Meeting report

Global 'worming'

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A report on the 16th International *Caenorhabditis elegans* Meeting, Los Angeles, USA, 27 June-1 July 2007.

Held every other year at the University of California, Los Angeles, the international *Caenorhabditis elegans* meetings feature exciting new research into all aspects of nematode biology. *C. elegans* has truly made the leap into the genomics era, with a number of groups reporting new developments in developing reagents (including targeted deletions and transposon collections) and mapping genome modifications. Resources such as the NEXTDB database of patterns of gene expression [http://nematode.lab.nig.ac.jp], databases of open reading frames, gene interactions and promoters (see, for example, the resources provided by the Vidal lab [http://vidal.dfci.harvard.edu/resources_index.htm]), and whole-animal reconstructions are being refined and made user-friendly. Here, we present a few interesting vignettes for the readers of *Genome Biology*; a complete list of abstracts presented at the meeting is freely available at [http://genetics.faseb.org/genetics/Celegans/2007meeting/absvolume.shtml].

In his keynote address, Gary Ruvkun (Massachusetts General Hospital, Boston, USA) addressed questions ranging from gene regulation to extraterrestrial life. On the roles of small noncoding RNAs, he predicted that RNAs 20 to 30 nucleotides long were likely to mediate genome surveillance and oncogene regulation, and act as systemic signals. He also showed evidence that a large suite of genes is involved in the positive as well as the negative regulation of RNA interference (RNAi) and of microRNAs (miRNAs), and that many of these genes are broadly conserved and likely to mediate processes involving small RNAs in many organisms. Ruvkun suggested that we are just beginning to realize the breadth of small RNA biology, predicting that changes in synaptic signaling between neurons is one place to look for likely miRNA functions. He noted that RNAi and miRNA pathways have already been implicated in retinoblastoma and lymphoma cell-fate transformations and may figure in other tumors as well. Ruvkun also discussed how RNAi is already transforming genetics and suggested that new surrogate genetic systems are likely to emerge as organisms with powerful RNAi are discovered. He warned the assembled worm biologists that small interfering RNA (siRNA) libraries in mammalian systems already allow full-genome screens for phenotypes that can be scored in cultured cells, but that whole-organism phenotypes, such as fat storage or aging, are still mainly the province of worm RNAi. Ruvkun rounded off his talk with a new direction that some of his group are taking. On the premise that life on Mars may be ancestrally related to life on Earth, they are attempting to identify potential life by amplifying highly conserved ribosomal sequences (16S) from Martian soil as part of the Search for Extra-Terrestrial Genomes (SETG) project.

Targeted genome modifications

On the technology front, researchers continue to chip away at the Achilles' heel of *C. elegans* - targeted genome modifications. Valérie Robert (EU NemaGENETAG Consortium, Ecole Normale Supérieure, Paris, France) reported on the considerable step in this direction made by the consortium, using a *Mos1* transposon approach to generate targeted mutations (MosTIC). She described the generation of a *Mos1* insertion library containing 55,000 entries. At first glance, no insertion 'coldspots' were obvious, suggesting that all genes can potentially be targeted. To create targeted mutations, consortium members identified strains with *Mos1* insertions in or very close to a gene of interest. Upon transposase expression, *Mos1* excision causes DNA double-strand breaks that are repaired by gene conversion from a template previously introduced into the strain as an extrachromosomal array. If the gene of interest contained in the array is modified (for example, by insertion of a point mutation or a green fluorescent protein tag), then the repaired chromosome will carry the modification. Robert

pointed out that two limitations of this approach - a moderate frequency of gene conversion (10^{-4} to 10^{-5} events per generation) and the short (around 500 bp) range of gene conversion from the *Mos1* insertion - are counterbalanced by the large number of *Mos1* insertions that have been generated. Hence, MosTIC could become an attractive tool for genomic engineering in *C. elegans*.

Christian Frøkjær-Jensen (University of Utah, Salt Lake City, USA) presented a strategy for low-copy transgene integration using a *Mos1* element located in a stretch of noncoding DNA. He and colleagues generated an extra-chromosomal array with a transgene of interest and a positive selection marker flanked by DNA homologous to the *Mos1* insertion site. Transposase expression induced double-strand breaks by *Mos1* excision, and through homologous recombination the transgene was inserted into this chromosomal locus. Integrants are identified by co-insertion of a positive selection marker and distinguished from animals carrying the array alone by the loss of a negative-selection marker contained on the array. Encouragingly, integration efficiencies of 1 in 100 transposase-expressing adults were observed, as was transgene expression in the germline, a site typically refractory to transgene expression.

The current gene-targeting paradigm in *C. elegans*, PCR identification of mutagen-induced random deletions together with other mutants identified by the *C. elegans* community, recently passed an important milestone. Speaking on behalf of the knockout consortium groups, Mark Edgley (University of British Columbia, Vancouver, Canada) described the identification of 5,000 deletion mutants in 4,000 genes, along with a comprehensive search of other mutant alleles in WormBase [http://www.wormbase.org] that added another 1,000 genes. This total of 5,000 genes identified by mutation corresponds to more than 25% of all the predicted *C. elegans* genes.

