## Drug resistance in cancer

**Activation of the Hedgehog (Hh) signaling pathway increases in medulloblastoma. Charles Rudin and colleagues report that administration of the Hh inhibitor GDC-0449 to an individual with metastatic medulloblastoma led to rapid (although temporary) tumor regression (*New Engl. J. Med.*, published online 2 September 2009; doi:10.1056/NEJMoa0902903). Molecular profiling of the tumor before treatment showed elevated expression of four Hh pathway target genes and mutation of the Hh receptor *PTCH1*. Despite significant tumor regression at all prior sites of the disease, tumor regrowth was observed three months after GDC-0449 treatment. In a parallel study, Robert Yauch and colleagues investigated the molecular mechanism of relapse in the same individual (*Science*, published online 3 September 2009; doi:10.1126/science.1179386). The authors identified a heterozygous missense mutation affecting another Hh pathway component, Smoothened (SMO), in a biopsy sample taken after relapse but did not detect the mutant allele in any normal or cancer tissue before GDC-0449 treatment. The *SMO* mutation had no effect on transduction of the Hh signal but disrupted the ability of GDC-0449 to bind SMO and suppress Hh signaling. Together, the studies show that GDC-0449 may offer an effective treatment for medulloblastoma, but they also emphasize the need to identify other drugs that could help patients who acquire GDC-0449 resistance.** *PC*

## IKKε and obesity

Although obesity and diabetes are associated with chronic inflammation, the molecular mechanisms that link inflammation to these conditions are not well understood. Alan Saltiel and colleagues report (*Cell* **138**, 961–975, 2009) that mice fed a high-fat diet have elevated IKKε expression in liver, adipose tissue and adipose tissue macrophages. Although IKKε knockout (KO) mice showed higher daily food intake than wild-type mice, KO mice were protected from obesity when fed a high-fat diet (HFD). The authors found that IKKε KO mice have significantly greater $O_2$ consumption, higher levels of the mitochondrial uncoupling protein UCP1 in white adipose tissue, and warmer body temperatures than wild-type mice fed a HFD, suggesting that the IKKε KO mice have higher energy expenditure. Although a HFD typically induces higher fasting glucose and insulin levels, IKKε KO mice did not show such increases, and they also had lower fatty acid and cholesterol levels than wild-type mice on a HFD. IKKε KO mice on a HFD also showed lower serum levels of three proinflammatory cytokines and reduced activation of the proinflammatory JNK pathway, indicating that loss of IKKε likely prevents inflammation that occurs in response to high-fat diets. The authors propose that IKKε may be an attractive target for anti-obesity drugs. *PC*

## Furry genes

Elaine Ostrander and colleagues report genome-wide association studies in over 1,000 dogs of 80 domestic breeds to three canine coat phenotypes of texture, length and curl (*Science*, published online 27 August 2009; doi:10.1126/science.1177808). For each trait, the authors genotyped dog breeds segregating the relevant coat phenotype using the Affymetrix version 2 canine SNP chip, and replicated the association in the CanMap dataset across different breeds. They continued with fine mapping and sequencing to resolve a single mutation associated with each trait. The authors showed that an insertion within the 3′ UTR of *RSPO2* is associated with the presence of a moustache and long eyebrows, which are characteristic of wire-haired dogs. A SNP in an exon of *FGF5* was found to be associated with long hair, following earlier associations of this gene to hair growth in mice and cats. Curly coat was associated to a SNP in *KRT71*, which encodes a keratin that has also been implicated in curly coat in mice. Combinations of these three mutations generated seven different coat phenotypes and together explained the coat phenotype of 95% of dogs in these studies. *OB*

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## First vertebrate PRE identification

Polycomb proteins are important in the regulation of gene expression in development and differentiation, but identifying sequence elements that recruit Polycomb proteins in vertebrates has been difficult. Now, Sabine Cordes and colleagues report the first identification of a vertebrate Polycomb response element (PRE) (*Cell* **138**, 885–897, 2009). The authors hypothesized that the mouse *kreisler* inversion (*kr*), which disrupts expression of the *Mafb* and *Nnat* genes in embryonic hindbrain rhombomeres, may affect a PRE. They used a *Drosophila in vivo* reporter assay to map silencing activity to a 3-kb region, called PRE-*kr*, and showed that mutations in *Drosophila* Polycomb proteins interfere with silencing activity. Investigations of PRE-*kr* in cultured mouse teratocarcinoma cells revealed that the Polycomb proteins Bmi1 and SUZ12 bind PRE-*kr*, and PRE-*kr* can recruit Bmi1 to ectopic sites. Bioinformatic analysis wasn't able to identify candidate PRE sequences based on known *Drosophila* PREs, but it revealed a region conserved between human, mouse and chick that contains consensus binding sites for the YY1 Polycomb protein. Although further work will be required to determine the extent to which PRE-*kr*–mediated recruitment of Polycomb proteins directs position-dependent gene expression, the identification of an entry site for Polycomb proteins in vertebrate genomes is an important step for the field. *EN*

## Y chromosome rearrangements

**Decay of the male-specific region of the human Y chromosome (MSY) is prevented, in part, through intrachromatid gene conversion events mediated via homologous recombination between opposing arms of large palindromic sequences, which comprise roughly 25% of MSY euchromatin. A new study by David Page and colleagues (*Cell* 138, 855–869, 2009) shows that aberrant interchromatid recombination events between palindromes can give rise to isodicentric Y chromosomes and sex disorders. The authors examined DNA samples from 1,550 men with spermatogenic failure and 830 additional individuals with Y chromosome abnormalities or sex reversal for the presence of isodicentric Y chromosomes. From this survey, they identified 60 individuals harboring such chromosomes, of which 51 apparently arose through interchromatid recombination events between opposing palindromes. Notably, 58 individuals had two copies of the testis-determining gene *SRY*, and among these 18 showed some degree of male-to-female sex reversal. The authors further noted that sex reversal correlated with increased intercentromeric distance and evidence of XO mosaicism, suggesting that sex reversal arose in these individuals through mitotic loss of the unstable isodicentric Y chromosome in the gonadal lineage. These findings highlight the range of disorders that can arise through aberrant recombination events in the MSY.** *KV*