Meeting report

Molecular helminthology in the Rockies

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A report on the Keystone Symposium on Molecular Helminthology, Copper Mountain, Colorado, USA, 9-13 April 2005.

Introduce most genome biologists to a parasitic worm and their thoughts are likely to turn rapidly to exit strategies. To the research community gathered recently for a Keystone meeting on molecular helminthology in Colorado, however, these organisms are fascinating highpoints of evolution, with biological tricks aplenty and many lessons to teach on the hows and whys of genomic diversity. They are also, of course, major determinants of human health and happiness worldwide. And even if there were faint-hearted fellow travellers at the meeting, 30 inches of snow closing both the airport and the interstate highway ensured that we were all trapped for the duration.

Helminthology is a phylogenetically incorrect discipline, encompassing widely separated parasitic platyhelminths (flatworms) and parasitic nematodes (roundworms). Platyhelminths are members of the Lophotrochozoa, a diverse superphylum of nonvertebrate animals that includes annelids and molluscs. Nematodes are members of the other major group of nonvertebrates, the Ecdysozoa, which also includes arthropods. Their conjunction as 'helminths' stems from outmoded systematic concepts but has been preserved because these parasites are usefully linked by their lifestyles as metazoan parasites of metazoan hosts. While only a small subset of helminth diversity was discussed, the content of the meeting should be of interest to anyone with a phylogenomic bent. In particular, it offered an overview of the first genome sequence from any lophotrochozoan and a richness of comparative nematode genome data to place alongside the *Caenorhabditis* model. Given that the parasites have coevolved with their hosts, the coevolution of immune effector and immune evasion strategies was also explored.

Platyhelminth genomes and functional genomics

Status updates on the two major parasitic helminth genome projects now underway were presented to the assembled research communities. The genome sequence from the trematode flatworm *Schistosoma mansoni* [http://www.schistodb.org] is nearing completion, as reported in a joint presentation by Najib El Sayed (The Institute of Genomic Research (TIGR), Rockville, USA) and Matthew Berriman (The Sanger Institute, Cambridge, UK). The *S. mansoni* genome is estimated to be approximately 300 megabases (Mb) in size, and extensive expressed sequence tag (EST) and open reading-frame expressed sequence tag (ORESTES) surveys have suggested the 'usual' nonvertebrate metazoan count of 15,000 to 20,000 protein-coding genes. TIGR and the Sanger Institute have been pursuing a whole-genome shotgun strategy, and reported a ninefold coverage assembly. A major issue in assembly has been polymorphism: the strain of parasite used was not particularly inbred (*S. mansoni* is an obligately sexual species), and thus assembly parameters have had to be finely tuned to accept allelic polymorphisms. The experience gained in assembly of this genome is likely to be invaluable as additional, 'wild' non-model organisms join the sequencing queues. The *S. mansoni* genome is very rich in repeats and retrotransposons, and this feature has made long-range assembly, particularly with fingerprint maps, difficult.

The availability of whole-genome shotgun and EST data has spurred much activity in functional genomic analysis of *S. mansoni*. The parasite has a complex life cycle involving two hosts (a snail and a human) and many morphological stages, some of which are difficult to access. New data on relatively robust, penetrant and persistent RNA interference (RNAi) using small interfering RNAs (siRNAs) directed against *S. mansoni* genes encoding a glucose transporter and a CD36-like scavenger receptor were presented by Timothy Yoshino (University of Wisconsin, Madison, USA). Jason

Correnti (University of Pennsylvania, Philadelphia, USA) described continuing RNAi effects on a cathepsin B protease from treated larvae through to adult schistosomes in the mammalian bloodstream. RNAi was also used to investigate the roles of possible drug targets such as peroxiredoxins, as reported by Ahmed Abd El-Aziz Sayed (Illinois State University, Normal, USA), and serotonin signaling, as described by Nicholas Patocka (McGill University, Montreal, Canada). In both cases RNAi identified these targets as essential for worm survival. RNAi could be used as a rapid first screen of the drug-target potential of genes identified in the parasite genome sequence. Christoph Grevelding (Institute for Parasitology, Giessen, Germany) reported attempts at transgenesis, but as yet only transient transfection has been achieved.

