The flies of Icarus: science with wings in Crete

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Around 100 researchers gathered at the eighteenth EMBO Conference on ‘The Molecular and Developmental Biology of Drosophila’, which took place in Crete in June 2012. Whether deconstructing or integrating at the genetic, cellular or organ level, the talks highlighted the synergy of combining methods, approaches and disciplines in this increasingly versatile model system.

Introduction

In ancient mythology, Icarus and his father were so desperate to escape from Crete that they made their own wings from feathers and wax and took to the sky. By contrast, around 100 researchers willingly made the opposite journey this summer, flying to Crete to discuss their latest findings at the 2012 ‘Crete Fly Meeting’. Armed with an expanding genetic tool-kit, Drosophila researchers are engaging with other scientific communities to study, for example, the physics of cell structure or the genomics of evolution. They are also becoming increasingly aware of the importance of reaching out to the general public (Fig 1). We highlight some exciting findings here, with an emphasis on new resources, emerging themes and unpublished data, and apologize to those whom we cannot cover due to space constraints.

The synergy of integrative approaches

Biological systems are fundamentally complex in that they consist of many parts working together. The powerful genetic tools developed in Drosophila allow this complexity to be tackled at an organismal level. Whether enabled by high-throughput technology or resulting from the intersection of different disciplines, ‘integration’ was a recurring theme at this year’s meeting in Crete.

Hugo Bellen (Houston, USA) presented MiMIC technology, which generates dispersed landing sites that can be used for generating transcript traps, tagging endogenous proteins and creating knockout animals. Markus Affolter (Basel, Switzerland) described his work with genetically encoded nanobodies that recognize GFP and, through their conjugated F-box, target GFP-fusion proteins for degradation. This opens up the possibility of removing proteins from cells in situations in which transcriptional regulation is not effective—for example, in the early embryo. Furthermore, the phenotypes can be followed by using live imaging as they develop. Susan Celniker (Berkeley, USA) presented a new release of the Drosophila genome that includes some forgotten regions—such as the Y chromosome—as well as an in-depth analysis of the transcriptome of the fly, which includes transcripts from a range of cell lines, tissues and experimental conditions. The Drosophila community depends on the long-running compendium of Drosophila genes and phenotypes embodied in FlyBase. Bill Gelbart (Boston, USA) described the efforts of FlyBase to keep up with the flood of new data, including tools to query expression data.

Several groups have already capitalized on these high- or medium-throughput approaches to integrate information regarding transcriptional regulation. By using a
new method to perform cell-type-specific ChIP, Eileen Furlong (Heidelberg, Germany) demonstrated that heterogeneous chromatin signatures are predictive of enhancer activity state during development. Their Bayesian model revealed a new link between the timing of RNA pol II occupancy on enhancers, and the precise timing of transcription factor occupancy and enhancer activation. Alex Stark (Vienna, Austria) presented an ongoing genome-scale screen for transcriptional enhancers by characterizing the temporal–spatial activity of 15,000 approximately 2 kb-long DNA fragments in transgenic embryos by in situ hybridization against a reporter transcript. Mike Eisen (Berkeley, USA) presented data on Zelda, a zinc-finger containing transcription factor that has a major role in early development by determining which regions of the genome will be in an active chromatin state at the blastoderm.

Other talks illustrated the synergy resulting from combining high-throughput descriptive approaches with classical genetics. By conducting expression profiling in the optic lobe, Claude Desplan (New York, USA) uncovered a temporal sequence of transcription factors active in the neuroblasts of the medulla. This is similar to the transcription factor sequence that patterns embryonic neuroblasts and their progeny, but the genes are different. This work further revealed patterning of the medulla neuroepithelium, which modifies the outcome of the temporal series and contributes to diversifying neurons. Richard Mann (New York, USA) presented a new approach for quantitative analysis of walking by adult flies on touch-sensitive glass. By using this method, he described data suggesting that, although flies generally rely on the so-called ‘tripod gait’, they might use distinct neural programmes when walking at different speeds.

