Organ-specific vasculature

Although key pathways required for general vasculature development have been elucidated, it remains unclear how organ-specific features such as the blood-brain barrier, which restricts free exchange of molecules between the blood and central nervous system (CNS), are established. Through a series of genetic studies in mice, Andrew McMahon and colleagues (*Science* 322, 1247–1250; 2008) now show that the assembly of the vasculature surrounding the developing CNS requires specific Wnt ligands secreted from the neural tube. The authors found that embryos devoid of Wnt7a and Wnt7b activity show a severe hemorrhaging phenotype that is restricted to the CNS. Similar phenotypes occur after ablation of Wnt7b from the neuroepithelium on the background of Wnt7a deficiency, and after ablation of the Wnt downstream effector β-catenin from vascular precursor cells. Expression of the glucose transporter GLUT1, which is normally expressed abundantly in the adult blood-brain barrier, was markedly reduced in the same mutant backgrounds. Conversely, ectopic expression of Wnt7a in scattered cells outside the CNS resulted in enhanced GLUT1 expression in adjacent endothelial cells, showing that Wnt7a signaling is sufficient to induce features characteristic of CNS vasculature. ***KV***

Blood serum metabolites

Karsten Suhre and colleagues report a genome-wide association study (GWAS) for metabolites present in human serum (*PLoS Genet.* **4**, e1000282; 2008). The study included 284 men 55–79 years of age, selected from within the KORA F3 population-based study in southern Germany. They measured a selection of 363 naturally occurring metabolites in serum of these men at a single time point. The authors corrected both for genome-wide SNP testing (on the Affymetrix 500k microarray), as well as for testing association with multiple traits, estimating an overall genome-wide significance threshold at 1.33×10^{-9}. Although no single SNP met this strict threshold for association with an individual metabolite concentration, several came close and were considered targets for further replication. Taking another approach, the authors examined the ratios of functionally related metabolites, reducing variance and highlighting more robust statistical associations. The study provides an interesting example of need to correct for associations with many functionally related traits within a single GWAS and suggests that one approach may be to consider grouping of related traits. The authors further found that four of their top candidate associations were also reported in several recent GWASs on multiple lipids traits, suggesting a functional relationship for these associations of medical relevance. *OB*

Pigmentation pathways

There are more than 120 gene products involved in coat color in mice, but far fewer genes underlying pigment variation in human skin have been identified. Anand Ganesan and colleagues now report a genome-wide siRNA-based screen of human melanoma cells for variation in melanin production (*PLoS Genet.* **4**, e1000298; 2008). The authors screened MNT-1 cells, which have a gene expression profile similar to that of normal melanocytes, using the Dharmacon siRNA library. They report 98 genes that, when knocked down, have an effect on melanin production. Approximately half of these genes seem to affect mRNA accumulation of both tyrosinase and its upstream regulator MITF. These genes fall into a wide range of categories, including G protein–coupled receptors, transcription factors, GTPases, kinases and peptidases, as well as at least two genes not previously known to affect melanosome trafficking or sorting. Of particular note were three genes involved in autophagy. Another gene that is required to trigger autophagosome formation (*BECN1*), but was not identified in the screen, impaired pigment accumulation when knocked down in MNT-1 cells, further implicating autophagy in melanogenesis. The authors suggest that gene products involved in autophagy may be required for the sorting of the melanin synthetic machinery. *AP*

Written by Orli Bahcall, Lily Khidr, Alan Packer & Kyle Vogan

PROMPTing transcription

DNA transcription produces many short-lived noncoding transcripts with a potential regulatory function, but most have escaped detection by present technologies. By depleting a core component of the human RNA exosome (hRrp-40) by RNAi in human cells, Pascal Preker and colleagues were able to effectively diminish the 5′–3′ exoribonuclease activity and, by doing so, identified a key region upstream of the transcription start site (TSS) that harbored peaks of stabilized RNA using microarray hybridization (*Science* published online, doi:10.1126/science.1164096; 4 December 2008). This RNA stabilization generated upstream of the promoter (PROMPTs) was unique to hRrp-40 depletion, as depletion of other molecules involved in RNA turnover had no effect. The PROMPT region is covered by markers of active chromatin comparable to the region at the beginning of a gene, whereas transcription initiation factors restrict their localization to the TSS. This highlights the dependence of robust bidirectional PROMPT transcription on the downstream gene promoter. So what do they do? The authors show, preliminarily, that PROMPTs may affect promoter methylation, and, interestingly, high levels of PROMPTs correlate with regions of high CpG score. PROMPTs present an as yet unexplored aspect of the mechanism of gene transcription, and the elucidation of their function will unravel the complex regulatory chromatin structure around the TSS. *LK*

Making sense of the transcriptome

Despite the ability to assess genome-wide transcript abundance in a cell, it has remained elusive which strand of the chromosome serves as the template for global transcription. Now, Yiping He and colleagues have developed a new technique called asymmetric strand-specific analysis of gene expression (ASSAGE) that allows unambiguous assignment of the DNA strand encoding a transcript (*Science* published online, doi:10.1126/science.1163853; 4 December 2008). By examining the number and distribution of tagged cDNA fragments from the entire transcriptome, He *et al.* garnered information about the level of gene transcription as well as the strand from which each transcript derives. In each of five different human cell types, they assessed the expression of over 10,000 genes and subsequently classified them into groups reflecting the predominance of sense and antisense tags. Across all cell types, they found a similar pattern of nonrandom distribution of antisense tags across the genome existing within exons, as well as in promoter and terminator regions of genes. However, the identity of the specific genes varied among the cell types, suggesting that the expression of antisense tags may be regulated in a cell- or tissue-specific manner, lending considerable support to the existence of antisense-mediated gene regulation in the human transcriptome. ***LK***