Meeting report

New developments in developmental biology

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A report on the 15th International Society of Developmental Biologists Congress, Sydney, Australia, 3-7 September 2005.

With the theme 'From egg to adult: constructing the complexity of life', the recent meeting of the International Society of Developmental Biologists (ISDB) in Sydney showcased recent progress in answering a broad range of questions on how the body of a multicellular organism is put together and how differences in body patterns evolve. This was the first ISDB congress since the publication of the initial sequence of the mouse genome in 2002, and there is no doubt that genome sequencing and the ability to study the expression of several thousand genes at once has facilitated progress in understanding how genes work to build an embryo. In his opening plenary lecture, however, Nobel laureate Sydney Brenner (The Molecular Sciences Institute, Berkeley, USA) warned that too much emphasis is placed on studying gene function. Brenner said we should thank the people who sequenced the genomes and tell them to go away, and cautioned against "high-throughput/low-output" research. He argued that rather than taking the 'bottom-up' approach of studying individual gene function, we should study the middle level, the cell. In his view, we need to know how many different cell types there are in the finished product, and then we can start to understand how they got there.

Cell lineages and differentiation

Focusing on the earliest cell lineages, Janet Rossant (Samuel Lunenfeld Research Institute, Toronto, Canada) presented work aimed at understanding the timing and mechanisms of segregation of the cell lineages in the mammalian blastocyst. Rossant is particularly interested in how the primitive endoderm (which does not contribute cells to the embryo itself) segregates from the rest of the inner cell mass, from which the embryo itself derives. The transcription factor Gata6 may be involved in the process because it is expressed in a reciprocal pattern with the gene *Nanog* (which is required for pluripotency) and *Gata6* expression is able to convert trophectoderm stem cells derived from the blastocyst into extraembryonic endoderm cells *in vitro*. Exactly how the primitive endoderm is differentiated from the inner cell mass *in vivo* remains unclear, however. One possibility is that several rounds of asymmetric cell divisions are responsible for lineage divergence, but Rossant used lineage tracing by labeling of individual cells of the inner cell mass to show that such polarized cell divisions do not fully explain the process.

Two talks revealed the resilience of developmental processes in embryos that do not show proper differentiation of cell lineages. Didier Stainier (University of California, San Francisco, USA) has performed a large-scale screen in zebrafish for mutants with endoderm defects. One mutant identified was *prometheus,* which completely lacks a liver in early development because of the loss of function of the signaling molecule *Wnt2b* from the mesenchyme surrounding the liver-forming region of the endoderm. Interestingly, these mutants are viable and develop a liver later in development. This liver is derived from exocrine pancreatic cells that actively migrate into the liver region and subsequently differentiate into hepatic cells. Also demonstrating the ability of embryos to recover from developmental defects, Marianne Bronner-Fraser (California Institute of Technology, Pasadena, USA) reported that migration of trunk neural crest cells through the somites (the precursors of the trunk muscles and skeleton) is defective in mice lacking the secreted signaling molecule Sema3f. Despite this, neural crest-derived dorsal root ganglia form in the normal segmental pattern, demonstrating that neural crest migration and segmentation of the neural system can be uncoupled.

Gene regulation in development and evolution

Denis Duboule (University of Geneva, Switzerland) described his laboratory's work on the colinear regulation of Hox genes in mouse limb and digit patterning. Duboule showed, utilizing a series of rearrangements within the Hox gene cluster, how expression of the HoxD group genes is regulated by the opposing forces of upstream and downstream regulatory elements in the early limb bud and forearm, while the later phase of expression in the digits is regulated by a single element, and is probably more recently evolved.

