Meeting report

Caenorhabditis elegans and friends in Los Angeles

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A report on the 15th Biennial International *C. elegans* Conference, Los Angeles, USA, 25-29 June 2005.

Since it was first described in 1900 by E. Maupas and chosen in the late 1960s by Sydney Brenner as a species for genetic study, the nematode *Caenorhabditis elegans* has come a long way. The 'worm' has made innumerable contributions to biology, including a deep understanding of the processes of organ development and programmed cell death. At the biennial international conference on *C. elegans* held in Los Angeles in June, more than 2,000 researchers met to discuss their newest findings covering all of worm biology (abstracts are available at [http://www.genetics-gsa.org/genetics/Celegans]). Here we will highlight progress in the areas of functional genomics, RNA interference (RNAi) and related phenomena, and evolutionary studies.

Large-scale approaches: genomics and other 'omics'

The genome of *C. elegans* was the first metazoan genome to be sequenced and the worm is likely to be the first multicellular organism for which deletion mutations in all confirmed and predicted genes will be available. Mark Edgley from the *C. elegans* Gene Knockout Consortium (Oklahoma Medical Research Foundation, Oklahoma City, USA), and Shohei Mitani (Women's Medical University School of Medicine, Tokyo, Japan), from Japan's National Bioresource Project on *C. elegans*, reported that their groups have together generated over 3,000 deletion mutants, representing about 15% of known genes. Ronald Plasterk (Hubrecht Laboratory, Utrecht, The Netherlands) described the construction of a clonal library from 6,000 mutagenized worms that is being directly sequenced for mutations in genes of interest. He estimated that, using this technique, nonsense mutations in essentially all worm genes would be identified in the next two years.

Philippe Lamesch (Harvard Medical School, Boston, USA) described progress towards the completion of the ORFeome resource, an effort to clone all *C. elegans* open reading frames (ORFs) into Gateway vectors. *C. elegans* has some 22,800 predicted genes, and so far, 12,500 ORFs have been cloned. Jean-François Rual (also at Harvard Medical School) described the beginning of a extensive series of yeast two-hybrid experiments at Harvard, which will use this ORFeome resource to build a complete map of interactions among the proteins expressed by 11,000 of the ORFs in the ORFeome project. This worm interactome map builds on an earlier version that revealed about 5,500 potential protein-protein interactions. Also making use of the ORFeome, Denis Dupuy and colleagues at Harvard Medical School have begun work on the *C. elegans* localizome project with the stated goal of generating maps of gene expression and protein localization for most genes throughout the different developmental stages.

A *C. elegans* hermaphrodite consists of only 959 somatic cells; this is ideal for tracking individual cells during development but poses challenges when researchers want to determine the gene-expression profile of individual tissues, many of which are composed of just a few cells. In independent studies Rebecca Fox (Vanderbilt University, Nashville, USA) and Kim Wong (Genome Sciences Center, Vancouver, Canada) used tissue-specific green fluorescent protein (GFP) reporters together with fluorescence-activated cell sorting (FACS) followed by microarrays or serial analysis of gene expression (SAGE), respectively, to tackle this problem. Fox reported on the profiling of cells from the embryonic motor circuit, where she not only found genes already known to be expressed there, but also discovered a large number of

G-protein-coupled receptors not previously known to be expressed in these cells. Wong constructed SAGE libraries from a variety of tissues, including muscle, gut, hypodermis and oocytes, and was able to detect over 400 different transcription factors in the developing embryos.

Double-mutant suppression (or enhancement) studies of synthetic interactions between two genes using whole-genome RNAi screening in mutant backgrounds reveal novel functions for genes that are missed in most forward genetic studies, where commonly just a single gene is perturbed. Andrew Fraser (The Wellcome Trust, Sanger Institute, Cambridge, UK) described the development of a highly automated system that allows around 1,200 genetic interactions to be probed in a day. Fraser is using this high-throughput system to identify 'interactor' genes that are synthetic lethal with genes of interest. One of the interacting pairs identified is *efl-1* (the worm equivalent of the transcriptional regulator E2F) and *lin-35* (the equivalent of the retinoblastoma protein Rb).

