Meeting report

Complex cell behaviors in development: recent progress and emerging challenges

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A report on the British Societies for Cell Biology and Developmental Biology Joint Spring Meeting, University of Warwick, Coventry, UK, 6-9 April 2005.

A central issue that developmental biologists aim to understand is how a single cell goes on to generate many different cell types, and how the resulting groups of cells organize themselves during development to produce specific structures. Central to this question is a deeper understanding of the genetic programs active in cells at any given time and the location of cells within the developing organism, as well as the emergent properties and coordinated behaviors of cell groups that underlies all developmental processes and their evolutionary relationships. While cell biologists concentrate on understanding the molecular basis of individual cell function, developmental biologists have generally aimed to understand developmental processes at the level of cell groups and how they influence each other in different developmental processes. Nevertheless, as demonstrated by the research presented at this meeting, the best answers to how organisms develop and function will undoubtedly come from the emerging integration and continuous interactions between the two levels of analysis.

The benefit of this approach was well captured in the opening talk by Cornelia Bargmann (Rockefeller University, New York, USA) describing work on oxygen sensing in nematodes. In her model, sensory inputs detected by the tail and head neurons are integrated and evaluated through a complex neuronal circuit. Taking advantage of mutant screens and a very stereotypically organized nervous system composed of only 302 neurons, the specific function of each neuron as it relates to movement control was assigned. Using an elegant oxygen-tension gradient maze, mutant and wild-type worms were then tested 'in the field' to observe their behaviors at different oxygen levels. These studies reveal that neurons at the tail and head of the worm use both spatial and temporal differences to evaluate oxygen levels and translate this external cue into coordinated movement, and that these movements in turn contribute to more advanced aggregation behavior.

The cell movements that occur during embryogenesis were reviewed by Alfonso Martinez-Arias (University of Cambridge, UK) who drew parallels between individual and group behaviors of cells in different animal model systems (*Drosophila*, *Xenopus*, zebrafish, chick and mouse). Using these most informative examples, Martinez-Arias highlighted a number of key questions that remain unanswered: how directional cues are read and interpreted by migrating cells; whether there are emergent properties of cellular interactions that can be extracted from cells responding to one another; and how the molecular noise that is probably present during cell signaling is kept under control allowing coordinated cell movement. This was followed by inspiring talks in which powerful advances in imaging, cell labeling and molecule tagging revealed new insights into how molecules control cell behavior. Cornelis Weijer (University of Dundee, UK) showed movies revealing the movements of mesodermal cells tagged with green fluorescent protein (GFP) after their ingression through the primitive streak of a chick embryo. The cells appear to be attracted by sources of a fibroblast growth factor (FGF4) and vascular endothelial growth factor (VEGF), and repulsed by FGF8. These activities are able to drive a highly stereotypic long-distance cell migration. The mechanisms by which these signals are integrated and couple to the cytoskeleton are under study and will benefit from some of the work on cytoskeletal dynamics and cell signaling *in vitro* that was also reported at the meeting.

Signals that drive cell behaviors have been identified in several other embryonic episodes, but much less is known about how they propagate. In his Beddington Prize talk, P.H. (Huw) Williams (University of Cambridge, UK) discussed his strategies for visualizing morphogen movement in the frog embryo. Mesoderm induction by members of the transforming growth factor-beta (TGFβ) family is the first and essential process for correct patterning of vertebrate embryos. The first stages in this induction occur when equatorial cells of the spherical embryo activate specific gene expression in response to vegetal morphogens. By tagging the secreted TGF-family member and vegetal morphogen Xnr2 with enhanced GFP (eGFP), Williams was able to exclude the active movement of Xnr2 by processes such as transcytosis or transport via cell-derived structures such as argosomes (extracellular vesicles) or cytonemes (long cell extensions). Instead, Xnr2 appears to move by restricted diffusion, pooling into extracellular spaces. These dynamic imaging studies have implications for other systems where it will also be interesting to discover the extent and mode of delivery of signals, such as the cytokines that direct inflammatory responses.

Staying on the theme of gastrulation, Enrique Amaya (University of Cambridge, UK) presented evidence for multiple roles of FGF signaling in mesoderm specification and the direction of morphogenetic movements in the frog. Although both these processes require FGF signals, it was not previously clear how they are coordinated during gastrulation. Amaya presented work showing that *Xenopus* Sprouty and Spred (both regulators of the FGF receptor tyrosine kinase) differentially modulate downstream FGF-receptor signaling during mesoderm specification and morphogenesis. While each promotes one process it also antagonistically inhibits the other. In this way, and in combination with the timing of expression of Sprouty and Spred, the FGF signal coordinates both mesoderm formation and gastrulation movements.

