA for HDGF and, following up on hints that it drives vascular cell growth, they have begun to explore the expression and activity of this poorly understood growth factor, especially its role in smooth muscle cells (SMCs). Cultured SMCs induce HDGF mRNA in response to mitogenic signals, and exogenous HDGF protein can prompt formerly quiescent cultures of SMCs to reenter the cell cycle. Normal aortic SMCs also express this protein under conditions of cell growth, activating its synthesis during cardiac development and in response to vascular injury but repressing it to nearly undetectable levels in healthy adult tissue. Rat arteries denuded of endothelial cells, as well as human atherosclerotic lesions, stain for HDGF, suggesting that suppressing HDGF function could control pathological SMC overgrowth. Remarkably, SMCs in culture or in vivo accumulate HDGF in their nuclei, where it codistributes with the proliferating cell nuclear antigen. The intracellular events that allow the HDGF to enter the nucleus are not known, but its sequence contains a putative nuclear [...]

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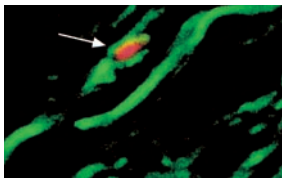
# In this issue

By John Ashkenas, Science Editor

## A growth factor found in the nucleus of proliferating cells

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## GNAS1 imprinting makes mice lean — or obese

(See article on pages 615–623.)

The ubiquitously expressed  $\alpha$  subunit of the heterotrimeric G protein  $G_s$  activates various second messenger systems in response to stimulation from multiple signal-transducing receptors, so it is not surprising that mice lacking all  $G_s\alpha$  expression die early in embryogenesis. However, the *GNAS1* locus is complex and encodes at least 2 other proteins,  $XL\alpha$ s and  $NESP55$ , in addition to  $G_s\alpha$ . The 3 gene products are expressed differentially from the maternal or paternal

alleles in specific cell types, so a mouse carrying a disrupted allele of *GNAS1* would be predicted to express different subsets of these proteins in different tissues, depending on whether it inherits the mutation from its mother or father. Yu et al., who previously disrupted the *GNAS1* gene and described its essential nature, now revisit the most prominent phenotypes seen in heterozygous animals, namely, differences in adiposity from wild-type littermates. Mice carrying the disruption on their maternal allele (denoted  $m^{-/+}$ ) often die several weeks after birth, but survivors have a low resting metabolic rate and are relatively inactive and obese. Their brown adipose tissue (BAT) is poorly developed, with few mitochondria and low expression of the uncoupling protein UCP1, suggesting that they are unable to dissipate excess calories in their diet as heat. Disruption of the paternal allele in  $+/p^{-}$  mice causes significant mortality shortly after birth, but survivors show a phenotype nearly opposite that of  $m^{-/+}$  animals: hypermetabolism, low adiposity, and highly active BAT with copious mitochondria and UCP1 expression.  $m^{-/+}$  animals seem to provide a faithful model of humans who carry maternally derived mutations in *GNAS1*. However, the effect of the paternally transmitted mutation differs between mice and humans, perhaps reflecting a more prominent role of BAT in energy balance in rodents.

## A versatile method to generate autoimmune disease models

(See article on pages 625–631.)

Amagai et al. have created a model for the autoimmune blistering disorder pemphigus vulgaris (PV). In this disease, antibodies to the desmoglein 3 (Dsg3) protein weaken intercellular adhesion within stratified epithelia like the skin. Taking advantage of the fact that mice genetically deficient in Dsg3 lack the usual tolerance for this protein, Amagai and colleagues immunized *Dsg3* knockout mice with recombinant Dsg3 and transferred their splenocytes into host animals that expressed the antigen normally. Crucially, the host animals carried a targeted mutation in the *Rag2* gene and were therefore immunodeficient, so the transferred splenocytes were not rejected, but persisted over many months. As predicted, the host animals developed many of the features of PV, including blistering on the skin and in the mouth. A similar strategy could be devised to produce autoimmune disease targeting any antigen whose gene has been disrupted, as long as the knockout model is viable and immunocompetent.

