

DEVELOPMENTAL BIOLOGY

Many areas of developmental biology have been galvanized by the application of molecular and genetic techniques. The Department is well-equipped for most kinds of fundamental research in these fields, with particular emphasis on the role of cell interactions in the development of pattern. Studies of development and cell differentiation in *Xenopus* and *Drosophila* are exceptionally well represented.

Organogenesis: development of excretory tissues in *Drosophila*

DR HELEN SKAER

Research in the lab is directed towards an understanding of the cellular activities that underlie organogenesis and in particular towards the role played by cell interactions in the regulation of these activities. Our aim in the longer term is to focus on the interdependence of cellular events and the way in which they are co-ordinated to produce a mature tissue of defined size and shape, in which the patterned differentiation of cells results in a functionally integrated structure. A particular interest is to understand how the physiological attributes of an organ are defined during development.

We use the embryonic development of *Drosophila* renal tubules and nephrocytes as model systems. The use of *Drosophila* allows us to combine the techniques of genetics, molecular biology, tissue culture and experimental cell manipulation, such as cell ablation and transplantation, as well as new advances in genomic and proteomic analysis. Focusing on the nephrocytes and renal tubules gives us clear physiological readouts of development so that we can analyse developmental events and correlate them with the onset of physiological activity.

Our recent work has uncovered parallels between insect and vertebrate nephrogenesis at the level both of cell behaviour and genetic regulation. For example, the gene mutated in human nephrotic syndrome (NPHS-1) has a homologue in the fly, which we have found is essential for normal nephrocyte development and function. We have also shown that the highly conserved TGF-beta and Wnt signalling pathways act, as in mammalian nephrogenesis, to regulate epithelial branching during renal tubule development. By analysing the role of such gene products, and their partners, in the fly we hope to reveal conserved functions in kidney development and activity.

More information is available on the web:

<http://www.zoo.cam.ac.uk/zoostaff/>

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Specification of the *Drosophila* Motor system and Development of Dendrites

DR MATTHIAS LANDGRAF

Our interest lies in understanding how neuronal networks assemble during embryonic development and how function emerges. As a model system we are working with the larval locomotor system of the fruit fly, *Drosophila melanogaster*. This system has many advantages: it is of intermediate complexity and it is composed of identified neurons that are amenable to genetic manipulation and electrophysiology. We have made several discoveries. First, we found that there is a clear organizational logic to the system, at least at the level of the motorneurons. The dendrites of the motorneurons, which are the branched structures that receive inputs from other cells, are distributed in the central nervous system so that they represent the positions of their body wall muscles in the periphery. Second, we investigated how this dendritic 'myotopic' map is formed. We found that motorneurons are specified to put their dendrites into specific regions in the central nervous system in response to global guidance cues but independent of their partner terminals or neural activity. We found that presynaptic terminals also grow to particular locations in the network, also in an autonomous target independent fashion. These results suggest that the functional architecture of the network is largely specified by cell intrinsic programmes, which deliver the terminals of pre- and postsynaptic partner neurons independently of each other to common 'meeting regions'. We are now conducting large scale genetic screens to identify other component cells (interneurons) of the network. These will allow us to study the organizational logic of the motor system on various levels. Third, during late stages of network formation we found that cell-cell interactions act on this 'groundplan' of the circuit and modulate dendritic growth through contact and activity dependent mechanisms. The tuning of neurons during the final phase of embryogenesis seems to be essential for the emergence of network function.

This experimental framework allows us to address fundamental issues of network specification and assembly. Using high resolution and live confocal imaging, 3-D reconstructions of complex neuronal structures and state of the art genetic approaches for manipulating neuronal activity we are currently investigating the mechanisms that:

- Regulate dendritic growth, branching and targeting.
- Regulate the interactions between pre- and post-synaptic partner neurons and the formation of synapses between them.
- Underlie the structural and electrical adjustment of neurons in a network, which is critical for network function to emerge.

Further information is available on the web:

<http://www.zoo.cam.ac.uk/zoostaff/ndd>

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Development and physiology of visceral neurons

DR I MIGUEL-ALIAGA

While we have learned a great deal about how neurons control the muscular system responsible for the voluntary movement of our limbs, our understanding of how the normal function of internal organs is regulated by the nervous system is somewhat more limited. Although largely involuntary, visceral motor circuits are not only essential to the control of visceral muscle fibres, they can also regulate visceral secretion and metabolism.

Research in the lab makes use of *Drosophila* to study how visceral neurons develop and regulate the function of their target tissues. We recently identified a visceral lineage that secretes an insulin-like peptide on the digestive and reproductive systems. Since then, we have characterized several other visceral neuronal lineages. Together, they constitute a simple and genetically defined system with which to investigate the interaction between the nervous system and its visceral targets, both during development and in the adult organism.

We are tackling this issue at multiple levels, from the genetic programs involved in the specification of visceral neurons in the embryo to their functional output and integration into mature circuits. We are also developing behavioural assays to determine the function of insulinergic and non-insulinergic visceral neurons in larvae and adult flies.

Given the evolutionary conservation of the molecular mechanisms orchestrating development and metabolism, we hope that our research will be relevant not only to vertebrate neuromuscular development and organismal physiology, but also to the regulation of insulin production and diabetes.

Further information is available on the web:

<http://www.zoo.cam.ac.uk/zoostaff/miguel-aliaga.html>

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Regulation of cell polarity by motor proteins and RNA localization during development

DR ISABEL PALACIOS

Research in the lab is directed towards understanding the mechanisms involved in the early development of an organism, including RNA processing and how asymmetries are generated at the single cell level. More specifically, we have been studying the function of the motor protein Kinesin in establishing these asymmetries, and the mechanism by which localised mRNAs are distributed within the cell. We are employing biochemical, cell biological and genetic approaches to study these processes in the fruitfly *Drosophila melanogaster*.

Molecular motor proteins such as Kinesin are responsible for many of the major microtubule-dependent transport pathways in neuronal and non-neuronal cells. Elucidating these pathways is an area of increasing importance and intense investigation, with possible implications in human diseases, such as neurodegeneration. We are using the *Drosophila* oocyte as a model system to study the nature of the cargoes moved by Kinesin, to identify the proteins that link kinesin to these cargoes and to analyse how the activity of Kinesin is modulated by these interactions.

One of the cargoes of Kinesin is *oskar* mRNA, whose localisation in the oocyte is essential to define the anterior-posterior axis of the embryo. In general, RNA localisation plays an essential role in the determination of cell polarity and body asymmetries. We are studying the Kinesin-dependent localisation of *oskar* mRNA as a model system to understand how RNAs are asymmetrically distributed to specific regions in the cell.

To further understand how mRNAs localise, we are also studying the proteins that directly interact with the transcript and form the localisation complex, such as the exon-exon junction complex. We have previously shown that this protein complex is conserved in mammals, where it functions in non-sense-mediated mRNA decay (NMD), a RNA surveillance mechanism that is essential for proper gene expression. The NMD pathway has a direct impact on hundreds of genetic disorders; about a quarter of all known mutations are predicted to trigger NMD. We are interested in analysing further what is the relation of these two post-transcriptional events: mRNA localization and mRNA surveillance.

Further information is available on the web:

<http://www.zoo.cam.ac.uk/zoostaff/palacios.html>

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