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Pushing the frontiers of development

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A joint meeting of the Japanese and French societies for Developmental Biology, entitled 'Frontiers in Developmental Biology', was recently held in Giens, France. The organizers, Patrick Lemaire and Shinichi Aizawa, showcased some of the rapid progress in the field that has been made possible through the use of modern large-scale network analyses, and of an increasingly sophisticated array of tools and ideas from microscopy, mathematics and computer science.

Introduction

This is an exciting time for developmental biologists as we move in earnest beyond describing gene expression patterns and gene functions to considering how gene networks specify cellular machinery, how this machinery operates within living cells to orchestrate the complex dynamics of animal development, and how it is tuned by evolution to carry out different tasks in different contexts. Armed with an ever-growing array of new technical capabilities and with influences from other scientific disciplines, we are venturing towards new frontiers in every direction. To highlight and promote this amazing progress, Patrick Lemaire (IBDML, Marseille France) and Shinichi Aizawa (Riken Center for Developmental Biology, Kobe, Japan) organized a special joint meeting of the Japanese and French Societies for Developmental Biology. For 4 days, participants gathered on a remote Mediterranean peninsula near the small French town of Hyeres to look into the future together and to describe what they see there. The themes that emerged most clearly were genetic regulatory networks (GRNs), morphogenesis and the interdisciplinary study of evolution and development.

Genetic networks and signaling pathways

The study of GRNs and signaling pathways is a central theme in developmental biology, and important findings were reported at the meeting that shed new light on the mechanisms by which GRNs and signaling cascades are employed during axis specification, somitogenesis and stem cell determination.

Axis specification

The specification of body axes is a process that is crucial for the correct patterning of the embryonic body plan. Hiroshi Hamada (Osaka University, Osaka, Japan) gave a keynote presentation on the mechanisms of anteroposterior (AP) axis determination in mice. He illustrated that within the inner cell mass of the early mouse embryo, the expression of Nodal, a transforming growth factor β (TGFβ) family member, is sufficient to induce the expression of its antagonist Lefty (Lefty1) in a cell population marked by the presence of the transcription factor GATA6. This population then contributes to the proximal region of the anterior visceral endoderm (AVE) and thereby defines the AP axis of the mouse embryo. The interplay between Nodal and Lefty was also shown to be important for the specification of the dorsoventral (DV) axis in sea urchins. Thierry Lepage (Université Pierre et Marie Curie, Villefranche-sur-Mer, France) convincingly illustrated that Nodal, which is expressed early in the presumptive ventral ectoderm, controls DV patterning (Duboc et al., 2004). He further described how its restricted expression could be explained by a reaction diffusion model in which Nodal activates both its own expression and that of its antagonist Lefty (Duboc et al., 2008). Both Hamada's and Lepage's results suggest that regulatory interactions between Nodal and Lefty provide a simple mechanism by which a weak asymmetry in Nodal expression can be amplified and maintained to stably define an embryonic axis. In further investigations of the mechanisms of asymmetry in early mouse development, Naoto Ueno (National Institute for Basic Biology, Okazaki, Japan) reported a novel and surprising function for the planar cell polarity (PCP) gene *Prickle1* in the regulation of apicobasal polarity in the epiblast. Finally, Hidehiko Inomata (RIKEN Center for Developmental Biology, Kobe, Japan) considered the mechanisms that underlie the robustness of DV patterning in frog embryos. Recent work implicates the local inhibition of chordin, a bone morphogenetic protein (BMP) antagonist, by dorsally expressed BMP proteases in the regulation of DV patterning. Inomata showed that the scaffold protein olfactomedin 1 (ONT1) binds chordin and the chordin-degrading enzyme BMP1 through distinct domains, with this binding enhancing chordin degradation. His work suggests that stable axis formation depends on two compensatory regulatory pathways involving ONT1 and BMP1, on the one hand, and dorsally expressed BMPs (ADMP and BMP2), on the other (Inomata et al., 2008).