Nematode genomic diversity

Nematode enthusiasts were also well served at the meeting, with one nearly complete and one preliminary whole-genome shotgun survey of parasite genomes and evidence of reliable RNAi and transgenesis in important parasite species. Of course, for the nematodes, stellar comparators are available, with the fully characterized genome of *Caenorhabditis elegans* and drafts for other *Caenorhabditis* species. Elodie Ghedin (TIGR) updated us on the genome sequence of *Brugia malayi*, a tissue-dwelling human parasite and a causative agent of elephantiasis, based on an 8.5-fold coverage whole-genome shotgun assembly. At 80 Mb the *B. malayi* genome appears to be smaller than that of *C. elegans* and, as average gene size is larger, *Brugia* may have less than 70% of the number of genes of its free-living distant relative. As many *B. malayi* genes are absent from *C. elegans* but present in other metazoans, the genetic disparity may be even more extreme. As Vincent Laudet (Ecole Normale Supérieure, Lyon, France) discussed in the keynote address, the *C. elegans* proteome is famously marked out by having more than 250 nuclear hormone receptors compared to the normal number of 20-30 in other metazoans. *B. malayi* has a normal number of nuclear hormone receptors, but it appears to have a superfluity of phospholipaseA2-like domains and von Willebrand factor domains. Are these associated with its parasitic lifestyle? Makedonka Mitreva (Washington University School of Medicine, St Louis, USA) presented a single-pass whole-genome shotgun of the genome of the hookworm *Ancylostoma caninum*, identifying a high proportion of repetitive sequence (approximately 28%) but so far only around 10,000 genes in 72 Mb of unique sequence. *A. caninum* is closer, phylogenetically speaking, to *C. elegans* than either is to *B. malayi*, and the comparison is likely to aid not just parasitology but also comprehension of the model organism genome.

Another idiosyncratic feature of the *C. elegans* genome is the presence of over 2,000 operons, consisting of two to eight genes cotranscribed from a single promoter. Pre-mRNAs from these operons are resolved into monocistronic mRNAs through *trans*-splicing. *Trans*-splicing is also used on many *C. elegans* genes not in operons. *Trans*-splicing is present in a wide phylogenetic range of eukaryotes, but its evolutionary origins remain obscure. While *trans*-splicing is found in apparently all nematodes, the enthusiasm of *C. elegans* (and close relatives) for operons may be a limited speciality as Ghedin reported identification of only around 40 operons in the *B. malayi* genome. Richard Davis (University of Colorado Health Sciences Center, Denver, USA) discussed the biology of *trans*-splicing, and suggested that the phenomenon may be associated more with sanitizing 5' UTRs (ensuring that they have no out-of-frame stop codons) than with mRNA stability or promotion of translation. Importantly, he reminded us that platyhelminths do *trans*-splicing too, and that components specific to *trans*-splicing may be excellent drug targets.

Parasites know more about our immune system than we do

A third theme of the meeting, involving both flatworms and roundworms, concerned the interactions between parasites and their hosts. Helminth parasites have been evolving side by side with the mammalian immune system for many millions of years, and 'know' how to manipulate it, often to devastating effect. Kalyanasundaram Ramaswamy (University of Illinois, Rockford, USA) has focused on the invasion of schistosome larvae through the skin, and reported the identification of unique flatworm products that have no detectable similarity to any of the mammalian components of the pathways affected but still effectively silence or divert the resident innate immune system. William Harnett (University of Strathclyde, Glasgow, UK) has identified a glycan modification on proteins secreted by filarial nematodes that is a potent downregulator of damaging allergic responses, even in murine models of arthritic disease. Maria Yazdanbakhsh (Leiden University Medical Center, Leiden, The Netherlands) described how helminth infections bias the whole of the immune system, making infected populations less susceptible to allergy. She has identified a single schistosome membrane lipid component that mirrors these immunomodulatory effects. Parasite-derived immunomodulators have promise as therapeutics for many immune-related pathologies, including asthma.

As metazoans, helminth parasites share core regulatory, developmental and homeostatic pathways with their hosts, and evidence is mounting that parasites sense, respond to and manipulate their hosts' signaling milieux. To reach maturity, *S. mansoni* requires host cytokine interleukin-7, as reported by Isabelle Wolowczuk (Institut Pasteur, Lille, France), and the thyroid hormone thyroxine, as described by James McKerrow (University of California, San Francisco, USA), but whether these effects are direct or via some local environmental changes remains unclear. The cestode *Echinococcus multilocularis*, another nasty flatworm parasite

with a predilection for the liver, has an ability to grow unnoticed by the host for years. Klaus Brehm (University of Würzburg, Germany) presented a stunning overview of conserved insulin, fibroblast growth factor and transforming growth factor-β (TGF-β) receptor pathways in *Echinococcus* that mediate its survival in an *in vitro* analog of the liver phase. Strikingly, *E. multilocularis* recognizes human insulin and bone morphogenetic protein 2 (a TGF-β-family ligand) through its insulin and TGF receptor pathways, and these stimulations were necessary for survival. This flatworm displays convergent recognition of mammalian cytokines and signals based on co-option of ancient, conserved signaling modules to new functions.

Plans are already in place to complete another 5 to 7 nematode genomes in the next two or three years, and the queue of successful species can only grow longer. The challenge now is to get the tools in place to analyze, interpret and test the functions implied by genome sequences. This meeting showed that the community is aware of this challenge and should be ready for the deluge of data expected.