

Meeting report

The not-so-humble worm

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A report of the Wellcome Trust meeting “*Caenorhabditis elegans* past, present and future: The not-so-humble worm”, Hinxton, UK, 10 September 2003.

This meeting was held to celebrate the award of the Nobel Prize in Physiology or Medicine for 2002 to Sydney Brenner, Sir John Sulston and Robert Horvitz for their work on the worm *Caenorhabditis elegans*. The invited speakers included all three Nobel laureates, together with some of the pioneering researchers who had worked with them in Cambridge on the worm. The list of speakers thus reads like a *Who's Who* of the worm community, and the topics discussed ranged across the whole of worm biology, from germline development and embryogenesis to dosage compensation, aging, touch-cell function and the newer field of host-pathogen interactions.

The Nobel laureates

Sydney Brenner (Salk Institute, San Diego, USA) began proceedings with a typically broad talk including a discussion of the ‘CAP criteria’ (comprehensive, accurate and permanent) that he has proposed as the gold standard for data. This provides a robust and lasting foundation that can be accessed and trusted by all researchers. One of the clearest examples of ‘CAP’ standard data is the construction of the complete fate map of worm development. John Sulston (Sanger Institute, Cambridge, UK), who was clearly central to the construction of that map, spoke principally about his involvement with the human genome sequencing project, particularly stressing the need to keep as much data as possible in the public domain. His view is unequivocal - that restriction of access to either data or the literature affects trust between researchers and impedes progress. It is precisely these principles of openness and community that have

always characterized worm research and made it such an attractive area to work in.

Robert Horvitz (Massachusetts Institute of Technology, Cambridge, USA) reiterated this message and congratulated worm researchers on maintaining a friendly and cooperative community. He gave a historical overview of research into programmed cell death, outlining the key steps in discovering the core pathway that has proved central to our understanding of apoptosis in all organisms. This perspective included the contributions of both Edward Hedgecock, who isolated the phagocytosis-defective *ced-1* strain in 1983, and Hillary Ellis, who identified the first death-defective mutant (in the *ced-3* gene). Horvitz outlined some of the questions he is pursuing at present: for example, we still do not know the cellular targets of CED-3, the key caspase in the worm, nor do we know why programmed cell death is activated in the 131 cells that die during hermaphrodite development.

Nematode genomes

One of the key recent advances in *C. elegans* research has, of course, been the reading of the complete sequence of its genome. Genome sequence is again an example of data that achieve Brenner’s CAP criteria. Robert Waterston (Washington University School of Medicine, St Louis, USA) and Richard Durbin (Sanger Institute) discussed progress in the analysis of the sequences of *C. elegans* and *Caenorhabditis briggsae*. In *C. elegans* - the only metazoan whose genome has been completed, with no gaps - one of the key areas still to be fully resolved is gene prediction. Whereas the number of predicted genes is going up by only a few hundred a year (and is thus fairly stable), the number of predicted protein isoforms is going up much more rapidly. More than 2,000 have been added in the past few years, and the number is sure to increase for a long time to come. Waterston also described an extensive test by reverse-transcriptase-coupled PCR (RT-PCR) of gene predictions in *C. elegans*. He

reported that 65% of predicted genes could be fully confirmed by RT-PCR and 15% partially confirmed; of the 20% that could not be confirmed, many may be real but undetectable by RT-PCR because they are expressed at too low a level. Together, these data imply that gene predictions are pretty accurate, although there is clearly some room for improvement. Such data should also help in tweaking gene-prediction algorithms to improve performance.

Durbin concentrated on comparisons between the *C. elegans* genome and the newly available *C. briggsae* genome sequence. The two worms share around 12,000 one-to-one orthologs, but each genome has approximately 2,000 genes with no obvious match in the other. There are also clear local expansions: *C. elegans*, for example, has more predicted genes involved in chemosensation than has *C. briggsae*. An odd fact is that around 20% of *C. briggsae* genes have an extra intron relative to their *C. elegans* counterparts; the cause and significance of this is unknown. No repeated sequences that can be traced back to the last common ancestor of the two worms have been detected; thus, all repeats in each genome appear to be new. The rate of rearrangement (0.5 breaks per megabase per million years (breaks/Mb/Myr)) is very high (compared with fewer than 0.01 breaks/Mb/Myr between human and mouse), and breaks are more frequent on the autosome arms than on the X chromosome. As more sequence is assembled from other nematode species, not only will gene prediction improve, but we should also become much better at identifying functional noncoding sequence elements. This should be a very fertile area in the future.