Mapping mutations and identifying the mutated genes still takes several months. At present, the most used approach involves genetic mapping using single-nucleotide polymorphisms (SNPs). Jason Maydan (University of British Columbia, Vancouver, Canada) presented an interesting way to expedite this process, using array comparative genome hybridization (array CGH) to identify deletions and point mutations rapidly. High-density oligonucleotide microarrays (with 385,000 features) probing the entire genome were generated. A genome alteration is identified as a decrease in the hybridization signal of mutant genomic DNA to specific probes in this array. Maydan described how the application of array CGH to wild *C. elegans* isolates (newly isolated from different geographical locations) has revealed deletions in an astonishing 3% or so of genes when compared to the wild-type strain N2 (Bristol). Most of these genes have been implicated in chemosensation and immunity, suggesting how local environments influence the genetic make-up of nematodes.

Environment-genome interactions

The extensive genetic variation described by Maydan made considerable sense in light of work reported by Joseph Coolon (Kansas State University, Manhattan, USA) on microarray experiments with *C. elegans* cultured on soil bacteria from the Konza Prairie Long Term Ecological Research site near Manhattan, Kansas. Expression of 202 genes varied on the different bacterial foods, and single deletion mutants in some of these genes showed reduced relative fitness on the bacteria that induced their expression. Coolon noted that this provides compelling evidence of how environmental differences create extensive gene-expression differences within populations of a given species, and also suggests that natural selection could act on regulatory mutations of these fitness genes.

Extending this concept, Matt Rockman (Princeton University, Princeton, USA) described work addressing how genetic variations in wild *C. elegans* isolates shape phenotypic variation. Around 200 recombinant strains homozygous for varying regions of either N2 (Bristol) or CB4856 (Hawaii) DNA have been generated and a high-resolution SNP map produced for each. He and his colleagues found an unexpected genetic incompatibility between N2 and CB4856 and also cloned one of the underlying loci. A recessive polymorphism in the *spat-3* gene has been identified that affects octanol responses in concert with other CB4856 loci, but not in an isogenic N2 background. These studies have uncovered functions and gene interactions inaccessible to genetic screens and suggest how genetic modules may evolve.

Caenorhabditis neurobiology

Behavioral responses have long been used in *C. elegans* to gain insights into the genes and mechanisms underlying the function of the nervous system. Two new behaviors and the genes underlying them were discussed at the meeting. Kenneth Miller (Oklahoma Medical Research Foundation, Oklahoma City, USA) described a *C. elegans* photophobic response in which the animals detect and avoid blue and shorter wavelengths of light. Genetic screens identified three loci that control this response. Interestingly, one of these genes, *lite-1*, encodes an eight-transmembrane member of the gustatory receptor family with no homology to G-protein-coupled receptors. Miller reported that although *lite-1* normally functions in neurons, transgenic expression of *lite-1* in muscle cells enables this tissue to respond to light, suggesting that LITE-1 may function as the light sensor.

Roberto de Araujo (Columbia University, New York, USA) described a *C. elegans* response to gravity. When he set wild-type *C. elegans* on agar plates oriented vertically, they distributed themselves randomly. However, mutations affecting the activity of subsets of neurons resulted in animals that moved to the top or bottom of the plates. The expression pattern of the affected genes identified sensory neurons that

may respond to gravity, as well as identifying a possible circuit for gravitaxis.

Understanding how neural circuits function remains a central challenge in modern neurobiology. Precisely controlled activation of most neuronal cell types (except sensory neurons that are accessible to external stimulation) in living organisms has been a difficult task. Martin Brauner and Alex Gottschalk (Goethe University, Frankfurt, Germany) described a light switch to turn neurons 'on' and 'off'. Channelrhodopsin-2 (ChR2) and the chloride pump halorhodopsin (NpHR) can excite and inhibit neurons, respectively, at different wavelengths of visible light. They presented details and potential applications of this powerful new technique (termed 'optogenetics') developed for *C. elegans*. A neuron expressing ChR2 can be activated with blue light, whereas a neuron expressing NpHR can be inhibited with yellow light, and so selective activation and inhibition of target cells can be achieved by coexpression of the two rhodopsin molecules. It is already apparent that optogenetics will change the way we study the neuronal interplay underlying different *C. elegans* behaviors.

On a lighter note, Paul Sternberg (Caltech, Pasadena, USA) announced a prize of $4,000, and the right to name the species, to go to the first person to isolate a sister species of *C. elegans*. One objective of Sternberg's program is to sample the genus *Caenorhabditis* and related genera for phylogenetic and evolutionary studies. We look forward to getting an update on this program and other developments at the next international *C. elegans* meeting in two years' time.