Cataloging inversions

Polymorphic structural variants, in the form of deletions, duplications and inversions, are unexpectedly common in the human population. Steve Scherer and colleagues (*PLoS Genetics*, published online 29 September 2005; doi:10.1371/journal.pgen.0010056.eor) now report the discovery of three new polymorphic inversions and a large number of candidate inversions through comparative analysis of human and chimpanzee genome assemblies. The authors identified 1,576 sequences, ranging from 23 bp to 62 Mb, present in opposite orientations in the human Build 35 and chimp draft sequence assemblies. They examined 27 of these candidates by fluorescence *in situ* hybridization or PCR and validated 23 as true inversions. They then surveyed these 23 human-chimp inversions in ten individuals from the Centre d'Etude du Polymorphisme Humaine study and found three that were polymorphic in the human samples. The largest of these, on 7p22, is 730 kb, spans more than 15 genes and shows a minor allele frequency of 5%. The second largest, on 7q11, is 13 kb and shows a minor allele frequency of 30%. Notably, the 7q11 inversion is in perfect linkage disequilibrium with a SNP present in the inverted segment, suggesting that SNPs could be used as surrogates for common inversion polymorphisms in disease association studies. ***KV***

Copy number polymorphism and testicular cancer

The MSY region of the Y chromosome contains many genes that exist in multiple copies and are important for germ cell development. Microdeletions that create copy number polymorphisms for genes in this region are associated with infertility due to spermatogenic failure. Several epidemiological lines of evidence suggest that there is a link between infertility and testicular germ cell tumors (TGCTs), which are the most common cancer in young men and have a strong genetic component to susceptibility. This link led Katherine Nathanson and colleagues to investigate the contribution of the most common MSY microdeletion associated with infertility, the gr/gr deletion, to susceptibility to TGCTs (*Am. J. Hum. Genet.*, in the press). Using cohorts of mostly European ancestry, the authors show that the gr/gr deletion is associated with a twofold increased risk of TGCTs. The association is stronger for cases with the seminoma type of TGCT, and for cases with a family history of TGCTs. Overall, the gr/gr deletion was identified in 3% and 2% of cases with and without a family history, respectively, and 1.3% of unaffected males, indicating that this polymorphic variant confers a small but measurable risk of TGCTs and probably acts in combination with other genetic factors. *EN*

Secrets of the 1918 influenza virus

Several new research studies published concurrently in *Science* and *Nature* provide new insight into the origin and virulence of the 1918 influenza virus, the cause of the Spanish flu pandemic and estimated to be responsible for 50 million deaths worldwide. Jeffrey Taubenberger and colleagues report the full genome sequence of the 1918 flu virus, including the final three genes (encoding polymerases) not previously published (*Nature* **437**, 889–892; 2005). The full sequence of the virus's eight genes supports the previous notion that the virus was purely avian in origin, as opposed to a reassortment of human and avian viral sequences. Ten sequence changes in polymerase proteins were consistently found to distinguish the 1918 and later human influenza sequences from avian viral sequences, suggesting these regions may have been important in allowing the virus to adapt to infect humans. Terrence Tumpey and colleagues used this final genome sequence to recreate the 1918 flu virus and studied its virulence in mice (*Science* **310**, 77–80; 2005). The strain showed very high virulence, killing mice in 3–5 d, with virus levels more than 50 times greater than observed for other infectious strains. Tumpey also found that the 1918 hemagglutinin and polymerase genes were required for the highly increased virulence observed in comparison to other influenza strains. *OB*

Gli proteins in cilia

Intraflagellar transport (IFT) proteins function as key regulators of vertebrate Hedgehog (Hh) signaling, but their exact role in Hh signal transduction remains obscure. New work by Brad Yoder and colleagues (*PLoS Genetics*, published online 26 September 2005; doi:10.1371/journal.pgen.0010053.eor) provides insight into this question by showing that Gli proteins, downstream mediators of Hh signaling that act in the nucleus to regulate target gene transcription directly, colocalize to the distal tip of cilia in limb bud cells. Limb bud cells deficient in the IFT protein Polaris are unable to produce efficiently the truncated repressor form of Gli3, which acts an important negative regulator of Hh target genes in the absence of pathway stimulation. By examining the subcellular localization of Gli proteins fused to GFP, they found that all three full-length Gli proteins colocalized with another Hh signaling component, Suppressor of Fused (SuFu), at the distal tip of cilia in primary limb bud cells. They further confirmed the ciliary localization of Gli3 and SuFu by immunofluorescence against the endogenous proteins. In contrast, the truncated repressor form of Gli3 did not localize to cilia. These findings suggest that cilia might directly couple the reception of Hh signals to the activation of downstream signaling components. *KV*

Stress and the beta cell

The forkhead transcription factor FoxO1 is a key regulator of pancreatic beta cell mass. Yukari Ido Kitamura and colleagues now show that it also protects against beta cell failure in response to acute oxidative stress (*Cell Metab.* 2, 153–163; 2005). FoxO1 typically shuttles between the nucleus and cytoplasm, but the authors show that incubation of beta cells with hydrogen peroxide induces predominantly nuclear localization. This redistribution is accompanied by the direct activation of NeuroD and MafA, two transcription factors that regulate insulin II gene expression. They also observed interaction of FoxO1 with nuclear Pml bodies, which targets FoxO1 for ubiquitin-mediated degradation. These data are tied together in a model for regulation of FoxO1. In response to hyperglycemia or oxidative stress, FoxO1 is acetylated and localized to Pml bodies. This blocks both ubiquitination of FoxO1 and its transcriptional activity. Association with Pml bodies then results in deacetylation of FoxO1 by Sirt1, leading to FoxO1-dependent transcription and rapid degradation of FoxO1. The authors propose that this mechanism may allow for the protection of beta cells against acute stress but not against the chronic effects of prolonged hyperglycemia, itself a cause of oxidative stress. ***AP***

Research Highlights written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan.