Beach mouse coat color evolution

Wild populations of deer mice (genus *Peromyscus)* vary in coat color, with mainland mice having a dark dorsum and a light ventrum. In contrast, recently colonized populations of beach mice have lighter coat colors and pigmentless faces, flanks and tails. Hopi Hoekstra and colleagues now report that *Agouti*, a well-known negative regulator of pigmentation, is the causal gene in coat color differences between mainland and beach mice (*Science* 331, 1062, 2011). Previously, three quantitative trait loci, including a quantitative trait locus containing *Agouti*, were shown to explain most coat color variation between mainland and beach mice. As there are no coding differences between beach and mainland mice Agouti sequences, the authors examined allele-specific expression of *Agouti* in different tissues. In the ventral skin of F1 hybrids, the beach mouse allele is expressed 17-fold higher than the mainland mouse allele. However, no allele-specific expression differences were observed in the testes, suggesting *cis*-regulatory mutations in *Agouti* are involved in coat color differences. *Agouti* was ectopically expressed in mainland beach embryos using ultrasound-assisted retroviral infection *in utero*. Although the effects on coat color in *Peromyscus* adults were not measured, ectopic expression of Agouti appeared to prevent the terminal differentiation of melanocytes and thus led to an absence of pigment production. ***PC***

Hedgehog signals in aggressive pontine glioma

Diffuse intrinsic pontine glioma (DIPG) is an extremely aggressive and fatal cancer. DIPGs typically occur during a specific time in childhood and are restricted to the ventral pons. Due to the lack of tumor samples and an appropriate animal model, little is known about DIPG, and no advances in treatment have been made in 35 years. Now, Michelle Monje, Phillip Beachy and colleagues identify a population of OLIG2+ neural precursor-like cells in the ventral pons that is present at the appropriate time and place coincident with DIPG (*Proc. Natl. Acad. Sci. U.S.A.*, published online, doi:10.1073/pnas.1101657108, 1 March 2011). Using DIPG tissue from a pediatric donor, the authors isolated Olig2+ cells consistent with the neural precursor-like cell type and transplanted them to mice. The resulting brain tumors had histopathology consistent with high-grade glioma. Similar to the unique biology of DIPG, infiltrating tumor cells were found in the brainstem. Using the same Olig2+ cells isolated from the donated tumor, the authors found evidence of active Hh signaling. Culturing these cells in the presence of an Hh antagonist reduced their self-renewal capacity, whereas activating Hh signaling appeared to increase self-renewal capacity. The authors suggest the Hh signaling pathway as a candidate therapeutic target in this deadly pediatric tumor. *PC*

Cancer epigenomics

Epigenetic alterations are known to be common in cancer, and comprehensive genomic maps of epigenomic alterations in cancer are eagerly anticipated. Now, Andrew Feber, Adrienne Flanagan, Stephan Beck and colleagues report a comparative DNA methylome analysis of peripheral nerve sheath tumors (*Genome Res.* published online, doi:10.1101/gr.109678.110, 1 February 2011). The authors used methylated DNA immunoprecipitation and next-generation sequencing to profile methylation in pools of genomic DNA from benign neurofibromas, malignant peripheral nerve sheath tumors (MPNSTs) and normal Schwann cells. Global hypomethylation is thought to be a common feature of tumors, but the authors found no evidence of global hypomethylation in the MPNSTs. However, they observed general loss of methylation of satellite repeats. Interestingly, regions of differential methylation between MPNSTs and normal Schwann cells were preferentially located in CpG island shores and in promoters not associated with CpG islands, but not in CpG islands themselves. Finally, the authors integrated their methylation data with published expression profiles of neurofibromas and MPNSTs. These analyses showed that the expression of genes located near differentially methylated regions located in CpG island shores and in non-CpG island promoters could discriminate between neurofibromas and MPNSTs. *EN*

KCNJ5 and aldosteronism

Aldosterone-producing adrenal adenomas (APAs) are benign tumors that result in constitutive hormone production and severe hypertension. A new study by Rick Lifton and colleagues (*Science* **331**, 768–772, 2011) shows that these tumors frequently harbor somatic mutations in the K^+ channel gene *KCNJ5*. The authors performed whole-exome sequencing of four APAs and matched blood samples and found two somatic mutations in *KCNJ5* affecting conserved residues located in or near the channel's selectivity filter. They followed up by sequencing *KCNJ5* in 18 additional APAs and identified the same two mutations (resulting in p.Gly151Arg or p.Leu168Arg) in six different tumors. Functional assays showed that both mutations result in loss of channel selectivity, increased Na^+ conductance and membrane depolarization. Next, the authors tested whether germline *KCNJ5* mutations might be responsible for a monogenic form of primary aldosteronism with bilateral adrenal hyperplasia. They sequenced *KCNJ5* in a family with an affected father and two affected daughters and identified a heterozygous mutation (resulting in p.Thr158Ala) causing a similar reduction in channel selectivity. The authors hypothesize that the membrane depolarization resulting from the *KCNJ5* mutations triggers activation of voltage-gated Ca^{2+} channels, leading to constitutive aldosterone production and deregulated growth. *KV*

Testing rare variant association

The increase in targeted resequencing, exome and whole-genome sequencing studies has highlighted a need for methods to test for rare variant associations. Several recently reported statistical tests for rare variant association, called 'burden tests', seek to increase power by combining across variants within a target region. Following on these, Benjamin Neale and colleagues now report an application of the C-alpha score-test to test for rare variant association within a target region using individual sequence data from a case-control study (*PLoS Genet.* 7, e1001322, 2011). In comparison to the previous burden tests, the C-alpha statistic tests for the variance instead of the mean. This approach tests for overdispersion in the number of variants in cases relative to controls compared to the expected binomial variance. They estimate a mixture model from the distribution of the direction of effects of the variants tested and the posterior probability of whether a particular variant has a risk, protective or neutral effect. Simulations show that when there is a mixture of protective and risk variants, the C-alpha test has greater power than burden tests and does not compromise power when effects are all in the same direction. ***OB***

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