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New inroads to development

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The 2006 symposium of the RIKEN Center for Developmental Biology in Kobe, Japan, was entitled 'Logic of development: new strategies and concepts'. The purpose of the meeting was to uncover how our understanding of the logic of developmental processes is changing in the light of novel techniques and strategies. The speakers provided a comprehensive overview of diverse topics, such as the power of functional genomics and imaging approaches, and the phenomenon of non-coding RNAs and their role in development. A wide range of processes and mechanisms at the molecular, cellular and organismic level were presented, as were many novel concepts and strategies, which together highlighted the importance of interdisciplinary approaches.

Introduction

The fundamental questions of developmental biology still capture our fascination: how is the single-cell egg transformed into the beautiful adult organism, whether it be a bird, fly, worm or plant; and how are the diverse cell types and tissues generated in a context-dependent manner (see Fig. 1)? However, in modern developmental biology, with its heavy dependence on technology, novel research strategies can change our understanding of processes and mechanisms dramatically. The 2006 symposium of the RIKEN Center for Developmental Biology (CDB), which was organized by Masatoshi Takeichi, Asako Sugimoto, Hiroki R. Ueda and Shigeo Hayashi (CDB, Kobe, Japan), and Steve Cohen (European Molecular Biology Laboratory, Heidelberg, Germany) covered many areas of developmental biology and searched for novel strategies and concepts. In this meeting review, I highlight some of the many outstanding contributions of this very successful and broad meeting.

Small RNAs

One central topic of the meeting was the function of microRNAs (miRNAs) and other small RNAs in gene regulation and development, which was covered in three sessions. With speakers from both the animal and plant fields, similarities and differences in miRNA function were illustrated and the changing thoughts about miRNA function were put into a historical perspective. In animals, miRNAs show imprecise pairing and mismatch with their target messenger RNAs (mRNAs). Victor Ambros (Dartmouth Medical School, Hanover, NH, USA) pointed out the important concept that the mismatch between the miRNA and its target mRNAs provides an opportunity for different mechanisms of gene regulation. Basically, three distinct network modes can be distinguished (Fig. 2). First, several miRNAs can converge on the regulation of the same downstream target (Fig. 2A). Alternatively, a single miRNA can regulate independent target genes, providing a divergent rather than a convergent principle (Fig. 2B). And finally, miRNAs can target genes in a linear one-to-one fashion (Fig. 2C). René Ketting (Hubrecht Laboratory, Utrecht, The Netherlands), Eric Miska (The Wellcome Trust/Cancer Research UK Gurdon Institute, Cambridge, UK) and Steve Cohen provided multiple examples of miRNA function in animal development from worms, flies and vertebrates. Haruhiko Siomi (University of Tokushima, Tokushima, Japan) demonstrated the function of the Argonaute protein Ago2 in the *Drosophila* RNAi pathway. In the final talk of the miRNA sessions, Cohen provided some useful numbers from his studies in *Drosophila* to exemplify the importance of small RNAs in the development and homeostasis of animals: *Drosophila* contains at least 55 well-characterized miRNAs (this number should increase over time), each of which has around 100 target genes. This adds up to more than 5500 target sites in ~3600 genes that are regulated by miRNAs, which themselves account for ~30% of the predicted *Drosophila* genes. Two aspects of miRNA function in animals are of general importance. First, regulation by miRNAs is commonly seen in developmental control genes, whereas genes involved in protein biosynthesis, RNA metabolism, DNA repair, RNA splicing and other 'housekeeping' functions are avoided in a statistically significant manner. Second, miRNAs are components that increase the temporal and spatial precision of regulatory processes and increase the robustness of development (Stark et al., 2005). This function of miRNAs is unlike that of transcription factors, which make developmental decisions and often work as developmental switches.

The current understanding of miRNA function reveals important differences in their function between plants and animals. Detlef Weigel (Max-Planck Institute for Developmental Biology, Tübingen, Germany) summarized several of these differences and provided an overview of the numbers of miRNAs and target genes in *Arabidopsis thaliana*. There are more than 200 confirmed miRNAs in plants, which fall into some 30 families. These families have conserved target sites, often in transcription factors genes. In contrast to animals, miRNA target motifs in plants are mostly in the coding sequence of their respective target. Most importantly, miRNAs in plants seem to have a narrow specificity, in contrast to the broad specificity of animal miRNAs (Schwab et al., 2005). One explanation for this important difference could be that miRNAs evolved independently in plants and animals, a hypothesis that remains to be tested. Taken together, the first observations of homology-mediated silencing mechanisms in plants and worms, which occurred a little more than a decade ago have meanwhile turned into an independent research branch on small non-coding RNA pathways (Pasquinelli, 2006). One aspect that all miRNA speakers agreed upon is that many important insights are to be expected from further studies on miRNA function and regulation.

Functional genomics

The second important topic of the meeting was functional genomics. John Hogenesch (The Scripps Research Institute, Jupiter, FL, USA) introduced cell-based screening approaches and their usefulness in the annotation of the mammalian genome. He demonstrated that when used with a powerful bioassay, cell-based screening approaches are able to reveal important functions for components of signaling systems and non-coding RNAs in a similar way. Nicolas Bertin from Marc Vidal's laboratory (Harvard Medical School, Boston, MA, USA) described the initial steps towards an objective, systematic, in vivo spatiotemporal localization of expression in *C. elegans*. This new biological map, the localizome,

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Fig. 1. The painting 'Clairvoyance' by Rene Magritte (1936) was the official poster of the symposium 'Logic of development: new strategies and concepts'. Copyright VG Bild-Kunst, 2006.

could be used to refine the current static protein-protein interaction map and also to gain a system-level understanding of gene regulation during the post-embryonic development of *C. elegans*.