The molecular mechanisms that underlie left-right (LR) axis specification were addressed in three talks, two of which highlighted the role of cilia in this process. Hiroyuki Takeda (University of Tokyo, Tokyo, Japan), whose group studies medaka development, described the characterization of the *kintoun* (*ktu*) medaka mutant, which is defective in both ciliary motility and LR axis specification (Omran et al., 2009). Positional cloning of the *ktu* gene identified a novel gene that is essential for ciliary motility from algae to humans. *ktu* encodes a protein that is required in the cytoplasm for the pre-assembly of dynein arm complexes, the mutation of which causes primary ciliary dyskinesia. Moving from fish to mice, Hamada showed in his keynote address that PCP signaling determines the posterior positioning of basal bodies in the epithelial cells of the node, which in turn determines the posterior tilt of nodal cilia required for directed flows and LR axis specification. Finally, Stéphane Noselli (Université de Nice, Nice, France) presented his recent findings on LR axis specification in *Drosophila*. Here, the LR axis is manifested by the direction of the 360° rotation of the male genitalia. Using time-lapse imaging, Noselli and his colleagues showed that the 360° genitalia rotation can be decomposed into two concomitant 180° rotations of the anterior and posterior regions of the genitalia A8 segment, with the directions of both rotations being controlled by the LR determinant myosin 1D.

Global control mechanisms

A trio of talks dealt with mechanisms that coordinate the expression of multiple genes during development. Two of these focused on Hox transcription factor genes, which are arranged in clusters in the

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genome. Hox gene transcription can be activated according to the spatial arrangement of the genes on the chromosomes, a phenomenon known as colinearity. The expression of Hox genes is tightly regulated, with the Polycomb Group (PcG) family of proteins being one of the most prominent repressors. Denis Duboule (University of Geneva, Geneva, Switzerland; Federal Institute of Technology, Lausanne, Switzerland) discussed the developmental and evolutionary significance of Hox gene colinearity. He illustrated how a global control region (GCR) located proximal to one of the Hox gene clusters acts as a module to drive the expression of Hox genes according to their position within the Hox cluster during vertebrate AP axis specification, digit determination and external genitalia development (Montavon et al., 2008; Tarchini et al., 2006; Cobb and Duboule, 2005). Giacomo Cavalli (Institute of Human Genetics, Montpellier, France) reported important findings on the mechanisms that maintain Hox gene expression patterns during *Drosophila* embryogenesis. He showed that Hox genes from different clusters, located on different chromosomes, colocalize within nuclear PcG bodies when they are co-repressed, but localize to different nuclear positions when differentially expressed. His work illustrates how the binding of a PcG repressor to PcG response elements can promote the long-range chromosome organization necessary for the maintenance of Hox expression patterns during embryogenesis. Finally, Mirana Ramialison (European Molecular Biology Laboratory, Heidelberg, Germany) reported the systematic identification of groups of spatially co-expressed genes, so-called synexpression groups, and their corresponding cis-regulatory regions through a bioinformatics analysis of the Medaka Expression Pattern Database. Her analysis also revealed the chromosomal clustering of co-expressed genes, hinting at the existence of novel GCRs that could play a fundamental role during development.

Somitogenesis

Somite formation, which requires at least Notch and Wnt signaling (Aulehla et al., 2003; Dequeant et al., 2006), has emerged as a central model for studying how temporal information (the segmentation clock) is transformed into spatial regulation (the formation of somites along the AP axis). Emilie Delaune (Laboratory of Sharon Amacher, University of California at Berkeley, CA, USA) reported the development and use of a Notch target GFP reporter in zebrafish to visualize the segmentation clock at cellular resolution, enabling a detailed analysis of how neighboring cells, which express Notch target genes, are coordinated to form a somite. Yumiko Saga (National Institute of Genetics, Mishima, Japan) presented her recent findings on how interactions among Notch and the transcription factors Mesp2 and Tbx6 iteratively define segmental borders and rostrocaudal pattern within forming somites. She showed that Notch signaling (a temporal factor) and Tbx6 (a spatial factor) cooperate to promote Mesp2 expression within a domain that prefigures the somite. Mesp2, in turn, suppresses Tbx6 expression via the ubiquitin-proteasome pathway to define the anterior border of the next Mesp2 domain (Fig. 1) (Oginuma et al., 2008). From these data, Yumiko Saga proposed Mesp2 to be the final output signal through which the translation from temporal information into spatial regulation occurs.