The valuable synthesis of developmental biology with ecological and evolutionary biology was exemplified by the work of three researchers who are investigating how differences in the regulation of single genes drive morphological diversity. Richard Behringer (University of Texas, Houston, USA) has found that *Prx1*, a homeobox transcription factor gene required for limb outgrowth, was differentially expressed during limb development in mice and bats. Behringer's group used the bat *Prx1* limb enhancer to drive expression of mouse *Prx1* in transgenic mice, resulting in mice that were normal apart from having longer forelimbs, suggesting that the expression of *Prx1* can account for some of the difference between the mouse and bat limb. In a similar vein, Cliff Tabin (Harvard Medical School, Boston, USA) showed that some differences in beak morphology among the famous Darwin's finches were due to differences in expression of the signaling protein BMP4. In support of this, Tabin was able to demonstrate that misexpression of BMP4 in the chick induced changes in beak morphology.

David Kingsley (Stanford University, Stanford, USA) described studies on the three-spine stickleback, which has marine and freshwater populations with morphological variations including armor plates, fins and spines. Divergent populations of these fish that do not normally interbreed in the wild can be crossed in the laboratory to map evolutionary variation in morphological traits to specific loci. Kingsley has mapped the presence or absence of the pelvic fin and variation in armor plates to the regulatory regions of the genes encoding the transcription factor Pitx1 and the tumor necrosis factor (TNF)-related factor Eda respectively, again demonstrating the importance of regulatory sequences that act during development in the manifestation of evolutionary change.

Single genes affecting identity and behavior

The transcription factors Tbx4 and Tbx5 are exclusively expressed in the hindlimb and forelimb, respectively, and had been thought to be important for the specification of different limb identities. Malcolm Logan and colleagues (National Institute for Medical Research, London, UK) have now shown that this is not the case. Logan described how his team used the Cre-lox conditional gene knockout technique to create mice with a limb-specific deletion of *Tbx5*, which were then made to express *Tbx4* in its place. Although forelimb outgrowth is rescued, the type of limb is not altered by the presence of the hindlimb-specific *Tbx4*. But addition of a second hindlimb-specific gene, *Pitx1*, does change the characteristics of the rescued limb to resemble a hindlimb, suggesting that this gene is involved in specifying limb identity.

Barry Dickson (Institute of Molecular Biotechnology, Vienna, Austria) presented data demonstrating that changes to single genes could also affect the development of complex behaviors, with a focus on male courtship behavior in *Drosophila*. The transcription factor gene *fruitless* is sex-specifically spliced so that a complete Fruitless protein is not made in females. By expressing the female isoform in males or the male isoform in females, Dickson could reverse their courtship behavior, showing that Fruitless is acting as a switch for male courtship behavior.

Regulation of development by microRNAs

MicroRNAs (miRNAs), small noncoding RNAs, are emerging as important regulators of developmental processes and may regulate up to 30% of human genes posttranscriptionally. Stephen Cohen (European Molecular Biology Laboratory, Heidelberg, Germany) discussed methods for predicting targets of miRNA regulation. He has made two important observations regarding miRNA and their targets: first, that genes involved in developmental processes such as differentiation and organogenesis are enriched for miRNA target sites, whereas genes involved in basic cellular processes tend not to have miRNA target sites; and second, that lineage-specific miRNAs do not target genes expressed in the same lineage but specifically target genes expressed in alternative lineages, which suggests a role in tissue identity and suppression of molecular noise during development. Cliff Tabin proposed a similar function for the mouse miRNA *miR-196* in regulating limb identity, concluding that *miR-196* acts as an additional level of transcriptional regulation to ensure complete lack of *Hoxb8* transcripts in mouse hindlimbs. Deepak Srivastava (Gladstone Institute of Cardiovascular Disease, San Francisco, USA) attributed a more specialized function for mouse *miR-1* in titrating the levels of a critical cardiac transcriptional regulator, *Hand2*, to control the balance between proliferation and differentiation during cardiogenesis. Overexpression of *miR-1* causes proliferation defects and failure in the expansion of ventricular cardiomyocytes.

Bioinformatic tools for miRNA-target predictions are now better able to distinguish between true targets and background, and this will help in assigning functions to the ever-increasing numbers of miRNAs that are being discovered. Validating the functions of these miRNAs will be of immense value in uncovering the role of these genes in development, and it seems likely that at the next ISDB Congress, in Edinburgh in

2009, we will hear much more about the vital functions carried out by these tiny regulators of development.

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