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In This Issue

John Ashkenas

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Leptin and obesity: all in the head? (See article on pages 1113–1121.) In the absence of leptin signaling, mice, like humans, grow extremely obese and develop many of the common sequelae of obesity in humans, such as diabetes and steatosis of the liver. Introduction of leptin directly into the hypothalamus potently reverses the overeating and obesity seen in leptin-deficient animals. Still, expression of the leptin receptor ObR is not limited to the hypothalamus and other regions of the brain but also occurs in the liver and many other sites. Hence, the possibility remains that some aspects of the leptin-deficient phenotype reflect the absence of peripheral signaling. To test the significance of various sites of central and peripheral leptin signaling, Cohen et al. have used Cre-lox technology to generate mice in which particular cell types delete the ObR gene by somatic recombination. Here, they describe the effects of ObR deficiency in the brain or the liver. Absence of neuronal ObR greatly increases body weight and induces the accumulation of fat in the liver, effects that are not seen when the ObR defect is restricted to the liver. Because obesity in the brain-specific knockout is not as severe as that in simple knockouts, it may be that OBR signaling in organs helps regulate energy homeostasis – effects that may still be revealed […]

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By John Ashkenas, Science Editor

Leptin and obesity: all in the head?

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In the absence of leptin signaling, mice, like humans, grow extremely obese and develop many of the common sequelae of obesity in humans, such as diabetes and steatosis of the liver. Introduction of leptin directly into the hypothalamus potently reverses the overeating and obesity seen in leptin-deficient animals. Still, expression of the leptin receptor ObR is not limited to the hypothalamus and other regions of the brain but also occurs in the liver and many other sites. Hence, the possibility remains that some aspects of the leptin-deficient phenotype reflect the absence of peripheral signaling. To test the significance of various sites of central and peripheral leptin signaling, Cohen et al. have used Cre-*lox* technology to generate mice in which particular cell types delete the *ObR* gene by somatic recombination. Here, they describe the effects of ObR deficiency in the brain or the liver. Absence of neuronal ObR greatly increases body weight and induces the accumulation of fat in the liver, effects that are not seen when the ObR defect is restricted to the liver. Because obesity in the brain-specific knockout is not as severe as that in simple knockouts, it may be that OBR signaling in organs helps regulate energy homeostasis — effects that may still be revealed in other Cre-*lox* experiments. However, the authors note that there was considerable scatter in their data and that those animals that had most efficiently removed the *ObR* gene from their neurons weighed the most. The complete absence of neuronal ObR, if it could be achieved using this technology, might therefore recapitulate all of the effects observed in Ob- or ObR-deficient animals.

Developmental control of tumor suppressor gene methylation

(See article on pages 1195–1204.)

Methylation at CpG dinucleotides, the best-understood epigenetic mechanism in mammals, allows cells to silence transcription of particular genes in a relatively stable manner. The inverse correlation between gene expression and methylation levels at CpG islands (promoter elements enriched in CpG sequences) has been seen in several contexts. For instance, the persistent silencing of one allele of imprinted genes or large regions of one X chromosome in normal female cells is associated with hypermethylation. A similar process seems to be at work during tumorigenesis in the epigenetic silencing of certain growth inhibitory genes. This effect has been documented with the tumor suppressor genes *p16* and *p15*, whose products INK4a and INK4b are well known inhibitors of cyclin-dependent kinases. These genes each carry CpG islands in their promoters, which become hypermethylated in various tumors. Sakashita et al. now show that this process mirrors events in normal development, when *p15* is silenced by methylation during hematopoesis. Methylation, they find, occurs in an all-or-none fashion throughout the CpG island and correlates with a developmental switch whereby hematopoietic precursor cells become committed to forming granulocytes and monocytes. This epigenetic change is transient and apparently specific for *p15*, since *p16* remains unmethylated throughout. The authors also show that global inhibition of CpG methylation favors the proliferation of hematopoietic precursor cells and blocks their differentiation along the myeloid lineage. This work raises critical questions about the nature and regulation of the demethylases that erase *p15* methylation in these cells.

Regulation of host responses by a bacterial peptide

(See article on pages 1221–1228.)

Helicobacter pylori, like many other pathogenic bacteria, secretes antibiotic substances that give it a competitive advantage over other species for growth in its host's tissues. One such antibiotic is a peptide termed Hp(2-20), a relative of the antibacterial protein cecropin, which is expressed by eukaryotes as diverse as flies and mammals. Betten and colleagues now show that Hp(2-20), a cleaved fragment of an *H. pylori* ribosomal protein, also acts directly on the host immune system, apparently allowing the bacterium to alter the course and outcome of an infection. This peptide stimulates monocytes via at least two related receptors, FPRL1 and 2. Activated monocytes respond with a burst of reactive oxygen species, which are not only toxic to bacteria, but also potentially carcinogenic to the host. Subsequent changes in NK cell function may also favor the formation of gastric tumors in *H. pylori* carriers, since exposure of these cells to oxygen radicals alters their pattern of gene expression and impairs their ability to activate antitumor immune responses. Interestingly, the high endogenous levels of histamine in the gastric mucosa appear to block the accumulation of these harmful metabolites, suggesting that histamine helps prevent gastric tumorigenesis in infected individuals.