Stem cells

Several talks dealt with GRNs in the context of stem cell specification and/or maintenance. The elegant work of Cédric Maurange and colleagues (National Institute for Medical Research, London, UK) addressed the fundamental issue of how stem cells 'decide' to stop dividing once sufficient numbers of neurons have been produced (Maurange et al., 2008). In *Drosophila*, neural progenitors express a temporal sequence of distinct transcription factors that endow their progeny neurons with different identities. Maurange reported that progression to the end of this sequence is necessary to promote cell cycle exit and stem cell apoptosis, explaining how the correct number of neurons with a given fate is produced during development (Fig. 2). Moving from *Drosophila* to mice, Daijiro Konno (RIKEN Center for Developmental Biology, Kobe, Japan) addressed the long-standing issue of the role of mitotic spindle orientation in brain neurogenesis in mice (Konno et al., 2008). Combining time-lapse microscopy with genetic perturbations of spindle orientation in the mouse cortex, he showed that during asymmetric divisions of neural progenitors, the maintenance of progenitor identity and proliferative potential correlates with the inheritance of the basal process.

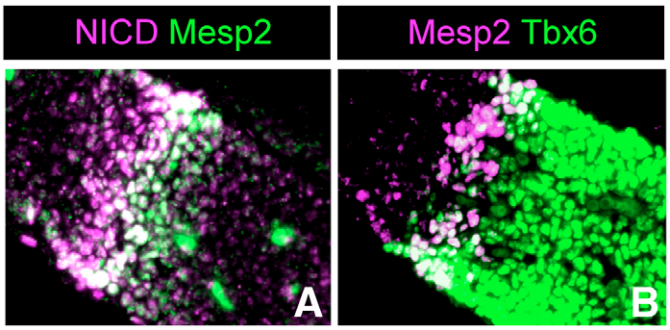

Fig. 1. Interactions between the temporal factor Notch and the transcription factors Tbx6 and Mesp2 in mouse somitogenesis. (**A**,**B**) The presomitic mesoderm of mouse embryos at embryonic day (E) 10.5, with anterior towards the left. Interactions between Notch, Tbx6 (a spatial factor) and Mesp2 iteratively define segmental borders and patterning within developing somites. Mesp2 is proposed to be the final output signal in the conversion from temporal to spatial regulation during somitogenesis. At a stage of this process during which *Mesp2* transcription is robust, (A) the expression domain of Mesp2 overlaps with that of the Notch intracellular domain (NICD) (Mesp2 in green, NICD in magenta), and (B) with that of Tbx6 (Mesp2 in magenta, Tbx6 in green), with Tbx6 beginning to be repressed. Reproduced, with permission, from Oginuma et al. (Oginuma et al., 2008).

Large-scale genetic network analysis

Four talks illustrated ways in which large-scale network analyses can yield fundamental insights into developmental mechanisms. Norbert Perrimon (Harvard Medical School, Boston, MA, USA) reviewed his ongoing work on the structure and complexity of signaling networks, suggesting that the notion of discrete modular pathways (Wnt, Hedgehog, Notch, etc.) may be overly simplified. Instead, he argued that the transmission of an external signal involves hundreds of satellite proteins surrounding the more limited 'canonical' sets identified by classical genetic approaches, with these satellite members of signaling networks making quantitative contributions to the network output. Whereas mutations with the highest contribution lead to a complete collapse of network function, the effects of mutations in components associated with more subtle functions are compensated. This model has implications: (1) for understanding how the genetic background influences variation in expressivity; (2) for the characterization of susceptibility loci associated with complex diseases such as cancer, diabetes and neurodegeneration; and (3) for the robustness and evolvability of