Elegant studies on the theme of coordinated cell migrations were presented for both *Drosophila* and zebrafish. For zebrafish, Erez Raz (Max Planck Institute for Biophysical Chemistry, Gottingen, Germany) described how primordial germ cell (PGC) migration is guided by the chemokine SDF1a and its receptor Cxr4b. Raz focused on the morphological changes in PGCs and their correlation with signal sensing. Migrating PGCs alternate between two modes of behavior: migratory (where the cells are polarized) and pausing (where the cells lose their polarity), thus showing how cell morphology appears to be responsive to signaling. Raz argued that these two modes are critical for continuous guidance-cue sensing by PGCs.

Darren Gilmour (EMBL, Heidelberg, Germany) described collective cell movements using the lateral line primordium (LLP; Figure 1) in zebrafish and the role of SDF1 in this process where it appears that, just as for PGCs, the Cxr4 receptor guides the LLP cells. Time-lapse movies of the migration showed that these cells are not all equal in their response to guidance cues; the leading cells appear to guide the more passive follower cells. It appears that all cells have the potential to be leaders, however, as is the case for some axon-guidance systems. In embryos depleted of Cxr4 but where the receptor is subsequently restored in a mosaic pattern, those lateral primordial cells having the functional receptor migrate to the front and assume the leader position. These cells are then able to guide the Cxr4-negative cells along the correct migratory route.

Even though such studies are an example of visualizing complex cell movements and cellular behaviors *in vivo*, it is still not a trivial task to link specific genes with these behaviors in developing embryos and this is one of the big challenges for the coming year and beyond. With the zebrafish genome sequence being predicted to be complete later this year and many additional techniques available such as targeting-induced local lesions in genomes (TILLING), which combines chemical mutagenesis with PCR screening, allowing fast isolation of new missense and nonsense mutant alleles of a gene of interest, more functional studies are likely to be possible soon. The huge benefit of these technologies for zebrafish studies was especially apparent in the talk given by Ruth Lehmann (Skirball Institute for Biomolecular

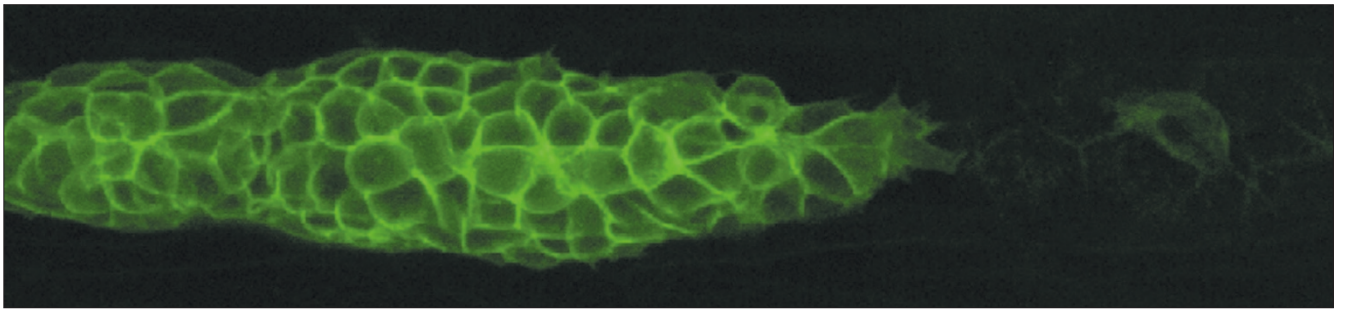

Figure 1
The zebrafish lateral line primordium labeled with green fluorescent protein.

Medicine, New York, USA) who described her laboratory's studies of germ-cell migration in the *Drosophila* embryo. Despite being genetically very tractable, *Drosophila* has not been very amenable to live imaging studies. Imaging techniques are now being improved in flies, however, and Lehmann showed that even in the early embryo the migration of PGCs can be imaged with good resolution using two-photon microscopy. With the marriage of elegant genetics and good imaging, her group was able to dissect the signaling required to direct the PGCs through the posterior midgut epithelium, and to identify the molecules involved at each step.

One of the emerging problems facing both cell and developmental biologists is to figure out the specific roles of individual genes as they relate to single cells, or in the context of tissues, and then how this relates to the whole developing organism. The next problem is to determine how well these processes and the molecules involved and their functions are conserved between different organisms. The answer to both of these questions, at least in part, will be found through the sharing of techniques and knowledge between the related disciplines of cell and developmental biology, as exemplified by this meeting: this is particularly true in the area of imaging. Further developments in functional genomics and bioinformatics as well as in systems biology will benefit future studies in all systems. These approaches will be especially useful in the analysis of gene networks, and of molecular noise and signals and how cells interpret them. Equally important for future studies will be developments in integrative computer display and analysis of biological data such as gene-expression patterns, signal modeling and cellular behavior. One example of this type of approach, its challenges and the progress being made, was discussed by James Sharpe (MRC Human Genetics Unit, Edinburgh, UK) during the systems biology session with respect to the generation of four-dimensional computer models of vertebrate limb development.

The coming year is full of exciting challenges and we all look forward to the next Joint Meeting of the British Societies for Cell Biology and Developmental Biology in 2006.