Pairing away the X chromosome

X-chromosome inactivation (XCI) results in one inactive X chromosome expressing the *Xist* gene and one active X chromosome. The process of XCI involves pairing between the two X chromosomes; pairing can be recapitulated in differentiating ES cells by fragments of the *Tsix* and *Xite* genes (*Nat. Genet.* 11, 1390–1396; 2007). Pairing mediated by the *Tsix/Xite* locus occurs between day 2 and day 4 of differentiation, about the time when one allele of the *Xist* gene is upregulated. Now Edith Heard and colleagues have identified another locus that brings the two X chromosomes together at an even earlier time point before the onset of X-inactivation (*Science* 318, 1632–1636; 2007). The authors showed that a BAC transgene containing the *Xpct* gene, located 200 kb upstream of *Xist*, can pair with an X chromosome in undifferentiated and early differentiating ES cells. Undifferentiated ES cells normally repress *Xist* expression, but the authors found that the presence of the transgene leads to expression and accumulation of *Xist* RNA. They suggest that early pairing may be the trigger for *Xist* upregulation. These findings identify a new player in the X-chromosome pairing phenomena and prepare the way for future studies to further define the function of *Xpct* and early pairing. ***EN***

Trex1-deficient cellular phenotype

Biallelic mutations in the gene encoding the 3′→ 5′ DNA exonuclease TREX1 cause Aicardi-Goutières syndrome, a disorder marked by severe encephalopathy and chronic systemic inflammation. Heterozygous *TREX1* mutations are also associated with various inflammatory diseases, including systemic lupus erythematosus, whereas Trex1-deficient mice develop an autoimmune-driven, inflammatory myocarditis. Now, Deborah Barnes and colleagues (*Cell* **131**, 873–886; 2007) describe the cellular phenotype associated with Trex1 deficiency. In the absence of stress signals, Trex1-deficient mouse embryonic fibroblasts show chronic activation of the ATM-dependent checkpoint signal, resulting in an accumulation of cells in G_1. The cells also have marked accumulation of a discrete population of 60–65 nucleotide single-stranded DNA molecules in the endoplasmic reticulum. These same features were also seen in a fibroblast cell line derived from a subject with Aicardi-Goutières syndrome harboring inactivating *TREX1* mutations. Although it remains to be seen how these cellular phenotypes relate to the diverse systemic inflammatory phenotypes associated with TREX1 deficiency *in vivo*, the work suggests a number of plausible mechanisms by which the clinical phenotypes might arise, including inappropriate activation of the DNA-sensing receptors of the innate immune system or dysregulation of pathways controlling lymphocyte self-tolerance. *KV*

2La inversion in *Anopheles gambiae*

2La is a common inversion polymorphism in the African malaria vector *Anopheles gambiae*; the frequency of this inversion varies with both geographic cline and season, and it is thought to have extended the range of malaria transmission. Nora Besansky and colleagues now report studies mapping the patterns of divergence within and near this inversion and discuss forms of selection that may act to maintain the inversion (*PloS Genet.* **3**, e217; 2007). The authors took five samples each of inversion heterozygotes (mosquitoes carrying either 2La/a or $2L+^a/+^a$) from a single village in central Cameroon. They examined genome-wide single-feature polymorphisms (SFPs) between samples and 2L arrangements, using the Affymetric GeneChip Anopheles/ Plasmodium Array. They found that the distribution of SFPs shows enrichment on chromosome 2L, and, using a hidden Markov model, they identified a 22-Mb region with significantly more SFPs observed than expected by chance; this region overlaps with the inversion. They further found two regions with significant clustering of SFPs; one each near the proximal and distal breakpoints. These findings were validated by targeted sequencing of an additional 24–34 chromosomes from the same population. Finally, the authors searched for evidence of selection that may have acted to maintain the inversion. *OB*

Apron strings

It has been proposed that maternal cells or antigens entering the bloodstream of the fetus may induce tolerance to non-inherited maternal antigens and affect the immune reactivity of the child. Now Anouk Feitsma and colleagues investigate whether non-inherited maternal HLA antigens can influence susceptibility to the autoimmune disease rheumatoid arthritis (RA) (*Proc. Natl. Acad. Sci. USA* **104**, 19966–19970; 2007). Alleles of the HLA-DRB1 locus that include the amino acid sequence DERAA are known to be associated with protection from RA. To determine whether maternal HLA-DRB1 alleles affect susceptibility to RA, the authors typed 179 families with a proband with RA (88 Dutch families and 91 English families) and found two pieces of evidence suggestive of a protective effect. They found a lower frequency of mothers carrying a DERAA-containing allele compared to both the general population and fathers ($P = 0.02$ in the Dutch families and $P = 0.01$ in the English families). And analysis of the 45 families with a DERAA-carrying parent and a noncarrier proband showed that mothers have a DERAA-containing allele less often than fathers (17 mothers versus 32 fathers, $P = 0.003$). Although further analyses with larger datasets will be needed to fully support the role of non-inherited maternal antigens in RA susceptibility, this study highlights an interesting potential epigenetic mechanism of genetic disease risk. *EN*

Random monoallelic expression

A small number of autosomal genes are known to show random monoallelic expression, but the extent of this phenomenon has yet to be analyzed on a genome-wide scale. Now, a large-scale analysis of allelic-specific expression in human clonal cells lines by Andrew Chess and colleagues (*Science* 318, 1136–1141; 2007) suggests that random monoallelic expression of autosomal genes is more widespread than previously suspected. To generate their data set, the authors developed a method to assess allele-specific expression using the Affymetrix Human Mapping 500K array set hybridized with cDNA prepared from RNA enriched for intronic sequences, where many SNPs interrogated by the array reside. After establishing that the method successfully detected genes subject to X-inactivation in clonal female cell lines, the authors examined 4,000 autosomal genes and found that 5–10% showed random monoallelic expression. They confirmed their findings *in vivo* by using RNA fluorescence *in situ* hybridization and by examining clonal patches of cells from female placenta marked by complete skewing of X-inactivation. As a category, genes encoding surface molecules were significantly enriched among the genes subject to random monoallelic expression, suggesting a possible role in modulating cell-cell communication. ***KV***

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