Another feature of integration is that it allows us to analyse biological variation as a property of the system, rather than an experimental nuisance. Along this line, Richard Carthew (Evanston, USA) presented a quantitative analysis of variation and microRNA function suggesting that canalization (robustness) can inhibit evolutionary adaptation. Alex Stark (Vienna, Austria) presented an ongoing genome-scale screen for transcriptional enhancers by characterizing the temporal–spatial activity of 15,000 approximately 2 kb-long DNA fragments in transgenic embryos by in situ hybridization against a reporter transcript. Mike Eisen (Berkeley, USA) presented data on Zelda, a zinc-finger containing transcription factor that has a major role in early development by determining which regions of the genome will be in an active chromatin state at the blastoderm.

The importance of context
Concurrent with this surge in integrative and high-throughput approaches, the talks this year also reflected the success of the contrary but complementary strategy of honing in on specific genes or cellular processes. Armed with new imaging technology and unprecedented temporal and spatial control of gene expression, Drosophila researchers are discovering that, when it comes to understanding gene function, context is paramount: it is all about time, space and even what the flies eat.

Two talks reported unexpected late functions for genes better known for their early roles. Bassem Hassan (Leuven, Belgium) reported a new role for Notch–Delta signalling in neighbouring postmitotic neurons, which use lateral inhibition to make wiring decisions in a non-deterministic neuronal circuit. This process might confer robustness to a developing neuronal circuit with intrinsic individual variability. Nick Baker (New York, USA) described an unexpected function for roughex (rux), a cell cycle regulator, in a subset of postmitotic photoreceptor neurons in the Drosophila eye. In rux mutants, these neurons re-enter the cell cycle, undergo an acetylkinetic mitosis and transport nuclei into their axons, raising new questions about why neuronal cell cycles might be detrimental.

Tissue or cellular context was the focus of other presentations. By using a combination of metabolomic and genetic analyses, Alex Gould (London, UK) has been investigating how the growth of neural stem cells is spared in conditions of reduced oxygen and nutrients. The underlying mechanism relies primarily on glycolysis rather than oxidative phosphorylation. Interestingly, his data point to different metabolic roles in neural stem cells compared with other tissues for genes traditionally regarded as ‘housekeeping’ genes. The ribosomal protein genes are the ‘poster children’ of housekeeping genes. Paul Lasko (Montreal, Canada) presented evidence that variant ribosomal proteins contribute to oogenesis and that elf4E-3, a variant cap-binding protein, is essential for spermatogenesis. The clear lesson is that genes encoding general functions can also function specifically in some contexts. Tim Megraw (Tallahassee, USA) has been investigating the mechanisms by which mutations in the ubiquitous protein centrosomin lead to a tissue-specific phenotype: viable but sterile adults. By using these mutations, which cause centriole amplification in testis, he showed that centrosomin negatively regulates centriole replication through a conserved domain independently of microtubule assembly regulation. In an imaging-based approach, Lynn Cooley (New Haven, USA) identified previously unrecognized diversity among the somatic follicle cells of egg chambers, which she found to cluster into ‘functional mosaics’ with regard to their ability to transport photoactivatable GFP and endogenous proteins through stable intercellular bridges known as ring canals. She found that follicle cell syncytia average eight cells, and that the syncyta correspond to mosaic patches of gene expression obtained with the Gal4/UAS system in follicle cells.

Finally, two speakers illustrated gene–environment interactions by uncovering diet-dependent phenotypes for metabolic genes. Carl Thummel (Salt Lake City, USA) presented studies of the Drosophila hepatocyte nuclear factor HNF4, showing that mutations in this factor result in a form of diabetes that closely resembles that found in human HNF4 patients. The late lethality of these mutants can be prevented only under certain dietary conditions, and studies are underway to characterize the underlying mechanisms. Pierre Leopold (Nice,
Deconstructing cells

As in the case of gene function, detailed dissection of the biology of cells also highlighted the importance of restricting subcellular processes in time and space. Advances in imaging have contributed to the characterization of this ‘cellular context’ by identifying new subcellular compartments and dynamic processes. Several talks this year began to show the functional significance of this dynamic compartmentalization.

