JORDI CASANOVA

Signalling in morphogenesis

Our research focuses on the genetic control of development, and in particular the role of cell communication mechanisms in development in the context of the whole organism. The work of many laboratories has allowed us to begin to elucidate the genetic logic behind development and we are now addressing how these mechanisms impinge on cell behaviour and how changes in individual cells sum up to generate organs and the whole organism. We are analysing these mechanisms in two model systems in *Drosophila*, namely Torso RTK signalling and the formation of the trachea. In particular, we have begun our work at the interphase between development and cell biology using tracheal formation to study how transcription factors and signalling pathways regulate the cellular mechanisms responsible for changes in cell shape and cell behaviour such as migration and invagination.

The major outcomes of our research in 2008 can be broken down into the following sections:

Modulation of intracellular trafficking regulates cell intercalation in the *Drosophila* trachea

Epithelial cells exchange places in a spatially oriented manner by means of intercalation, a fundamental mechanism underlying elongation during morphogenesis (Pilot and Lecuit, 2005). Epithelial cells are tightly coupled through distinct intercellular junctions, including adherens junctions. Whether trafficking-mediated regulation of adhesion through adherens junctions modulates intercalation *in vivo* remains controversial (Pilot and Lecuit, 2005; D'Souza-Schorey, 2005). In *Drosophila melanogaster*, cells in most branches intercalate during tracheal development. However, Wingless (Wg)-promoted expression of the transcription factor Spalt (Sal) in the dorsal trunk inhibits intercalation (Ribeiro *et al*, 2004) by an unknown mechanism.

In collaboration with Marta Llimargas (at IBMB-CSIC), we have examined the role of trafficking in tracheal intercalation and found that it requires endocytosis, whereas it is opposed by *Rab11*-mediated recycling in the dorsal trunk. Subapical Rab11 accumulation is enhanced by *sal* and elevated *Rab11*-mediated recycling occurs in the dorsal trunk, thereby suggesting that upregulation of Rab11 is one way in which *sal* inhibits intercalation. We found that *dRip11*, which regulates Rab11 localisation and function (Ribeiro *et al*, 2004), is regulated by *sal* and can modulate intercalation. Finally, we observed that expression of E-cadherin (DE-cad), an

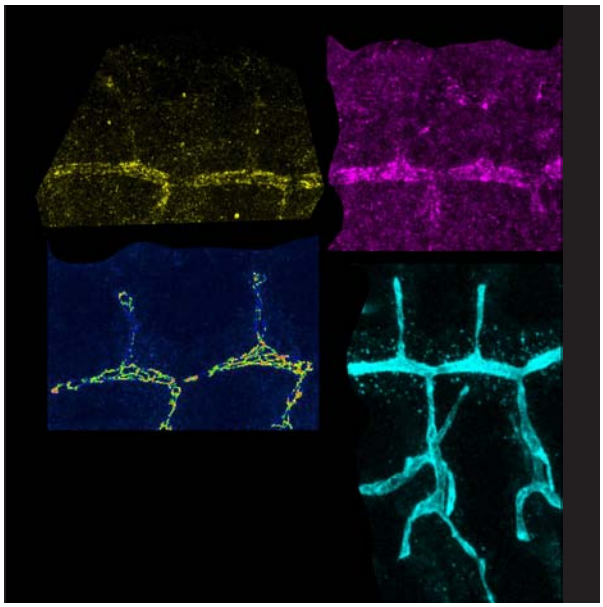

Figure 1. *During Drosophila tracheal development, upregulation of dRip11 (yellow) in the dorsal trunk enhances Rab11 (magenta) accumulation, which increases junctional cadherin expression (shown in rainbow panel). This up-regulation of adhesion prevents cell intercalation in this branch, and thus helps to sculpt the shape of the tracheal network (labelled by Sas, in teal; figure from Dan Shaye).*

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adherens junction component (Oda *et al*, 1994), and Rab11-compartment cargo (Classen *et al*, 2005; Langevin, 2005; Lock *et al*, 2005) are dynamically regulated by trafficking during tracheal development, and that such regulation modulates intercalation. Our work points to a mechanism by which trafficking of adhesion molecules regulates intercalation and shows how this mechanism is modulated *in vivo* to influence cell behaviour (Figure 1).

