This Month in Genetics

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VLDL Receptor Stands Tall

An increased brain volume and the ability to walk upright are two key evolutionary features of humans. But mutations in a single gene can rob people of the full development of both of these features. These individuals have Unertan syndrome, which is characterized by mental retardation, the inability to articulate properly, truncal ataxia, and the fact that they walk on their hands and feet. These features are accompanied by cerebellar and cortical hypoplasia, as well as simplification of the gyri in these regions. Homozygosity mapping suggested that the relevant locus for Unertan syndrome is on chromosome 9p24. Residing therein is *VLDLR*, which encodes the very low-density lipoprotein receptor. In addition to its involvement in lipid cycling, VLDLR also binds to Reelin, an interaction that induces a signaling cascade directing neuronal migration. In two of four families with Unertan syndrome, Ozcelik et al. identified homozygous truncating *VLDLR* mutations. The relevance of these mutations is supported by the fact that a deletion of *VLDLR* was previously reported in Hutterite individuals with Dysequilibrium syndrome, a syndrome with a phenotype that is strikingly similar to that of Unertan syndrome except for a lack of quadripedal gait. Ozcelik et al. suggest that perhaps the individuals with this larger deletion are so severely impaired that they cannot even achieve the primitive quadripedal gait used by the individuals with Unertan syndrome. Perhaps greater understanding of the underlying defect in these people will help us to understand how most of us are able to stand tall.

Ozcelik et al. (2008). Proc. Natl. Acad. Sci. 105, 4232–4236. 10.1073/pnas.0710010105.

A Shocking Role for Alu Repeats

Although they make up an estimated 10% of the human genome, Alu elements are generally thought of as useless junk. There is some evidence that Alu sequences can play a role in the regulation of certain genes, particularly as *cis*-acting elements, but these are generally thought of as gene-specific mechanisms. Mariner et al. demonstrate a greatly expanded role for Alu elements in gene regulation with their finding that, after heat shock, Alu RNA acts in *trans* as an RNA polymerase II (Pol II) repressor that shuts off the expression of several genes. Binding of Alu RNA to Pol II is a part of this process, but it is not sufficient for transcriptional repression. In addition, one of two unstructured domains of Alu must be present to mediate its repressive effect, which occurs prior to transcription initiation. The lack of structure, rather than the sequence of the repressor domains, appears to be key to their function. Indeed, Alu RNA has a repressive effect similar to that of B2 RNA, a short interspersed element from mice, despite a lack of sequence similarity between the two repetitive elements. If, as the authors believe, Alu RNA inhibits transcription prior to initiation by gumming up Pol II, the question remains as to how some genes avoid repression by Alu at times of stress.

Mariner et al. (2008). Molecular Cell 29, 499–509. 10.1016/j.molcel.2007.12.013.

BBS Proteins Deliver the Goods

Bardet-Biedl syndrome (BBS) affects many different systems, and phenotypic features include, among others, retinal dystrophy, learning difficulties, obesity, and polydactyly. So far, twelve BBS genes have been discovered, and seven of them form a stable complex that appears to participate in vesicular transport to cilia. Because of the cognitive features of BBS, Berbari et al. wanted to explore the effects of the BBS complex on protein localization to the primary cilia of central neurons. They report two G protein-coupled receptors, the somatostatin receptor 3 (Sstr3) and the melanin-concentrating hormone receptor 1 (Mchr1), that lack ciliary localization in neurons of *Bbs2* or *Bbs4* knockout mice. The mislocalization of these receptors is observed despite the fact that primary cilia on central neurons appear to be normal in structure and number and that there is proper localization of other ciliary proteins. Thus, it seems as though the BBS complex is choosy about its protein cargoes. Because Mchr1 is involved in regulation of the feeding and energy balance, the authors are tempted to speculate that mislocalization of this signaling molecule is behind the hyperphagic obesity seen in individuals with BBS.

Berbari et al. (2008). Proc. Natl. Acad. Sci. 105: 4242–4246. 10.1073/pnas.0711027105.

miRNA Promotes Skin Differentiation

Thankfully, and despite our best efforts to burn it, cut it, and scrape it, our skin can renew itself as a result of the

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presence of stem cells in the innermost basal layer of the epithelium. As cells migrate up into the suprabasal layer of the epithelium, they lose this ability to proliferate, and they undergo differentiation. MicroRNAs are known to be involved in skin development, but their regulatory targets have not been clear. Yi et al. found that miR-203 is a key miRNA in this transition and that it does this by negatively regulating the expression of certain proliferation-promoting genes as cells become part of the differentiating suprabasal layer of the epithelium. Transcripts for p63, a protein that helps maintain stem cells, are a direct target of miR-203, and reductions in p63 protein expression occur at the same time as increased miR-203 expression in the differentiating epithelium. Reductions in miR-203 expression result in expansions of p63 expression, increased cellular proliferation in the suprabasal epithelial layer, and a thickened epidermis. Although self-renewal of skin is a great thing, miR-203 helps epithelial cells know when enough is enough and prompts them to turn off this proliferative capacity to become the differentiated outer layers of skin.

Yi et al. (2008). Nature 452, 225–229. 10.1038/nature06642.

Mitochondria and Fat

We all learn in our early biology classes that mitochondria are the cellular powerhouses crucial for energy. But what if this energy production slows down? Pietilainen et al. suggest that obesity is the result. From the Finnish population registry, they collected a sample of monozygotic twins who were discordant for body mass index—one twin was obese and the other wasn't—and they studied variation between the two in gene expression from fat samples. Their rationale was that the twins would share a genetic and early environmental background, so any differences observed between the twins is likely to be due to the acquired obesity in one twin. Genes involved in inflammation, the cytoskeleton, cell growth, and intracellular transport were the most likely to be upregulated in the fat of the obese twins, whereas genes involved in branched-chain amino acid catabolism—many of them mitochondrial—were the most significantly downregulated. This led the authors to investigate the mitochondria, and although no sequence changes were observed between the twins, the mtDNA copy number in the fat samples of obese twins was an average of 53% lower than that in the non-obese twins, despite equal levels of mtDNA in leukocyte samples. The role of reduced mtDNA copy number in obesity was also supported by the fact that one obese twin gained 10.7 kg between study visits, and there was a concomitant 44% decrease in mtDNA copy number in fat samples from this individual. The authors propose that decreases in mtDNA copy number disturb mitochondrial energy metabolism, particularly the catabolism of branched-chain amino acids, and this has effects on the utilization of fat for energy.

Pietilainen et al. (2008). PLOS Medicine. Published online March 11, 2008. 10.1371/journal.pmed.005051.