Rheumatoid arthritis genome scan

Peter Gregersen and colleagues (*N. Engl. J. Med.* advance online publication 5 September 2007; doi:10.1056/NEJMoa073491) report interim results of a genome-wide association scan for genetic variants associated with rheumatoid arthritis. To minimize effects of disease heterogeneity, the authors selected individuals seropositive for autoantibodies against cyclic citrullinated peptide (CCP); to maximize power, they combined data from two independent scans performed on samples collected from North America and Sweden. In their combined analysis, involving 297,086 polymorphic SNPs, 1,522 cases and 1,850 controls, the authors detected strong associations at two previously confirmed risk loci, *HLA-DRB1* and *PTPN22*, and identified a third cluster of SNPs on chromosome 9 strongly associated with the disease. The authors subsequently tested and replicated this association in a large independent collection of CCP-positive rheumatoid arthritis cases and matched controls from the same populations. Notably, the associated region includes two genes, *TRAF1* and *C5*, previously known to act as modulators of immune and inflammatory responses. Additional fine mapping, combined with functional studies, will be required to unravel how variation at this locus influences disease risk. It will also be important to examine whether this locus, like *PTPN22*, confers risk of other autoimmune diseases. *KV*

Estrogen and bone loss

Maintenance of bone mass is a dynamic process controlled by osteoclasts, which resorb existing bone, and osteoblasts, which form new bone. Estrogen deficiency in postmenopausal women is frequently accompanied by osteoporosis; this loss of bone mass is caused by an imbalance between bone deposition and resorption and can be attenuated by estrogen treatment. Now Shigeaki Kato and colleagues show in mice that estrogen induces apoptosis in osteoclasts through upregulation of Fas ligand expression, providing a mechanism for the osteoprotective action of estrogen (*Cell* **130**, 811–823; 2007). To investigate the role of estrogen in regulation of osteoclasts, the authors engineered a conditional knockout of estrogen receptor α (ERα) in osteoclasts. This conditional ERα knockout resulted in osteopenia in female mice, characterized by accelerated bone resorption and increased numbers of osteoclasts. The phenotype could not be rescued by estrogen treatment, suggesting that this is a cell-autonomous effect. Microarray profiling of estrogen-regulated gene expression revealed dysregulation of apoptosis-related genes in ERα knockout bone. Further investigation confirmed that estrogen induced expression of *FasL*, which encodes an apoptotic factor, and apoptosis in bone in wild-type mice but not in ERα knockout mice. *EN*

STAT4 and autoimmune disease

Linkage studies have implicated chromosome 2q as harboring risk factors for rheumatoid arthritis and other autoimmune diseases. Peter Gregersen and colleagues (*N. Engl. J. Med.* **357**, 977–986; 2007) now report that variants in *STAT4*, one of several candidate genes contained within the linkage peak, are associated with risk of both rheumatoid arthritis and systemic lupus erythematosus (SLE). The authors examined 13 candidate genes in the region for association with rheumatoid arthritis and found significant association with a variant in *STAT4*, which encodes a transcription factor that acts downstream of several key cytokines. By testing additional SNPs in the region, the authors localized the association signal to several variants in the third intron of *STAT4*. They then tested and replicated the association with rheumatoid arthritis in two additional case-control studies. Because the 2q region has also been linked with susceptibility to SLE, the authors tested the *STAT4* variants for association with SLE in three independent case-control series, and, in all three studies, they found significant association with the disease. Notably, the variants confer a higher risk to homozygotes and seem to confer slightly higher risk of developing SLE than rheumatoid arthritis. *KV*

Neuroligin-3 and autism

Rare mutations in the gene encoding neuroligin-3, a postsynaptic adhesion molecule, have been found in individuals with autism spectrum disorders (ASDs). Neuroligin-3 is a member of a family of such molecules found at the synapse, but its precise role in synaptic transmission has been unclear. Katsuhiko Tabuchi and colleagues now report the generation of mice carrying a neuroligin-3 allele with one of the human mutations, R451C, and show such mice to be a potentially useful model of ASDs (*Science*, published online 6 September 2007; doi:10.1126/science.1146221). Tabuchi *et al.* show that mice carrying a knock-in allele of neuroligin-3 R451C have forebrain neuroligin-3 levels about 90% lower than mice with a normal allele. Measurements of markers for inhibitory synapses and of synaptic function suggest that they also have increased inhibitory synaptic transmission, most likely owing to a gain-of-function in the mutant form of neuroligin-3. By characterizing the behavior of the mice, the authors show that they have both impaired social behavior and enhanced social-learning abilities. Finally, they conclude that a change in the inhibitory/excitatory balance of synaptic transmission contributes to the development of ASDs and suggest that attenuating inhibitory synaptic transmission may ameliorate the behavioral abnormalities associated with autism. *AP*

Transgenerational epigenetic instability

In plants, METHYLTRANSFERASE1 (MET1) propagates ^{m}CG patterns, and other methyltransferases methylate non-CG cytosines. Now Jerzy Paszkowski and colleagues show that in plants ^{m}CG is required for epigenetic stability and ^{m}CG influences RNA-directed DNA methylation (RDRM) (*Cell* 130, 851–862; 2007). Loss of MET1 function results in complete loss of ^{m}CG but only partial lethality, with 2% of expected homozygotes for the null *met1* allele surviving with morphological defects. By studying these survivors, the authors determined that ^{m}CG loss triggers new aberrant patterns of non-CG methylation and H3K9 methylation and alters heterochromatin structure; these changes are not stably inherited in subsequent generations. The aberrant DNA methylation changes require functional DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2) function. DRM2 is a *de novo* methyltransferase directed by siRNAs in the RDRM pathway. Thus, ^{m}CG loss causes misdirection of the RDRM pathway. A combination of the null *met1* allele with a *drm2* mutant allele resulted in exacerbated morphological abnormalities, suggesting that induction of aberrant methylation patterns is an attempt to compensate for ^{m}CG loss. This work illuminates previously unknown regulatory interactions between epigenetic pathways and indicates the importance of ^{m}CG for epigenetic stability in plants. *EN*

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