Meeting report

Rats go genomic

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A report on the meeting 'Rat Genomics and Models', Cold Spring Harbor, USA, 8-11 December 2005.

The rat genomics research field is developing and maturing fast. Undoubtedly, the mouse has played an important role in this process as the rat's 'big' sibling from whom a lot has been learned. Indeed, as witnessed by contributions to a recent meeting on rat genomics at Cold Spring Harbor, technologies that have been developed for the mouse over the past decade are being rapidly transferred to the rat, and the collection of bioinformatics tools and biological resources is growing fast. At the same time the rat is distinguishing itself by providing valuable unique data.

A valuable model organism

Over the past decades, the isolation of over 200 different inbred rat strains that are unique models for complex diseases such as hypertension, diabetes, cancer and neurological disorders has proved the rat's value as a model for human disease. Currently, more than 1,000 quantitative trait loci (QTLs) have been identified and, as became clear during the meeting, this list is still growing. Although several causal polymorphisms in QTL regions - that is, polymorphisms that affect the trait in question - have been reported, the minimal genomic QTL segments that are obtained often contain hundreds of genes and are thus still too large for the identification of the causal gene. Moreover, the identification of causal polymorphisms in minimized QTL regions and characterization of the molecular processes underlying a given phenotype is posing a major challenge, as several such regions were presented that seemed to lack any protein-coding sequences.

A solution to the problem of finding candidate genes responsible for complex diseases lies in a systems biology approach, according to Tim Aitman (Imperial College, London, UK). He presented a combination of genome-wide microarray expression analysis and the identification of expression QTLs (eQTLs), genomic regions that are associated with a significant change in the expression of a specific gene, in a panel of phenotypically characterized rat recombinant inbred strains. This systematic approach resulted in the mapping of many novel *cis*- and *trans*-regulatory control elements. A study of the *cis*-regulated gene expression of the most highly linked eQTLs revealed attractive candidate genes for previously mapped QTLs for metabolic and cardiovascular disease phenotypes. The *trans*-regulatory eQTL dataset is more likely to reveal a complex network of transcriptional regulation.

Knockout technology is also likely to make an increasing contribution to novel rat models and the elucidation of genotype-phenotype relationships. Since the first presentation of rat knockout technology in the previous 'Rat Genomics and Models' meeting in 2003, several labs have produced a total of 15 targeted ethylnitrosourea (ENU)-induced knockout models and over 60 mutants with amino-acid replacements in a variety of genes. Howard Jacob (Medical College of Wisconsin, Milwaukee, USA) presented a program for genomics applications with the aim of knocking out more than a hundred genes. Most of the existing knockouts currently undergo outcrossing/incrossing and subsequent phenotypic characterization. Two rat knockouts were presented in more detail at the meeting: the serotonin transporter (SERT) knockout by one of us (B.S.) and the adenomatous polyposis coli (APC) knockout by James Amos-Landgraf (McArdle Laboratory for Cancer Research, Madison, USA). Interestingly, these both revealed striking differences in phenotypes compared with the corresponding mouse knockouts. Although preliminary, these specific rat knockouts seem to reflect human biology better than the mouse knockouts, indicating that rat models provide added value to existing models.

Resourcing the rat

The rat research community is growing in number, and as genomics technologies improve, the amount of genomics data and resources for the rat increased almost exponentially. Howard Jacob presented the latest developments for the Rat Genome Database (RGD) [http://rgd.mcw.edu], which has now become an indispensable platform for many researchers, as witnessed by the rapidly growing number of online users. RGD is continuously collecting and integrating this information into a database with a user-friendly interface. RGD already fulfills a unique role as a 'genome database' by integrating not only physical data from other vertebrates but also comprehensive QTL and phenotypic information from human and mouse. To meet the needs of disease-oriented research, RGD now has a Neurological Disease Portal and will release a Vascular Disease Portal soon. Jacob announced on behalf of RGD that the database has now set a goal of manually annotating all rat genes within the next 3 years.