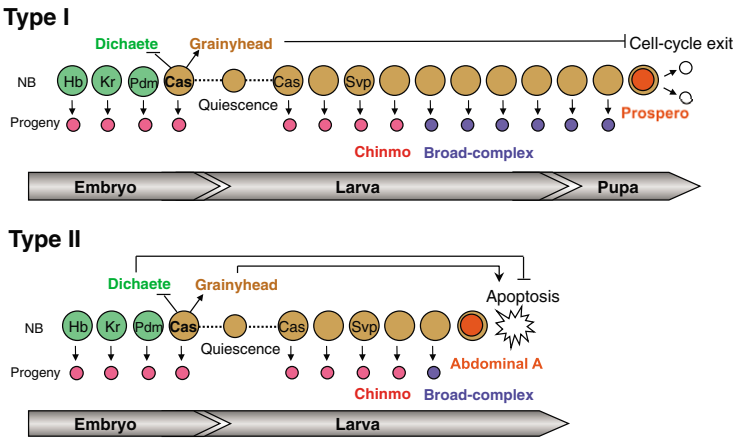

Fig. 2. The temporal series regulates neuroblast potential and termination. In *Drosophila*, multipotent neural progenitors called neuroblasts (NBs) divide asymmetrically to self-renew and to generate progeny that differentiate into neurons and/or glia. A single neuroblast can sequentially express a series of temporal transcription factors such as Hunchback (Hb), Kruppel (Kr), Nubbin (Pdm), Castor (Cas), Seven-up (Svp) and probably others, yet unknown. Progression through this series during development schedules the switch from generating Chinmo^{+} to Broad-complex^{+} neurons and also terminates neuroblast division, either via Prospero-dependent cell cycle exit (Type-I neuroblasts) or Abdominal-A dependent apoptosis (Type-II neuroblasts). As neuroblasts progress through the temporal series, their properties alter. For example, indirect feed-forward from an early burst of Cas, mediated via a long-lasting switch from Dichaete to Grainyhead, is necessary for the much-later event of termination. Images courtesy of Cedric Maurange and Alex Gould (NIMR, London, UK).

signaling networks. Marc Vidal (Harvard University, Cambridge, MA, USA) described his ongoing efforts towards the construction and analysis of comprehensive protein-protein interaction networks, drawing on examples from humans, yeast and worms. He illustrated some of the ways in which this analysis can yield fundamental biological insights. For example, he showed how combining global network analysis with protein and transcription profiling can help to identify susceptibility loci associated with cancer.

A very stimulating pair of talks highlighted ascidian embryos as attractive models for the analysis of early developmental processes. Yutaka Satou (Kyoto University, Kyoto, Japan) presented an impressive update on his group's efforts to reconstruct the GRNs that underlie early cell fate determination in ascidians. Combining expression profiling with loss-of-function studies, his group has identified provisional genetic circuits underlying cell states at single cell resolution. He described current efforts to validate these circuits using chromatin immunoprecipitation assays. In a complementary study, Lionel Christiaen (UC Berkeley, Berkeley, CA, USA) has analyzed the next step – the conversion of a transcriptional state into the unique morphogenetic behaviors that underlie cardiac cell migration in the ascidian embryo (Christiaen et al., 2008). He showed that cardiac cell migration is controlled through the transcriptional regulation of effector genes involved in most cellular processes that are required for directed migration, including polarity, membrane protrusion and cell-matrix adhesion. His work hints at how complex morphogenetic behaviors could arise through the combinatorial activation of conserved cellular modules by tissue-specific GRNs.

Asymmetric cell division in *C. elegans*

Understanding the cellular dynamics that underlie the asymmetrical inheritance of developmental potential is an important issue in the development of multicellular organisms, and three talks focused on the *C. elegans* zygote as a model system in which to analyze this. Asako Sugimoto (RIKEN Center for Developmental Biology, Kobe, Japan) presented a beautiful analysis of P-granule (germ granule) assembly in *C. elegans*. She showed that among 14 previously identified P-granule components, two (PGL-1 and PGL-3) are sufficient to form granules when expressed in cultured mammalian cells. The granules that formed contained endogenous poly(A)-binding protein and mRNA, sequestered some of the other co-expressed P-granule components and had a layered structure that is also found in *C. elegans* P-granules. These studies provide an exciting first glimpse of the dynamic principles that govern germ granule self-assembly in *C. elegans* and in other organisms. Francois Nedelec (EMBL, Heidelberg, Germany) described elegant work in which he and his colleagues used direct high-resolution observations of microtubule dynamics in the *C. elegans* zygote to identify novel feedback interactions between microtubule dynamics and spindle pole motions (Koslowski et al., 2007). They then used detailed computer simulations to show how these feedback interactions could explain the spindle pole oscillations and AP displacements that are observed during asymmetric cell divisions. Ed Munro (Center for Cell Dynamics, University of Washington, WA, USA) described using a similar synthesis of models and experiments to explore how a system of biochemical and mechanical interactions among the generally asymmetrically localized Par proteins, small GTPases and the actomyosin cytoskeleton could explain the zygote's ability to form and stabilize polarized cortical domains in response to a transient polarizing cue. These studies emphasize how the factors that regulate force generation in embryonic cells are often redistributed by the very forces they control.