A functional antagonism between the pgc germ-line repressor and torso in the development of somatic cells

Segregation of the germ-line is a fundamental event during early development (see Strome and Lehmann 2007). In *Drosophila*, germ cells are specified at the posterior pole of the embryo by germplasm, and as zygotic expression is activated germ cells remain transcriptionally silent (Van Doren *et al*, 1998) owing to Polar granule component (Pgc), a small peptide present in germ cells (Martinho *et al*, 2004; Hanyu-Nakamura *et al*, 2008). Somatic cells at both embryonic ends are specified by the Torso (Tor) RTK and in *tor* mutants the somatic cells closest to the germ cells do not cellularise properly (Schüpbach and Wieschaus, 1986; Degelmann *et al*, 1986). In collaboration with Rui Martinho (Gulbenkian Institute) and Ruth Lehman (New York University), we have shown that extra wild-type gene copies of *pgc* cause a similar cellularisation phenotype and that both excessive *pgc* and lack of *tor* are associated with an impairment of transcription in somatic cells. Moreover, lack of *pgc* partially ameliorates the cellularisation defect of *tor* mutants, thus unveiling functional antagonism between *pgc* and *tor* in the specification of germ-line and somatic properties. As transcriptional quiescence is a general feature of germ cells, similar mechanisms might operate in many organisms to "protect" somatic cells that abut germ cells from inappropriately succumbing to such quiescence (Figure 2).

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González-Reyes A and Casanova J. Developmental biology. Return to the proliferative pool. *Science*, **321**(5895), 1450-51 (2008)

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Research networks and grants

Ajut per a grups de recerca singular
Agency for Administration of University and Research Grants (AGAUR), SGR-2005-00508 (2005-2008)
Principal investigator: Jordi Casanova

Cellular properties and morphogenesis. From genes to shape: analysis of morphogenesis in Drosophila and vertebrates
Spanish Ministry of Science and Innovation, CSD-2007-2008 (2008-2012)
Principal investigator: Jordi Casanova

Mecanismos de señalización celular y morfogénesis en el desarrollo de Drosophila
Spanish Ministry of Science and Innovation, BFU2006-01935/BMC (2006-2009)
Principal investigator: Jordi Casanova

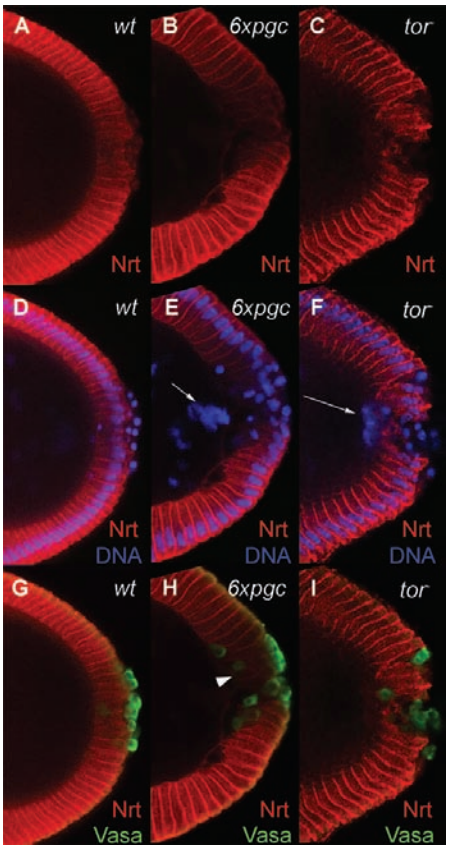

Figure 2. *Posterior poles of wild-type (A,D,G), 6x[pgc] (B,E,H) and tor (C,F,I) embryos. In red, anti-Neurotactin (Nrt) labels somatic but not germ cells; DAPI labels nuclei; in green, anti-Vas labels germ-cells. Groups of nuclei fall into the yolk in 6x[pgc] and tor mutants (arrows in E and F), some cells fail to complete cellularisation as shown by the lack of a basal membrane (ie, see arrowhead in E) and many cells have lost the typical epithelial elongated shape. Occasionally, a few nuclei fall into the yolk in wild-type. In 6x[pgc] (H) and tor (I) embryo, germ cells are found in the 'hole' between the somatic cells (figure from Jose M de las Heras).*

Collaborations

A functional antagonism between the pgc and torso
Ruth Lehmann, New York University (New York, USA)

Intracellular trafficking regulates cell intercalation in the Drosophila trachea
Marta Llimargas, Institut de Biologia Molecular de Barcelona (Barcelona, Spain)