RNA interference and microRNAs

RNAi was initially discovered in *C. elegans* and much of our understanding of its mechanism comes from studies in the worm. At the meeting it became clear that worms have still more to offer. Testing individual candidate genes, Nathaniel Dudley (University of North Carolina, Chapel Hill, USA) reported the identification of six new genes, including genes for chromatin-associated factors, that are required for RNAi. In contrast, John Kim (Harvard Medical School) has undertaken a genome-wide screen to identify genes required for RNAi and has identified 90, including Piwi/PAZ proteins, DEAH helicases, RNA-binding/processing factors, and chromatin-associated factors, among others. Thomas Duchaîne (University of Massachusetts Medical School, Worcester, USA) described a biochemical approach to identifying proteins that interact with DCR-1 (Dicer) using multidimensional protein identification technology (MudPIT) and has found known and novel proteins that act negatively and positively on RNAi as determined by mutant analysis, as well as proteins involved in the microRNA (miRNA) pathway. Three independent groups are examining the role of RNAi as an antiviral mechanism in *C. elegans* and have set up *in vitro* systems for infection of *C. elegans* cells. Morris Maduro (University of California, Riverside, USA), Courtney Wilkins (University of Arkansas, Little Rock, USA) and Daniel Schott (Harvard University, Cambridge, USA) reported that the cells respond by silencing the expression of exogenous RNA and that the silencing is compromised in RNAi-deficient mutant cells.

The most surprising of the presentations on miRNAs came from Shveta Bagga (University of California, San Diego, USA). She challenged the view that miRNAs regulate their targets at the translational level, and suggested that much of the regulation is occurring at the mRNA level. Bagga found that mRNA levels of the *let-7* miRNA target *lin-41* decrease markedly when *let-7* is expressed, but that there is no change in mRNA levels in a *let-7* mutant background. Similar results were observed for the miRNA *lin-4* and one of its targets. Further work will be needed to determine if the effects seen are caused directly by the miRNAs and to establish the generality of these findings with respect to other miRNAs and organisms.

Evolutionary comparisons

With the genomes of *C. elegans* and the related species *C. briggsae* sequenced and assembled, and with another eight nematode species in the pipeline, worms provide a robust platform for comparative genomics and evolutionary studies. Sheldon McKay (Cold Spring Harbor Laboratory, USA) presented an update on genome-wide sequence analyses and new computational tools for comparative genome analysis using *C. elegans*, *C. briggsae* and *C. remanei* sequences. The *C. remanei* sequence is currently being assembled. McKay's initial findings reveal surprising conservation of synteny and colinearity among the three genomes, in addition to conservation of operon structures. Ray Hong (Max-Planck Institute for Developmental Biology, Tübingen, Germany) reported on the current status of the genome-sequencing project on the nematode *Pristionchus pacificus*, which has reached 1x coverage. Karin Kiontke (New York University, USA) described a phylogenetic study using sequences of three nuclear genes of 47 nematode species in the order Rhabditida and their relatives, which led her to propose that hermaphroditism evolved independently at least ten times from species with males and females. Kiontke also presented support for the inclusion of the model organism *P. pacificus* in the Rhabditida. Marie-Anne Felix (Pasteur Institute, Paris, France) presented a detailed study on the evolution of vulval patterning in the genus *Caenorhabditis* down to the level of molecular pathways involving a Ras signaling cascade. Finally, Min Hua Xiao (also at the Max-Planck Institute for Developmental Biology) reported surprising differences in the role of Wnt signaling during vulva induction in *C. elegans* as compared to *P. pacificus*, and described the introduction of antisense morpholino oligonucleotides as a new tool for functional genetics studies in *P. pacificus*.

With a rich toolkit including multiple genome sequences, ways of generating high-throughput knockouts, and whole-genome RNAi screens, *C. elegans* is poised to make major contributions to the various research trends currently described as 'systems biology'. In recent years the worm has given us RNAi and short RNAs, what can we expect next?