Morphogenesis and pattern formation

Morphogenesis remains one of the most fascinating but poorly understood processes in developmental biology. However, new efforts and approaches are beginning to lead towards a more functional and mechanistic understanding of the underlying processes. Bénédicte Charrier (UPMC, Paris, France) and Bernard Billoud (Centre National de la Recherche Scientifique (CNRS), Roscoff, France) described the use of a simple cellular automata model – in which a finite number of states are assigned to the cells of a grid and through which interactions between groups of grid cells can be studied – to explore how different empirically derived rules or hypotheses about local cell growth, division and differentiation, and their modulation by cell-cell communication could explain multicellular patterns observed during the development of the filamentous brown alga *Ectocarpus siliculosus*. In plants, Jan Traas (Ecole Normale Supérieure de Lyon, CNRS-Institut National de la Recherche Agronomique, Lyon, France) illustrated how growth seems to be partially coordinated by a cytoskeleton-based sensing of stress in tissues. Computer simulations show that such a mechanism would be sufficient to generate the shape changes observed during organogenesis in plants. Anne-Gaëlle Rolland-Lagan (University of Ottawa, Ottawa, Canada) emphasized the need for quantitative descriptions of

pattern formation as a starting point for the construction and analysis of theoretical models. To this end, she described a suite of algorithms that she is developing to quantify and analyze leaf vein patterns at high spatial resolution. Moving from plants to animals, Thomas Lecuit (CNRS-Institut de Biologie du Développement de Marseille Luminy, Marseille, France) described recent collaborative work with physicist Pierre-François Lenne (CNRS-Institut Fresnel, Marseille, France) that combines computer simulations and physical perturbations to show how anisotropic tension governed by the local bipolar recruitment of Myosin 2 could explain cell intercalation and tissue elongation during *Drosophila* gastrulation (Rauzi et al., 2008). He emphasized a key role for dynamic adhesive contacts during cell rearrangement (Cavey et al., 2008) and showed that bipolar recruitment of Myosin relies on a spatial bias in branched versus unbranched actin network assembly mediated by Scar and Diaphanous, two regulators of actin polymerization. Francois Robin (IBDML, Marseille, France) described joint work with Kristin Sherrard (Center for Cell Dynamics, University of Washington, WA, USA) that identifies a two-step mechanism for ascidian endoderm invagination: apical constriction and columnarization followed by basolateral shortening around tight apical collars. This is accompanied by the sequential accumulation of active myosin at apical and then basolateral surfaces. Using a detailed computational model, they showed that this two-step mechanism could account robustly for the dynamics of cell shape change and tissue deformation that are seen during invagination. Yohanns Bellaïche (Institut Curie, Paris, France) analyzed the mechanisms that coordinate growth and morphogenesis in proliferating epithelia. Using novel mathematical tools to quantify the morphometric effects of cell division and cell growth. This work underscores an essential need to understand the interplay between cell cycle control and morphogenesis.

Finally, Shigeru Kondo (Nagoya University, Nagoya, Japan) presented an elegant analysis of pigmentation patterns in zebrafish. He showed that empirically determined rules for interactions among distinct pigment cell types (melanophores and xanthophores) fulfill all the requirements for a classical Turing-style pattern-formation mechanism. He showed further that this basic mechanism can explain the dynamics of pattern formation observed in wild-type and in many mutant embryos or hybrid combinations.