Asako Sugimoto (RIKEN CDB, Kobe, Japan) described her work towards generating a detailed 'developmental phenome' of *C. elegans*. Using RNAi approaches, her laboratory is providing a systematic phenotypic description of gene knockouts during embryonic and post-embryonic development (Sugimoto, 2004). Such large-scale functional descriptions can profit tremendously from computational technologies that enable quantitative analyses. Shuichi Onami (Keio University, Yokohama, Japan) showed his very powerful strategies to quantify structures and features in the *C. elegans* embryo. Using high-resolution image processing and computer simulation, the phenotypic analysis of gene knockdowns by RNAi becomes possible in an automated manner.

Finally, Duncan Davidson (MRC Human Genetics Unit, Edinburgh, UK) introduced the audience to the mouse expression pattern database. Given the complexity of the mammalian genome and, more importantly, the complexity of the developing embryo with its three-dimensional structures, highly sophisticated computational tools are necessary to generate information that seems more straightforward in worms and flies. The functional genomics sessions covered a diverse array of topics, but they had in common that the application of computational approaches to experimental studies represents a key research strategy in modern developmental biology.

Systems biology and live-cell imaging

In the past 5 years, functional genomics and miRNAs have changed the strategies and concepts in developmental biology tremendously. However, additional approaches for studying developmental processes are coming of age, two of which were given separate sessions at the meeting. Systems biology was introduced by two speakers, who illustrated well the different ideas and approaches of systems biology. Ron Weiss (Princeton University, Princeton, NJ, USA) introduced pattern formation in synthetic biology. He highlighted how multi-cellular systems can be synthetically generated by engineering and that such systems will help us to

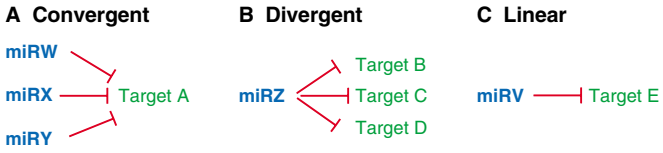

Fig. 2. Network modes for different mechanisms of gene regulation by miRNAs. (**A-C**) Several miRNAs can converge on the regulation of the same downstream target, a single miRNA can diverge to regulate independent target genes and, finally, miRNAs can target genes in a linear fashion.

understand the quantitative aspects of cell-cell communication and pattern formation in natural systems. From a completely different angle, Hiroki R. Ueda (RIKEN CDB, Kobe, Japan) summarized his studies on the analysis and synthesis of biological networks. Using the mammalian circadian clock as a case study, he described how the combination of bench work – studying the regulatory circuits of transcription factors – and modeling studies can help to elucidate a comprehensive understanding of circadian systems (Ueda et al., 2005). As with the functional genomics studies, Ueda's work shows the importance of combining experimental and computational studies.

Atsushi Miyawaki (RIKEN Brain Science Institute, Wako, Japan) introduced the audience to the spatial and temporal patterning of signaling processes in the brain. He demonstrated how the combination of GFP-related imaging systems with fluorescence cross-correlation spectroscopy (FCCS) and the use of novel fluorescent probes provides new solutions for understanding the temporal, as well as the spatial, patterns of signaling systems. Yasushi Okada (The University of Tokyo, Japan) used high-speed live imaging techniques to study nodal flow and its function during left-right axis specification in mice. He introduced a hydrodynamic mechanism and employed wonderful fluorescent recordings of surface lipids to visualize the directed transport of particles that might trigger the final developmental decisions during left-right axis specification (Okada et al., 2005). At this point, the participants of the meeting finally became aware of how important high-resolution and high-speed imaging systems are for the understanding developmental mechanisms.

Conclusions

Taken together, the CDB 2006 symposium on the logic of development covered a wide area of developmental biology and demonstrated, in an exciting way, the power of modern approaches for studying developmental systems. As pointed out by Steve Cohen in his closing remarks of the meeting, one of the most exciting insights to be gained from this meeting is the enormous potential that is inherent in combining experimental and computational approaches, a strategy that is constantly gaining in importance. In addition, the generation of new data in large-scale functional genomic approaches requires intelligent retrieval strategies to make these data accessible to biologists. The participants of the meeting left Kobe in the optimistic spirit that these long-standing problems of high-throughput approaches – storage, quantification and resolution of data – could be solved.

As usual, there is a 'but'. At the same time as computational biology and large-scale approaches are becoming more important as a research strategy in the analysis of model organisms, lessons from evolution should not be forgotten. In the evolutionary session, Detlev Arendt (EMBL, Heidelberg, Germany) and Kiykazu Agata (Kyoto University, Kyoto, Japan) showed how different animals with a

different body plan are constructed, by describing their work in the annelid *Platynereis dumerilii* and in planarians, respectively. But one does not have to study members of different phyla to learn about important differences in the regulation and the logic of development, as shown by recent comparisons in distinct species of nematode, *Pristionchus pacificus* and *C. elegans* (Zheng et al., 2005).

In conclusion, lessons and concepts from an extraordinarily broad range of biological and developmental research fields have outlined the multitude of inroads into modern developmental biology. To finish with the final words of Victor Ambros: 'this was an exciting meeting, helping life's wonders to be rediscovered'.

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