Meeting report

Understanding embryonic development: from screens to genes

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A report on the 64th Annual Meeting of the Society for Developmental Biology, San Francisco, USA, 27 July-1 August 2005.

The elucidation of the complete genome sequences of various model organisms, in conjunction with the development of new screening methods, provides a type of functional genomics that has been unavailable to developmental biologists in the past. The collaboration between novel computational and molecular biological techniques and traditional embryology was evident in the outstanding research presented at the annual meeting of the Society for Developmental Biology held in San Francisco this summer. The underlying theme of the meeting was how a partnering between different disciplines can be extremely fruitful in enabling both gene discovery and the understanding of how genes work in concert to carry out developmental processes.

Highly pertinent to this theme were discussions about RNA interference (RNAi) screening. Julie Ahringer (Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK) discussed the work in her laboratory that uses genome-wide RNAi screening to understand the molecular basis of cell polarity in the nematode *Caenorhabditis elegans*, in which RNAi is readily achieved by feeding worms with bacteria containing DNA sequences encoding interfering RNAs. Using an RNAi library consisting of 16,757 such bacterial strains, covering 86% of the *C. elegans* genome, Ahringer's group has identified 1,722 genes with an RNAi phenotype (1,200 of which are novel) by performing a dissecting microscope screen for worms showing lethality, abnormal morphology or movement, or slow growth. The lethal mutants isolated in this first screen were subsequently examined for various polarity defects, and 541 out of 945 lethal genes were identified that fit these criteria. Two of these genes, *chp-1* and *CK1* (encoding casein kinase 1), are involved in spindle position and orientation. *chp-1* is also known to function in maintaining the balance between anterior and posterior PAR (partitioning-defective) proteins. CHP-1 normally localizes to the cytoplasm and is thought to play a role in degrading those PAR proteins with anterior localization; the *chp-1* RNAi phenotype shows symmetric cell division. The *CK1* RNAi phenotype leads to the production of an asymmetric, unstable spindle such that both pronuclei go to the anterior end of the cell. Casein kinase 1 normally localizes to the asters and has a punctate distribution in the cytoplasm, helping to position the spindle through forces that involve the activity of the G-protein regulators GPR-1 and GPR-2 (GPR1/2). CK1 functions upstream of phosphatidylinositol-4-phosphate 5-kinase (PPK-1), a protein that generates phosphatidylinositol diphosphate (PIP_2) through the phosphatidylinositol signaling pathway. Ahringer described how RNAi against both *GPR-1/2* and *CK1* showed that GPR-1/2 works in a signaling cascade with CK1 and PPK-1 to allow the asymmetric localization of PIP_2, which is required for the maintenance of both PAR asymmetry and spindle position. Taking the broader view, her laboratory has generated a unique RNAi library to facilitate new genome-wide screens for other phenotypes.

Many laboratories have been working on defining stem cells in various organisms, and how the stem-cell niche influences the process of self-renewal. Minx Fuller (Stanford University, USA) described how, using *Drosophila* spermatogenesis as a model system, she and her colleagues have identified the ligand Unpaired (Upd) as a protein secreted by the stem-cell niche, a specialized environment consisting of ten support cells that maintains the *Drosophila* stem cell in the testis. Upd in turn activates the JAK/STAT signaling pathway in the male germline, the downstream targets of which regulate the self-renewal property of stem cells. Using DNA microarrays, a screen was carried out to compare a strain that ectopically expresses *upd* and a wild-type strain in an attempt to identify genes upregulated by JAK/STAT signaling in the stem cells. In this system, 175 genes were found to be upregulated, 15 of which have predicted STAT consensus binding sites upstream or within the first intron, as defined by the program Target explorer [http://trantor.bioc.columbia.edu/Target_Explorer]. One of these genes, *lola*, which has at

least 20 splice variants, is expressed ubiquitously in early germ cells (but not in the hub), and is required to act within the germ cells for maintenance of the male germline. Thus, clones of male germline cells that do not express *lola* lose their stem cells over time, as the cells differentiate along the path of spermatogenesis and lose their ability to self-renew. *lola* is similar to the mouse *plzf* gene, which is required for the maintenance of germ cells in adult males.

