DNA contortions

Unruly DNA accounts for a previously unexplained form of mental retardation, according to three studies in *Nature Genetics* (**38**, 999–1001, 1032–1037, 1038–1042).

All three studies examined a region of DNA on chromosome 17 that contains several large low-copy-number repeats, also known as segmental duplications. Such regions are particularly prone to homologous recombination with nonallelic regions of the genome—a process that can lead to deletion. One haplotype in particular, present in 20% of Europeans, has an architecture that seems especially prone to deletion.

The studies provide evidence that deletions in this region arise *de novo* and result in a seemingly clinically distinct form of mental retardation. Such deletions may account for as much as 1% of the cases of mental retardation.

It's unclear how deletions in this region, which contains several genes, lead to disease. But the study highlights the role that peculiar DNA architecture may play in previously unexplained disorders. One of the studies, for instance, interrogated 130 potentially unstable regions in people with mental retardation and identified rearrangements in four other regions containing segmental duplications. *–CS*

Undermining insulin secretion

Studies have suggested that type 2 diabetes has a genetic component, but few diabetes-related genes have been identified. Andrey Babenko *et al.* now examine a cohort of children with unexplained neonatal diabetes and find dominant, hyperactivating mutations in a single gene (*ABCC8*) that account for 12% of these cases (*N. Engl. J. Med.* 355, 456–466).

***ABCC8* encodes the sulfonylurea receptor (SUR1), a pancreatic membrane ion channel that indirectly senses proper glucose levels. When glucose levels rise, SUR1 closes, depolarizing the membrane and leading to insulin exocytosis. The newly identified mutations disrupt the ability of SUR1 to respond to increased glucose levels, thus leading to decreased insulin secretion.**

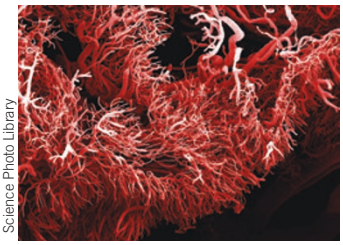
The mutations do not, however, inhibit the response of SUR1 to sulfonylureas, which cause channel closure—so some of the children and their parents who harbored these mutations have been taken off insulin and placed on sulfonylurea therapy. *–RL*

Bystander hit twice by HIV

In HIV-infected individuals, death of uninfected $CD4^+$ T cells—so-called bystander T-cell death—is thought to contribute to the immunosuppression that eventually leads to AIDS. Lucile Espert *et al.* show that autophagy, an alternative form of cell suicide accompanied by formation of intracellular vesicles, may play a role in this bystander death (*J. Clin. Invest.* **116**, 2161–2172; 2006).

Previous work had shown that the viral envelope glycoproteins encoded by the HIV-1 Env gene induce apoptosis of uninfected T cells that express CXCR4, the HIV-1 coreceptor. Using a cell culture system, Espert *et al.* found that cells expressing Env triggered both apoptosis and autophagy of CXCR4-expressing T cells—but that blocking only autophagy prevented both forms of cell death. Whether autophagy operates this way in HIV-infected people is unclear, but the findings hint at new routes to prevent T-cell loss in HIV-1 infection. *–AF*

p53 takes on angiogenesis



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Can p53 stop this?

The famed tumor suppressor p53 is best known as a DNA repair agent and a cell cycle cop—but its ability to inhibit angiogenesis may also help the molecule fend off tumors, according to Jose Teodoro *et al.* (*Science* 313, 968-971).

These investigators report that p53 inhibits angiogenesis by upregulating an enzyme that liberates antiangiogenic fragments of collagen (*Science* 313, 968–971). These fragments include the well-characterized anti-angiogenic molecules endostatin and tumstatin. Xenografted tumors derived from p53-deficient cells were highly vascularized and had large areas lacking tumstatin staining.

The researchers went on to show that cells expressing the enzyme could inhibit tumor growth *in vivo*. *–CS*

Macroregulating microRNAs

Researchers have come one step closer to understanding how miRNAs are regulated during development and cancer (*Genes Dev.* **20**, 2202–2207).

Generally, expression of most miRNAs increases sharply during development as cells begin to differentiate. But it seems that the primary transcript for these miRNAs does not spike. Instead, J. Michael Thomson *et al.* conclude that miRNA processing seems to be regulated at a step mediated by the enzyme Drosha—a ribonuclease that liberates a stem-loop structure that is later chopped down into smaller RNAs. Drosha regulation also seems to underlie the widespread reduction in miRNA expression during cancer, findings from a bank of tumor samples suggested.

The results are consistent with the notion that loss of miRNA expression reflects a loss of cellular identity in cancer cells. But how Drosha might turn miRNA expression on and off remains largely unexplored. *–CS*

Ligand location

CpG-containing oligonucleotides can elicit an immune response and are being tested in clinical trials for treating allergy, asthma, cancer and infectious disease. But different types of oligonucleotides produce different types of reactions; Cristiana Guiducci *et al.* find out why (*J. Exp. Med.* 203, 1999–2008).

Immunostimulatory CpG-containing oligonucleotides all activate signaling through Toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells. But the response differs depending on the class of oligonucleotide. Type A oligonucleotides induce high levels of interferon, type B induce dendritic cells to mature and promote adaptive immune responses, and type C do both.

The key to these different responses is intracellular location—which is in turn determined by the physical structure of the oligonucleotide: type A are highly aggregated and trigger TLR9 in early endosomes, whereas type B are single-stranded and preferentially located in late endosomes. Type C can localize to both early and late endosomes, but when modified so that they can interact with TLR9 only in late endosomes they lose the ability to induce interferon. *–CT*

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