The immortal strand

Thirty years ago, John Cairns proposed the 'immortal strand hypothesis' (ISH), which suggested that dividing stem cells might asymmetrically segregate chromosomes bearing the oldest DNA templates. Such a mechanism could reduce the number of DNA synthesis–associated mutations that a stem cell would carry. Although the evidence in ensuing years has been mixed, new data from Phillip Karpowicz and colleagues provides strong support for the ISH in neural stem cells (*J. Cell Biol.* 170, 721–732; 2005). Karpowicz *et al.* cultured neural stem cells derived from adult mouse forebrains in 5-bromo-2-deoxyuridine (BrdU), which allowed them to follow the fate of old and new strands after different culture protocols. The results consistently show that nestin-positive neural stem cells retain at least some BrdU well beyond the point at which population doublings extinguish any remaining label in symmetrically dividing fibroblasts or embryonic stem cells. Real-time imaging confirmed that cells with asymmetric partitioning of BrdU retain the label in undifferentiated precursors rather than differentiated progeny. Although the molecular mechanism of this uneven segregation is unknown, the authors suggest that an epigenetic marking of the leading and lagging strands during DNA synthesis could explain their observations. ***AP***

HCV replication and miR-122

Hepatitis C virus (HCV) is an RNA virus that infects liver cells and is a major cause of chronic liver disease. A new study by Peter Sarnow and colleagues (*Science* **309**, 1577–1781; 2005) now shows that the accumulation of HCV viral RNA in hepatocytes requires miR-122, an abundant, liver-specific miRNA. Sarnow and colleagues identified two potential miR-122 binding sites in the 5′ and 3′ noncoding regions of the HCV genome and found that blocking miR-122 function led to a substantial reduction in viral RNA levels. They then showed, using mutagenesis and rescue experiments, that a functional miR-122 binding site mapped to the predicted sequence in the 5′ region of the viral RNA. Notably, they found that mutating this miR-122 binding site had no marked effect on RNA translation or stability, suggesting that miR-122 acts at the level of viral RNA replication. Although the endogenous targets of miR-122 in liver cells remain unknown, these findings suggest that HCV exploits this abundant liver-specific miRNA to facilitate its own replication, identifying miR-122 as a potential target for antiviral therapy. *KV*

Expression over time

John Storey and colleagues present a new statistical method that accounts for the dynamics in the regulation of gene expression over time and apply this to identifying genes that show statistically significant changes in gene expression in microarray time-course experiments. (*Proc. Natl. Acad. Sci. USA* **102**,12837–12842; 2005) These new methods were tested in two studies involving expression data from human studies, with either independent or longitudinal sampling. The first study compared 72 human kidney cortex samples from individuals ranging in age from 27 to 92 years, with each individual representing an independent sample, and asked what genes were differentially expressed with age. A high proportion of immune response genes tested showed increased expression with age, and other changes were found in genes involved in cell signaling, growth and genome stability. The second study considered the mechanism of endotoxin and the onset of inflammation in blood leukocytes, by comparing longitudinal sampled time course expression patterns within an individual and between treated and control groups over time. The most upregulated genes were involved in immune response, inflammatory disease, cellular movement and cell death, and downregulated genes were involved in protein synthesis, transcription and energy production, reflecting a shock response and an expected reallocation of resources. *OB*

Missing heme transporter found

Iron is absorbed from dietary intake in two forms: nonheme iron from plant sources and heme iron from meat sources. Nonheme iron is absorbed in the intestine by the Slc11a2 transporter. Andrew McKie and colleagues now report the identification of an intestinal heme transporter in mice (*Cell* **122**, 789–794; 2005). They took advantage of the known intestinal gradient of heme absorption (duodenum has the highest capacity for heme absorption and ileum has the lowest) by using a subtractive hybridization approach to identify cDNAs expressed in duodenum but not ileum. One of the cDNAs corresponded to a gene, named *HCP1* or heme carrier protein 1, with nine transmembrane domains and homology to bacterial metal tetracycline transporters. The authors determined that HCP1 mediates heme uptake and is regulated by hypoxia, which induces iron absorption. The subcellular localization of HCP1 in duodenal enterocytes is influenced by iron status; HCP1 is located apically in iron-deficient mice and cytoplasmically in iron-loaded mice. In addition to the duodenum, *HCP1* expression was also detected in adult liver. There may be additional intestinal heme transporters, but this work provides a missing piece in our understanding of iron uptake pathways. *EN*

Brain size determinants under selection

Primary microcephaly is an autosomal recessive condition characterized by a severe reduction in brain size. Several of the known genes underlying this disorder evolved adaptively in the evolutionary lineage leading to humans. Bruce Lahn and colleagues now report (*Science* 309, 1717–1720 and 1720–1722; 2005) that two of these genes, *MCPH1* and *ASPM* (also called MCPH5), have experienced strong positive selective sweeps since the emergence of anatomically modern humans. Lahn and colleagues sequenced *MCPH1* and *ASPM* in ~90 ethnically diverse individuals and discovered for each gene a very abundant haplogroup that accounted for a disproportionate fraction of haplotypes in the panel. In each case, they inferred that the abundant haplogroup was derived from a single ancestral copy that was driven to high frequency in relatively recent times under what seems to be strong positive selection. The nature of the selective pressures remains unknown, but the established roles of these genes in regulating brain size suggests that adaptive changes linked to brain function drove the rapid spread of these haplotypes through the human population. ***KV***

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