Meeting report

Gene function in the mammalian genome, courtesy of the mouse

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A report on the 16th International Mouse Genome Conference, San Antonio, USA, 17-20 November, 2002.

The main focus of the 16th International Mouse Genome Conference was our growing understanding of functional genomics, with random mutagenesis by N-ethyl-N-nitrosourea (ENU) being the dominant approach reported for exploring the association between the genome and phenotypic expression. The release of the mouse draft genome sequence in April 2002 has had an enormous impact on mouse genomics. The availability of both mouse and human draft genomic sequences provides a powerful base for comparative genomic studies and highlights the role of the mouse as a valuable experimental resource for understanding human biology and disease.

The release of the mouse genome sequence has inspired a rethink of how analysis of the genome might move forward. Eric Green (National Institute of Health, Bethesda, USA) showed how comparative genomics is enhancing the identification of novel coding and non-coding regulatory elements and improving our understanding of genome evolution. He suggested that the availability of more phylogenetically divergent mammalian sequences, such as those of marsupials and monotremes, would assist in the identification of regulatory elements. Our group, represented by Kerstin Lindblad-Toh (The Whitehead Institute, Cambridge, USA) revealed the startling mosaicism of *Mus musculus domesticus* and *Mus musculus musculus* haplotypes across the inbred laboratory mouse genome and showed how the use of genome-wide haplotype mapping might enhance positional cloning. Many talks introduced, or announced updates on, web-based tools and databases to assist the mouse genome researcher. The Jackson Laboratories website (http://www.informatics.jax.org) now provides extensive information on mouse genes, strain polymorphism, gene-expression patterns and homology data. The US National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/genome/guide/mouse) introduced a new browser option for finished sequence contigs and improved genomic annotation of the mouse genome, and the Wellcome Trust/Sanger Institute (http://www.sanger.ac.uk) announced improved mouse genome annotations and gene predictions. The Institute for Genome Research (TIGR; http://www.tigr.org) highlighted their extensive BAC-end sequence collection and their BAC-synteny map, while Oak Ridge National Laboratory (ORNL; http://bio.lsd.ornl.gov/ mgd/) discussed a collection of web services developed to support collaborative bioinformatics projects. Notable was the presentation by Yoshihide Hayashizaki (RIKEN Genomic Sciences Center, Yokohama City, Japan) who introduced FANTOM2 (http://www.gsc.riken.go.jp/e/FANTOM/), an expanded mouse genome 'encyclopedia' representing a collection of over 40,000 specific cDNA sequences.

Mutagenesis

Many novel functions for existing proteins, and indeed novel proteins, can be revealed by studies employing ENU mutagenesis, gene trapping and targeted mutagenesis. Miriam Meisler (University of Michigan, Ann Arbor, USA) discussed what has been learned of human neurological disease, and epilepsy in particular, from mice with mutations affecting sodium channels where it has been shown, for example, that seizures are related to neuronal hyperexcitability caused by altered channel porosity. Nancy Jenkins (Fredrick Cancer Research and Development Center, National Cancer Institute, USA) presented an interesting study of novel vesicle-transport mutations in the mouse. She described a small protein (Rab27a) of previously unknown function that is now thought to be an organelle receptor for an actin-based motor and part of the Rab GTPase protein family (participants in many protein trafficking mechanisms - often as determinants of vesicle-targeting specificity). Rab27a is thought to form part of a mechanism that distributes pigment granules to the neuronal-cell periphery and may have implications for sensory disorders. Allan Bradley (Wellcome

Trust/Sanger Institute, Hinxton, UK) outlined current approaches for establishing gene function in mutant mice. Balancer chromosomes make use of large (several megabase) chromosomal inversions to inhibit chromosomal recombination and maintain the association between a disease allele and an associated phenotypic marker (such as a coat color marker). When combined with ENU and targeted-gene mutagenesis, balancer chromosomes become a powerful tool for identifying individuals carrying a specific mutation, enabling all phenotypes to be distinguished, the screening effort to be minimized and the mutation to be localized on the chromosome. The characterization of complex traits was discussed by Ward Wakeland (University of Texas, Dallas, USA) in the context of a murine model of systemic lupus erythematosus (SLE), a debilitating chronic inflammatory disease that disproportionately affects females. He made functional genomic characterization seem easy with an elegant mouse congenic study that demonstrated how different genes interact to affect the combination of disease symptoms expressed and their severity.

Development

Developmental genetics was strongly represented at the meeting, with the genetics and genomics of axial arrangement of the mammalian embryo provoking much discussion. Elizabeth Robertson (Harvard University, Cambridge, USA) commemorated the late Rosa Beddington (National Institute of Medical Research, London, UK) in her talk on axis patterning under the control of 5′ and intronic enhancers of the patterning gene *nodal*. Robertson concluded that mediated reciprocal signaling is required between the epiblast and both the endoderm and visceral endoderm by the transforming growth factor β-related ligand to establish the anterior-posterior embryonic axis. Christine Disteche (University of Washington, Seattle, USA) discussed the transcriptional insulating role of binding sites for the CCCTC-binding-factor protein CTCF in the inactivation and reactivation of the X chromosome. On the silenced X chromosome most genes are inactivated but around 10% escape inactivation; one of these is the *SMCX* locus, which codes for a protein of unknown function. A number of CTCF binding sites occur in the region of this locus and are considered to play a role in insulating the locus from inactivation. The role of CTCF is thought to be blocking of transcriptional enhancement.

Alexander Agulnik (Baylor College of Medicine, Houston, USA) gave an interesting presentation on the mechanisms of testicular descent under the control of the *crsp* locus. He showed how the interaction of two genes, which encode the INSL3 hormone (an insulin-like protein) and its cognate receptor GREAT (a G-protein coupled receptor), affect the occurrence in males of cryptorchidism - failure of the testes to descend. Defects in the orthologous genes in humans have been shown to recapitulate the phenotypes observed in mice with mutations at these loci.

Disease

The theme of the mouse as a model for human disease continued throughout the conference, one focus being on the elucidation of gene function and gene networks using techniques ranging from retroviral tagging to microarray analysis. The study of neuronal genetic networks and signaling was well represented. Michel de Chaldee (Commisariat à l'Energie Atomique Saclay, France) discussed a study of the transcriptome of the murine brain that has revealed 126 expressed genes, many of them novel, including 20 new markers for brain regions. Function was able to be ascribed in many cases using serial analysis of gene expression (SAGE). Hee-Sup Shin (Korea Institute of Science and Technology, Seoul, South Korea) outlined a role for calcium channel regulation in mood disorders. T-type Ca^{2+} channels control the firing pattern of thalamic neurons; misfiring can create sleep-cycle disturbances and sleep-absence seizures. Mice lacking a particular class of channel (1G T-type channels) demonstrated manic behaviors, suggesting that these channels play a crucial role in mood regulation.

No short report can effectively convey the breadth of mammalian biology covered by this meeting, and we can fully expect that in the coming year the mouse will continue to reveal the secrets of mammalian genomic function and regulation. The 17th International Mouse Genome Conference is scheduled to take place in Braunschweig, Germany in November 2003.