Development and sex determination

Genetics has proved a powerful approach to dissecting the signaling pathways and developmental decisions that lead to the precisely determined cell lineage in the worm. Jim Priess (Fred Hutchinson Cancer Research Center, Seattle, USA) and Judith Kimble (University of Wisconsin, Madison, USA) discussed signaling in mesoderm determination and the germline, respectively. Priess described how correct mesoderm development requires signaling through the Wnt pathway to set up a repeated series of asymmetric cell divisions and Notch-mediated signaling events. These, in turn, affect complex interactions between transcription factors, including POP-1, members of the T-box family and basic helix-loop-helix proteins. The single-cell detail at which this kind of patterning can be understood in the worm illustrates beautifully the power of having a fixed (and painstakingly worked out) lineage for the animal.

A Notch signaling pathway is also used by the distal tip cell of the worm gonad to signal to the germline, regulating the decision of potential germ cells to proliferate or to enter meiosis. Kimble described how, whereas entry into the mitotic cell cycle is promoted by a family of Fem-3 binding factor (FBF) RNA-binding proteins, entry into the meiotic cell cycle is

regulated by three germline differentiation (GLD) proteins; the balance between these two groups of factors is critical for germline function. Furthermore, the finding that both *Drosophila* and *C. elegans* germline stem cells are maintained by FBF-related proteins suggests that this may be an ancient mechanism for controlling germline stem cells.

Sex in worms is determined uniquely by X-chromosome dosage: males have a single copy of the X and hermaphrodites have two. In humans, dosage compensation is achieved by silencing one of the two copies of the X chromosome in females, but in hermaphrodite worms it is achieved by reducing transcription from both X chromosomes. Barbara Meyer (Howard Hughes Medical Institute, University of California, Berkeley, USA) presented an overview of the dosage compensation complex (DCC) in worms, which is a complex of proteins that are involved in repressing transcription of X-linked genes. On the basis of weak homology of the DCC to components of the condensin complex, she suggested a possible common origin for the DCC and the mitotic cohesin complex, which holds sister chromatids together. The main focus of Meyer's talk was the way by which the DCC discriminates between the X chromosome and the autosomes. Following a series of elegant experiments involving duplications of regions of the X, she suggests that X chromosomes contain multiple independent recruitment sites for the DCC. Her laboratory has mapped one of these sites to a region of around 900 base-pairs that is also strongly conserved in *C. briggsae*. The mechanism by which these sequences are recognized by the DCC is still not known, nor is it known whether they are transcribed.

Other *C. elegans* research

The complex genetics of interactions between *C. elegans* and its pathogens is a relatively new field of research, and Jonathan Hodgkin (University of Oxford, UK) described his recent work in this area. Worms infected with the pathogenic bacterium *Microbacterium nematophilus* show a swelling response that appears to be protective in nature and which involves local activation of a mitogen-activated protein (MAP) kinase cascade. Overexpression of the kinase MEK-2 causes swelling, whereas MAP kinase loss-of-function prevents it. Intriguingly, while many of the MAP kinase cascade components can be shown to affect the swelling response, the small GTPase Ras, which acts as an activator of the cascade in other developmental contexts, does not appear to be involved; it will certainly be interesting to see what lies further upstream in this particular pathway. Screens for genes required for swelling have identified around 20 *bus* (bacterially unswollen) loci, most of which appear to be novel genes. There should be much progress in this emerging area of worm biology in the next few years.

One great quality of the nematode as a model organism is its simple and well-defined nervous system. Martin Chalfie

(Columbia University, New York, USA) has devoted years of research to understanding the worm's mechanosensory system. He gave a beautiful overview of mechanosensation and progress in understanding the touch cells (the sensory receptors for gentle touch in the worm) from the first steps of following their cell processes by electron microscopy of serial sections to identification of the components of the putative 'touch complex'. This complex includes channel components, extracellular-matrix proteins and cytoskeletal proteins. Chalfie also described recent experiments in which purified populations of touch cells have been used as a basis for microarray experiments aimed at identifying touch-cell-specific genes: as there are only six touch cells per animal this is an impressive feat. His lab has identified around 70 genes that have increased expression in touch cells, including many of the *mec* genes previously identified as positive regulators of mechanosensation.

In recent years the worm has become notable for how easily RNA interference (RNAi), can be used to severely reduce the expression of any desired gene. Cynthia Kenyon (University of California, San Francisco, USA) presented recent data from RNAi screens designed to identify genes involved in aging, and described attempts to pin down the tissues in which DAF-16 (a key forkhead transcription factor involved in determining life span) needs to be expressed to affect aging.

Finally, in the course of describing the history of the study of cytokinesis in the worm from its earliest days, John White (University of Wisconsin, Madison, USA) raised the intriguing possibility that cytokinesis in animal cells may be more similar to that in plant cells than previously thought. This is based on a recent demonstration that targeted secretion is required for the completion of cytokinesis in the worm as it is during plant cytokinesis.

Overall, this meeting was a beautiful presentation of the enormous progress that has been made in the worm field over the past 30 years, along with a promise of much more to come. It has been a great year for the worm community, and this relaxed meeting was a perfect way to celebrate the huge contribution of the three Nobel Prize winners.