RPGRIP1L, *FTO* and obesity

RPGRIP1L **is one of several genes located in the obesity-associated** ***FTO*** **region, and the risk-associated SNP in intron 1 of** ***FTO*** **has been proposed to influence** ***RPGRIP1L*** **expression. To further evaluate a potential role for** ***RPGRIP1L*** **in obesity-related traits, George Stratigopoulos, Rudolph Leibel and colleagues (*Cell Metab.* 19, 767–779, 2014) examined the phenotype of mice heterozygous for a null allele of** ***Rpgrip1l*****. They found that these mice exhibited increased weight gain and markedly increased adiposity, accompanied by increased energy intake and increased serum leptin levels. Because RPGRIP1L has previously been implicated in regulating trafficking of the leptin receptor (Lepr) to cilia, the authors examined the hypothalamus in** ***Rpgrip1l*** **heterozygous mice and observed reduced levels of Lepr ciliary localization and of downstream markers of leptin signaling. They also observed increased expression of orexigenic genes encoding Neuropeptide Y (*Npy*) and Agouti-related protein (*Agrp*) in the hypothalamus of** ***Rpgrip1l*** **heterozygous mice compared to wild-type controls. These findings support the hypothesis that the effects of the obesity-associated SNP in the** ***FTO*** **region might be mediated, in part, through altered** ***RPGRIP1L*** **expression and downstream effects on leptin signaling.** ***KV***

RGS2 rescues LRRK2 pathogenicity

Mutations in *LRRK2* are associated with risk of Parkinson's disease. James Collins, Benjamin Wolozin and colleagues have now used a systems biology approach to find new regulators of *LRRK2* (*Hum. Mol. Genet.* doi:10.1093/hmg/ddu202, 2 May 2014). They integrated data from 119 publicly available microarray experiments using RNA from the brain and blood of individuals with Parkinson's disease and controls to build a coexpression network centered on *LRRK2* that confirmed known interactions and predicted many new regulators. To validate these predictions, the authors targeted 181 *Caenorhabditis elegans* genes and 200 human genes (corresponding to 506 putative *C. elegans* orthologs) exhibiting *LRRK2*-coordinated expression using RNA interference (RNAi) in worms expressing human *LRRK2*. They found that 40% of the genes affected neurite shortening and dopaminergic neuron toxicity, phenotypes associated with *LRRK2*-driven Parkinson's disease. They further identified RGS2 as a regulatory hub in the network and confirmed that RGS2 physically interacted with LRRK2 *in vitro* and *in vivo*. They also found that RGS2 interacted synergistically with LRRK2 to inhibit its kinase activity. Finally, they found that Parkinson's disease cases with the common LRRK2 Gly2019Ser alteration, as well as sporadic cases, had lower levels of RGS2 protein in caudate striatal tissue compared to controls. *BL*

iPSC models of ALS

Dominant mutations in *SOD1* (encoding superoxide dismutase 1) cause amyotrophic lateral sclerosis (ALS) and its hallmark feature, motor neuron death. Now, Su-Chun Zhang and colleagues (*Cell Stem Cell* doi:10.1016/j.stem.2014.03.004, 3 April 2014) and Kevin Eggan and colleagues (*Cell Stem Cell* doi:10.1016/j.stem.2014.02.004, 3 April 2014) have independently generated induced pluripotent stem cells (iPSCs) from individuals with *SOD1* mutations and investigated early pathological events in motor neurons derived from these iPSCs. Both groups created isogenic controls through TALEN-mediated genetic correction of the *SOD1* mutation. Zhang and colleagues found that *SOD1*-mutant motor neurons exhibited neurofilament aggregation and altered stoichiometry for the neurofilament subunits. They showed that mutant SOD1 binds to the 3′ UTR of the *NFL* gene and decreases the amount of *NFL* mRNA produced. Eggan and colleagues characterized transcriptome changes in *SOD1*-mutant motor neurons and showed that these cells expressed markers of an unfolded protein response and endoplasmic reticulum (ER) stress. They showed that some of these transcriptional changes are also present in motor neurons derived from the iPSCs of individuals with ALS caused by pathogenic repeat expansions in the *C9orf72* locus, suggesting that these distinct disease-causing mutations act through common pathways. *EN*

Immune cell–specific eQTLs

Christophe Benoist, Barbara Stranger, Philip De Jager and colleagues conducted expression quantitative trait locus (eQTL) profiling of $CD4^+$ T cells and monocytes purified from the blood cells of 461 healthy volunteers from a multi-ancestry cohort (*Science* **344**, 519–523, 2014). They identified *cis*-eQTLs in each cell type in individuals of African, European and East Asian ancestry within this cohort, finding that over 90% of these loci were shared across ancestry groups. They identified cell type–specific *cis*-eQTLs, including 39% specific to monocytes, 8% specific to T cells and 62% shared by both cell types. They also identified 482 *trans*-eQTL associations involving 55 genes specific to monocytes, 31 specific to T cells and 4 shared by both cell types. They examined the overlap of eQTLs with SNPs associated with disease in the US National Institutes of Health (NIH) catalog of published genome-wide association studies (GWAS) and used a regulatory trait concordance score to identify those suggested to tag the same functional variant. They found an enrichment of *cis*-eQTLs in SNPs associated with autoimmune disorders. Some diseases showed marked cell type specificity: SNPs associated with multiple sclerosis, rheumatoid arthritis or type 1 diabetes were enriched for T cell–specific *cis*-eQTLs, whereas SNPs associated with Alzheimer's disease, Parkinson's disease or type 2 diabetes were enriched for monocyte-specific *cis*-eQTLs. *OB*

Polar bear genomics

Rasmus Nielsen, Eske Willerslev, Jun Wang and colleagues have performed a population genomics study of polar bears to gain insights into their evolutionary history and the genetic mechanisms underlying their adaptation to the Arctic environment (*Cell* 157, 785–794, 2014). The authors generated a ***de novo*** **assembly of the polar bear genome through deep sequencing of a single polar bear and obtained population diversity data by performing lower-depth sequencing of 79 polar bears and 10 brown bears. From these data, they estimate that polar bears diverged from brown bears roughly 400,000 years ago, with continuous gene flow from polar bears into North American brown bears since their divergence. They also looked for genomic signatures of adaptation and found evidence that genes associated with cardiovascular function and adipose tissue development have evolved under strong positive selection in the polar bear population. The strongest signature of positive selection was found at** ***APOB*****, which encodes a protein important for the transport of lipids in blood and their uptake by cells. They also found signatures of positive selection at two pigmentation genes that might underlie the phenotype of white coat color in polar bears.** ***KV***

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