Cryptic immunity

Mutations in *CARD15* (also called *NOD2*) confer increased risk of Crohn disease, a form of chronic inflammatory bowel disease. But does the gene normally contribute to innate antibacterial defense or to the regulation of inflammation in response to bacterial challenge? It seems to do both. Kobayashi *et al.* (*Science* 307, 731–734; 2005) found that mice homozygous with respect to a null *Card15* allele were proficient in adaptive T cell–mediated immunity. But the null mice were susceptible to *Listeria* and *Mycobacterium paratuberculosis* infection upon gastric challenge. Unlike the wild type, their ileal crypt Paneth cells did not produce cryptdins (antibiotic peptides like the α-defensins) in response to challenge with the bacterial wall peptidoglycan muramyl dipeptide (MDP). Maeda *et al.* (*Science* 307, 734–738; 2005) made mice with the most common allele of *Card15* associated with risk of Crohn disease, which lacks 33 C-terminal amino acids, to show that this is a gain-of-function allele with no effect on signaling by MDP through Toll-like receptor 2. In these mice, macrophages isolated from bone marrow processed and released elevated levels of the inflammatory cytokine IL-1β when challenged with MDP. When their mucosal epithelium was compromised, the mutant mice were also more susceptible to inflammation caused by bacteria. ***MA***

Comparing genomes

Comparative genomics seeks to identify functional elements in the human genome by finding conserved regions among diverse organisms. How many genomes are needed for comparison, and which would be most informative? In a new study, Sean Eddy develops a statistical model to address these questions (*PLoS Biol.* **3**, 95–102; 2005). His model is generally applicable to any genome and sequence length, allowing, for example, the comparison of regulatory or coding elements of a particular gene. Key model parameters include the number of genomes being compared, the length of the target sequence and the rate of evolution of the sequence. As defined by the model, a conserved sequence may vary and is allowed to have up to a threshold number of changes in compared genomes. The lessons from these simulations, though intuitive, are important to quantify. There is an inverse relationship between sequence length and the number of genomes needed to show conservation. In addition, when there is a close evolutionary distance between genomes, a surprisingly large number of genomes can be required for an informative comparison. For example, comparing human sequences with those of the more closely related baboon requires approximately seven times as many comparative genomes as comparing human sequences with those of the mouse. *OB*

RNA polymerase IV imposes silence

Eukaryotes contain three classes of RNA polymerase, each specialized to carry out unique cellular functions. Plants encode subunits for an additional fourth RNA polymerase whose functions remain largely unknown. David Baulcombe and colleagues (*Science* advance online publication, 3 February 2005; doi:10.1126/science.1106910) now report that RNA polymerase IV functions with known siRNA pathway components to silence transposons and repetitive DNA sequences. Previous studies identified a mutant, *sde4*, defective in transgene silencing and linked the phenotype to defects in siRNA production. Baulcombe and colleagues now show that the *sde4* mutation disrupts the largest subunit of RNA polymerase IV, RPD1. Plants deficient in the second largest RNA polymerase IV subunit, RPD2, also showed delayed silencing in regions of active growth. The authors propose a model in which RNA polymerase IV generates transcripts that are converted into double-stranded RNA by an RNA-dependent RNA polymerase. This double-stranded RNA is then cleaved by a Dicer-like enzyme to produce siRNAs required for silencing. They suggest that the unique properties of RNA polymerase IV could make it refractory to normal chromatin silencing mechanisms, allowing it to transcribe heterochromatin and maintain the silenced state. *KV*

Feedback circuit in the hindbrain

The developing vertebrate hindbrain is divided into seven rhombomeres, which eventually contribute to the ordered arrangement of sensory and motor nerves in the brainstem. Although the patterning of the hindbrain by retinoic acid–dependent activation of *Hox* genes is well-established, the full network of interactions governing rhombomere segmentation is not yet understood. Patricia Serpente and colleagues now show that the gene encoding retinoic acid receptor β (*Rarb*) is a direct transcriptional target of class 4 *Hox* genes, suggesting that there is a cross-regulatory loop between the two (*Development* **132**, 503–513; 2005). Serpente *et al.* observed that the expression patterns of *Rarb* and *Hoxb4* are initially out of register in the hindbrain but by E10.5 are perfectly aligned at the border between rhombomeres 6 and 7. They show that the initial pattern of expression of each is established by retinoic acid, but the subsequent maintenance of each requires cross-regulation that serves to sharpen and fix the anterior limit of expression. This work provides a mechanism for generating sharp boundaries between metameric structures and identifies a new target of Hox transcription factors that may be acting in a wide range of embryonic tissues. *AP*

A genomic approach to chromatin

Chromatin imposes higher-order structure on the genome and allows it to respond to changing environments. The roles of histones and histone modifications in cellular processes and at specific loci are hot areas of research, and now a recent study has brought a genome-wide view to mammalian chromatin structure (*Cell* 120, 169–181; 2004). Eric Lander and colleagues profiled histone modifications across 39 Mb of the human genome, including chromosomes 21 and 22, using a ChIP-chip approach to map the locations of modified H3 histones. This analysis uncovered a punctate pattern of methylation modifications, with enrichment of trimethylated Lys4 at transcription start sites. An interesting exception was seen in the Hox clusters, where there were broad swaths of methylated histones. By profiling histone modifications at orthologous loci in the mouse, they determined that modification patterns are highly conserved, but sites of modification are not correlated with higher levels of sequence conservation. These studies identify general features of mammalian chromatin and demonstrate the feasibility of large-scale analyses of chromatin structure. Perhaps even more interesting was the identification of differential histone modifications in a limited number of cell types, hinting at the potential use of this approach to understand the role of chromatin in cellular differentiation. ***EN***

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