Single-nucleotide polymorphisms (SNPs) are clearly of increasing importance in rat research. Not only are they versatile genetic markers that can be genotyped with increasing density and efficiency using emerging SNP-typing technology, but they are also expected to underlie most of the phenotypic differences observed between strains. Haplotype-based rat genetics is currently gaining momentum. Norbert Hübner (Max-Delbrück-Centrum für Molekulare Medizin, Berlin-Buch, Germany) described a new initiative funded by the European Union that aims to generate a haplotype map for the rat. The goal is to genotype about 100,000 SNPs in several hundred different inbred strains by the end of 2006. These genotyping data will be useful to correlate phenotypes with the ancestral origin of a strain, allowing the identification and narrowing down of the critical regions responsible for specific traits. Through the inclusion of essentially all important rat strains that are used around the world for QTL mapping experiments, researchers will be able to reduce the critical interval by linkage analysis using shared segments between their strains of interest, or select ideal strain combinations for intercross/backcross experiments.

In regard to SNPs, Jacob announced that the rat genome sequencing consortium will initiate a large SNP discovery effort by shotgun sequencing eight commonly used inbred rat strains, aiming at the discovery of more than 250,000 SNPs. On behalf of RGD, Jacob announced that it will release integrated SNP views on its genome browser within 6 months, which will allow individual researchers to make efficient use of this overwhelming amount of data on genetic variation.

Adding to the toolkit

One of the most versatile new tools for the rat presented at the meeting is likely to be transposon-mediated germline mutagenesis, a technique originally developed for the mouse. Colin Bishop (Baylor College of Medicine, Houston, USA) reported a proof-of-principle study of this tool for the rat. Germline transposition of the Sleeping Beauty (SB) transposon could be followed by the expression of the SB-encoded tyrosinase minigene, which is silenced in the transgenic construct but becomes active upon transposition, resulting in rat progeny with a range of different colored coats. The insertion points of the transposon can easily be retrieved by degenerate oligonucleotide PCR and sequencing. This method potentially allows the generation of a repository of inbred rat strains each carrying a defined loss-of-function mutation in a different gene. Transposons have the tendency to jump around locally in the genome after activation, making genome-wide coverage from a limited number of donor sites unlikely. This characteristic can also be exploited, however, as it would allow local saturation screens - for example, targeting all genes in a QTL region. As embryonic stem cell-based technology is still not available for manipulating the rat genome, transposon- and ENU-mediated germline mutagenesis are currently the only methods for producing loss-of-function mutations in a targeted fashion.

Novel tools and resources are being developed at a rapid pace. Phenotyping, which used to be a laborious and specialized job, is also becoming more high-throughput. Melinda Dwinell (Medical College of Wisconsin) described the PhysGen program at the College, which has generated and characterized two panels of consomic rat strains (in which a whole chromosome from one strain is introgressed onto the background of another strain), as well as ten inbred strains for hundreds of parameters. In total, nearly 400,000 physiological measurements were generated that are publically accessible from the PhysGen site [http://pga.mcw.edu]. The National Bio Resource Project [http://www.anim.med.kyoto-u.ac.jp/nbr] based in Kyoto, Japan, was reported on by Birger Voigt (Institute of Laboratory Animals, Kyoto University, Japan). The project is running an ambitious high-throughput phenotyping program aiming to characterize 283 rat strains for more than a hundred parameters related to a wide variety of disciplines. Currently, 113 rat strains have already been phenotyped for 109 parameters and, in addition, 122 strains were genotyped for 357 microsatellite markers. Together, these efforts will ultimately result in an extremely valuable resource for the scientific community.

Historically, the rat has been the favored model organism of physiologists, who generated lots of valuable phenotypic data. The rat genetics field has been moving over the years from QTL mapping of complex traits to positional cloning of candidate genes and is now facing the problem of identifying the causal polymorphisms. For this last step in particular, systems biology approaches and the need for tools to manipulate the genome become increasingly important. As was clear from this meeting, the combined efforts of rat researchers from all over the world have produced essential resources

and technologies and resulted in the rapid maturation of the rat as a model organism for genetic and genomics. We expect that we will witness the molecular dissection of many interesting genotype-phenotype relationships at the next meeting in two years time.