Evolutionary developmental biology

Last, but not least, a very exciting session showcased some new approaches and recent progress in understanding the evolution of developmental mechanisms. Per Ahlberg (Uppsala University, Uppsala, Sweden) discussed how fossil data can be used to sharpen inferences about the evolution of developmental mechanisms made from the comparative study of living taxa, drawing on his recent studies of digit homologies and the neural crest origins of the neck and shoulder (Boisvert et al., 2008; Matsuoka et al., 2005). He highlighted the need to reconstruct soft anatomy from fossil data as a key challenge, because it is the soft anatomy, not bone morphology, that correlates most strongly with developmental boundaries. He presented a novel and exciting approach that uses sub-micron resolution synchrotron scans to map muscle attachments to fossil bones in 3D that holds great promise for soft-tissue reconstructions in many other contexts. Shigeru Kuratani (RIKEN Center for Developmental Biology, Kobe, Japan) discussed the rib-derived turtle carapace as an evolutionary novelty, which results from the arrest and dorsolateral confinement of rib growth, leading to a turtle-specific infolding of the lateral body wall (Nagashima et al., 2007). He showed that the carapacial ridge – a turtle-specific structure that lies along the line of infolding – does not play an inductive role in carapace patterning as previously thought, but instead appears to have co-opted elements of the Wnt signaling pathway for the control of carapace growth.

Marie-Anne Félix (Institut Jacques Monod. INRS-UPMC, Paris, France) described an elegant quantitative analysis of robustness and evolvability of vulval patterning in *C. elegans* and related species. She showed that vulval patterning is buffered against both genetic and environmental variation; the errors that do occur depend on both genotype and environmental conditions. This buffering appears to have allowed extensive cryptic evolution of the vulval patterning network within the *Caenorhabditis* genus, associated with quantitative changes in the Notch and EGF signaling pathways (Félix, 2007; Braendle and Félix, 2008; Milloz et al., 2008). Claude Desplan (New York University, New York, NY, USA) presented his beautiful work on AP patterning in the wasp *Nasonia*. *Nasonia*, like most insects, lacks the morphogen Bicoid, which establishes anterior identity in *Drosophila*. He showed that several highly conserved genes (*orthodenticle*, *caudal* and *giant*) are localized as mRNA in the *Nasonia* egg and that together they subsume the various functions of Bicoid (Brent et al., 2007; Lynch et al., 2006). Both talks emphasized how, by tinkering with the same toolkit of genes and preserving most of their interactions, nature tunes GRNs to preserve similar functions under different conditions.

Other talks emphasized how similar tinkering can lead to evolutionary innovation. Benjamin Prud'homme (IBDML, Marseille, France) discussed his recent work with colleagues Nicolas Gompel and Sean Carroll, which identifies the molecular bases for the evolution of male specific *Drosophila* wing pigmentation patterns (Prud'homme et al., 2006). He showed how these patterns have been modified by changing specific cis-regulatory elements of pigmentation gene, leading to the co-option of pre-patterned regulatory inputs from wing-development genes such as *engrailed*. Jessica Cande (UC Berkeley, Berkeley, CA, USA) reported two changes in the GRN that underlies heart formation in beetles: one is a gain in an expression domain of *tinman*; the other is a switch in the expression patterns of two neighboring genes that appears to be morphologically silent. Francois Parcy (CNRS Grenoble, France) discussed insights into the origins of angiospermy that were gained from the analysis of LEAFY – a key regulator of floral development whose DNA-bound structure has recently been determined (Hamès et al., 2008). Homology modeling and biochemical analyses suggest that variations in the DNA-binding specificities of LEAFY and its interactions with other binding partners may have contributed to the appearance of flowers.

Conclusions

The future challenge in developmental biology is obvious: to integrate the increasingly sophisticated characterizations of GRNs and signaling pathways with the emerging physical descriptions of the cell behaviors that underlie pattern formation and morphogenesis. Using genome-wide gene profiling to identify points of regulatory control across this interface is a key step. But it will be equally important to understand the targets of this control – to understand the dynamics of embryonic cell behavior from a physical perspective and how local cell behaviors are integrated across tissue scales during pattern formation and morphogenesis. This meeting highlighted some of the many ways in which researchers are beginning to take a more interdisciplinary approach to developmental biology, combining classical molecular genetics

with novel methods for imaging and physical perturbation, quantitative analysis, physical modeling and computer simulation, thus offering a glimpse of how the field is likely to develop in the near future.

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