The use of comparative genetics and genomics has been particularly successful in elucidating the evolution of new traits in vertebrates, a point highlighted by David Kingsley (Stanford University, USA). Evoking the theme of understanding genes and the processes they regulate, Kingsley reported work being done in his laboratory using the three-spine stickleback as a model organism to determine what genotypic changes are required to achieve major phenotypic changes, and whether these changes are dominant or recessive, or in coding or regulatory regions. One such trait is that of armored plates, as ocean sticklebacks have 36 plates (high-plate sticklebacks), while their freshwater counterparts have far fewer (low-plate sticklebacks). The Kingsley lab has found a genomic region that is responsible for 80% of the variation observed in armored-plate number, and through a chromosome walk using BAC clones and a comparison of microsatellite markers, they have identified the *ectodysplasin* (*EDA*) gene as a possible candidate for controlling armored plate formation. This gene gets its name from the condition resulting from mutations in the human *EDA* gene result called ectodermal dysplasia, in which the affected individual has sparse hair and other defects in hair, teeth and sweat glands. In another fish, the medaka, a mutation in the gene for the ectodysplasin receptor (*EDAR*) renders the fish scaleless. To gain further evidence of the involvement of *EDA* in armored plate formation, a mouse *EDA* cDNA clone was injected into the eggs of low-plate sticklebacks. The resulting transgenic fish formed plates in the middle and tail regions, which normally lack such structures (Figure 1). EDA is involved in a tumor necrosis factor (TNF)-type signaling pathway in humans and mice, and mutations in the ligand (EDA), the receptor (EDAR) or the adaptor protein Edaradd give similar phenotypes. In addition, the mutation that gives low numbers of armored plates is in the *cis*-regulatory region of the *EDA* gene. Similar studies using ocean and freshwater sticklebacks have also been conducted by the Kingsley laboratory to understand the loss of the hindlimb in the freshwater stickleback.

Winding up the meeting, John Gerhart (University of California, Berkeley, USA) highlighted the origin of chordates through a comparison between chordate gene expression and that in the hemichordate *Saccoglossus kowalevskii*. Hemichordates are strikingly similar to chordates in that they are bilaterally symmetrical, have structures analogous to gill slits and a post-anal tail, but they have no real dorsal hollow nerve cord. Instead, the nervous system is highly

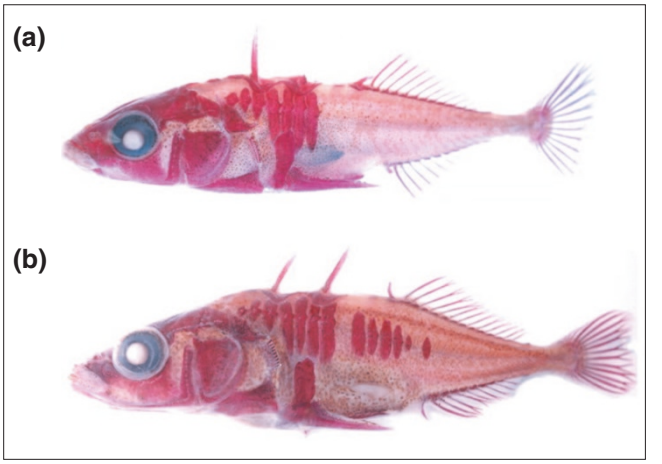

Figure 1
Arming the stickleback. Introduction of mouse *ectodysplasin* cDNA into **(a)** low-plate sticklebacks yields **(b)** transgenic fish with an increased number of armored plates. Adapted with permission from Colosimo *et al.*: *Science* 2005, **307:**1928-1933.

diffuse, with a dorsal-ventral axon tract and an outer body layer full of nerves. Orthologs to 41 neural patterning genes in chordates were identified as having similar anterior-posterior expression mappings in hemichordates, with *Wnt1* and *Fgf8* being found at the level of the first gill slit in hemichordates compared to the midbrain-hindbrain junction in chordates. Thus, comparisons can be made between the marker genes identifying the brain and spinal cord structures in chordates and their distribution along the anterior-posterior axis in hemichordates.

Gerhart described his group's findings that the stomochord, a structure found in *Saccoglossus*, and the notochord are not homologous structures, as the stomochord expresses molecular markers similar to prechordal endomesoderm. Moreover, Gerhart's group has found that patterning along the dorsal-ventral axis in *Saccoglossus* occurs through a bone morphogenetic protein (BMP)-chordin gradient, but that this gradient is inversely oriented in comparison to chordates: the dorsal midline in hemichordates expresses BMPs, while the ventral midline expresses chordin. In a remarkable experiment, exogenous BMP added to the water in which hemichordate fertilized eggs are kept resulted in the radial expansion of genes that are normally expressed only in the dorsal midline and in the loss of the mouth structures (a ventral structure) in the developing embryos. Conversely, when BMP expression was suppressed by small interfering RNAs at the fertilization stage, this resulted in the expansion of the ventral domain, coupled with an enlargement of the mouth and the eventual elimination of the entire head structure. From these experiments the researchers concluded that many aspects of anterior-posterior patterning have been conserved in hemichordates and chordates, but that there was an alteration in dorsal-ventral patterning in the chor-

date lineage, leading to the centralization of the nervous system and the development of a notochord.

The meeting showed that a more interdisciplinary approach to developmental biology that couples traditional embryological approaches with molecular biology and computational techniques has allowed us to understand, at a molecular level, the role of various genes and the products they regulate during different developmental processes. We look forward to more results from these collaborative efforts emerging over the next year, and to hearing about them at the next annual meeting of the society at the University of Michigan, Ann Arbor, in 2006.