Shigeo Hayashi (Kobe, Japan) focused on the secretory–endocytic pathways of the epithelial cells that form the tracheal network. He showed that Rab9 and the retromer complex control tracheal tube length by regulating endocytic recycling of the luminal chitin deacetylase Serpentine. This pathway functions independently of the secretory pathway that regulates tube diameter, suggesting that, by allocating specific cargoes to different vesicles, the length and diameter of a tracheal tube might be separately controlled. In addition to segregating vesicular pools in space, the importance of confining endocytosis to specific temporal windows was highlighted by the findings of Stefano de Renzis (Heidelberg, Germany). By quantifying apical endocytic dynamics with high-resolution imaging of an endogenously tagged Rab5–GFP in cellularizing embryos, he found that the morphology of the apical surface during epithelial morphogenesis is controlled by fine-tuning the rate of tubular endocytosis, and he identified that the Rab5 effector Rabankyrin-5 is a crucial regulator of the budding and processing of these tubular membranes. The importance of compartmentalizing subcellular events in both space and time was further, and strikingly, illustrated by Kazuo Emoto (Osaka, Japan), who reported localized calcium transients in the dendritic branches of C4da sensory neurons during metamorphosis. Such transients are mediated by calcium influx through voltage-gated calcium channels. Interestingly, channel blockage impaired dendrite pruning, suggesting that the localized calcium transients act as temporal and spatial cues promoting pruning.

The functional importance of new subcellular structures is also beginning to be elucidated. By using a combination of live imaging and genetic approaches, Isabel Guerrero (Madrid, Spain) presented data pointing to a role for long actin-rich cellular protrusions in the formation and establishment of a Hedgehog gradient, and suggested that Hedgehog-containing exosomes might be transported across tissues along these protrusions. Her findings indicate that Hedgehog co-receptors promote both protrusion formation and stability, as well as the localization of Hedgehog to these subcellular structures.

Thinking outside the box

Whether deconstructing or integrating, perhaps some of the most unexpected findings came from re-examining long-standing questions from a slightly different perspective. Starting from a screen for planar cell polarity regulators, Helen McNeill (Toronto, Canada) uncovered roles for Fat—a cadherin with a ‘canonical’ cell surface function—in an unexpected place: mitochondria. Laura Johnston (New York, USA) described studies of the homeostatic process that recognizes differences in cellular fitness within growing tissues, known as cell competition. During cell competition, weak but normally viable cells are killed when confronted with a relatively more robust cell population. She reported that apoptosis of the ‘loser’ cells during cell competition is dependent on the NF-κB pathway. This pathway, the components of which are normally engaged in response to pathogenic infection, might represent a particularly ancient form of the innate immune-sensing pathway.

In vivo imaging of well-studied processes also revealed some surprises. Enrique Martin-Blanco (Barcelona, Spain) analysed the gradient dynamics of proteins involved in establishing and maintaining planar cell polarity. His stunning movies of abdominal epidermal cells revealed that the gradients of the Four-jointed and Dachsous proteins are reversed in the posterior compartment of each abdominal segment relative to the anterior. This is puzzling because it suggests that the positioning of the trichomes in the posterior compartment occurs against the gradient. His data also indicate that Dachs, a downstream protein, is also expressed against the gradient at the anterior edge of the posterior compartment. Finally, by imaging the asymmetrical division of male germ line stem cells in vivo, Xin Chen (Baltimore, USA) made the surprising observation that the pre-existing canonical histone H3 is selectively inherited by the self-renewed stem cell. By contrast, newly synthesized H3 is enriched in the other daughter cell that undergoes differentiation. Unlike DNA replication, this suggests that at least some epigenetic events are conservative.

Concluding remarks

Two complementary approaches, based on integration or deconstruction of genetic, cellular or organ context are yielding important and unexpected results. Although the former approach is uncovering how biological components work together, be it proteins in a cell or organs in an organism, the latter is revealing that every cell or even subcellular structure does things slightly differently—warning against the reductionism of oversimplified integrative models. Icarus’s flight might ultimately have ended in a watery grave but, as we flew away from Crete, we felt sure that these two opposing forces will continue to bear the wings of our favourite model system aloft for years to come.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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