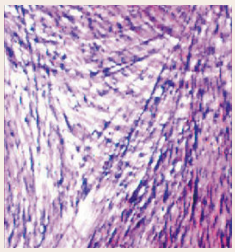
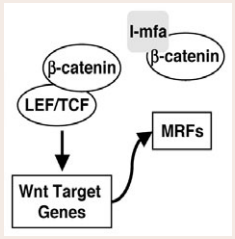
# In this issue

by Jane Bradbury



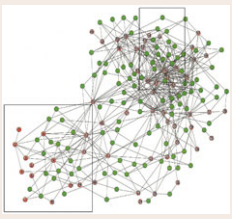
## Myogenesis: making contact and giving the right signals

Cell-cell contacts are important during development in part because they initiate signals that regulate differentiation. During myogenesis, the formation of cadherin-based adhesions between committed but proliferating myoblasts triggers their exit from the cell cycle and terminal differentiation. Now, Jennifer Pell and co-workers report that cadherin-mediated activation of the small GTPase RhoA and p38 MAP kinase (p38 MAPK) links the formation of cell-cell contacts to the synthesis of the pro-myogenic growth factor IGF-II (see p. 4828). p38 MAPK is essential for myogenesis but what regulates its activity during this process had remained unclear. The authors first noticed a correlation between the initial density of mouse myoblasts and N-cadherin levels, p38 MAPK phosphorylation, *Igf2* expression and myogenesis. They then used N-cadherin, dominant-negative N-cadherin, constitutively active and dominant-negative forms of RhoA, and p38 MAPK constructs to investigate how cell-cell adhesion is linked to myogenesis. They conclude that N-cadherin activation through cell-cell contact activates RhoA. This then activates the α- and β-isoforms of p38 MAPK, which in turn stimulates IGF-II synthesis and myogenesis.



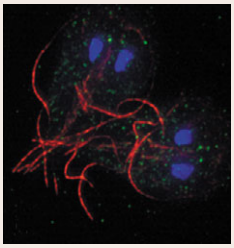

## β-catenin flexes its muscles

Canonical Wnt signalling plays many important roles during embryogenesis. During myogenesis, for example, the stabilization of β-catenin by Wnt signalling activates the transcription factor TCF/LEF-1, which upregulates the expression of myogenic regulatory factors (MRFs). On p. 4850, Lin Li and co-authors identify a second role for β-catenin in myogenesis. They show that it also counteracts the effect of I-mfa, a transcriptional repressor that inhibits expression of both TCF/LEF-1 and MRFs. β-catenin interacts with I-mfa and relieves I-mfa-mediated suppression of MRFs. The authors show that endogenous I-mfa suppresses myogenesis in pluripotent P19 carcinoma stem cells by inhibiting the expression of TCF/LEF-1. β-catenin, they report, competes with I-mfa for binding to TCF/LEF-1 and thus relieves the inhibitory effects of I-mfa overexpression on myogenesis. The dual mechanism by which β-catenin regulates TCF/LEF-1-dependent transcription, suggest the authors, might help to fine-tune cellular responses to changes in Wnt signalling during development and other physiological processes and during pathological processes such as cancer.



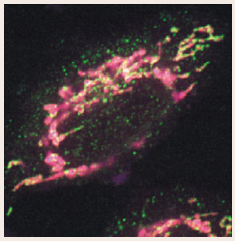
## Cell migration – the bigger picture

Cell migration is essential during embryonic development and in processes such as wound healing. Numerous genes involved in cell migration have been identified, but to get a more complete picture Jean Schwarzbauer and co-authors have undertaken the first comprehensive RNAi screen for genes that interfere with gonad formation in *C. elegans* (see p. 4811). In this organism, distal tip cells (DTCs) from the gonadal primordium migrate post-embryonically to form two U-shaped gonad arms. Gonadal defects caused by aberrant DTC migration are clearly visible in the transparent adult worms. From their screen, the authors identify 99 genes that are required for DTC migration, including genes previously implicated in this process and orthologs of migration genes from mammalian and other systems. The authors then use published genetic and physical interaction data to assemble a network of 59 genes that may drive the migration of DTCs. Detailed analysis of this network, they suggest, should improve our understanding of the multi-factorial processes that control cell migration in *C. elegans* and other organisms.



## Double trouble in *Giardia* mitosis

Mitosis and cytokinesis in the binucleate intestinal parasite *Giardia intestinalis* must ensure that both daughters inherit one copy of each parental nucleus and a full set of the complex cytoskeletal structures required for parasite virulence. Previous work has suggested that mitosis in *Giardia* involves unconventional mechanisms for chromosome segregation. But, on p. 4889, Zacheus Cande and colleagues report that, although it does have several distinctive aspects, the major cytological events of *Giardia* mitosis (including chromosome segregation) resemble those in other organisms. The authors use 3D deconvolution light and transmission electron microscopy and conserved cytological markers to analyse mitosis and cytokinesis in *Giardia*. One distinctive aspect they reveal is a 'semi-open' mitosis in which the two spindles are outside the nuclei and access the chromatin through openings in the nuclear membranes, which remain intact throughout mitosis. Overall, the authors propose that lateral chromosome segregation along the left-right axis and cytokinesis along the longitudinal plane (perpendicular to the spindles) ensure that *Giardia* progeny inherit one copy of each parental nucleus with mirror-image symmetry.



## Make or break time for mitochondria

Mitochondria are dynamic structures, constantly undergoing fusion and fission. These two processes play important roles in cellular physiology and cell death, and key components of their machinery have been identified. However, what regulates the balance between fusion and fission is unclear. Katsuyoshi Mihara and colleagues now identify a mammalian protein – mitofusin-binding protein (MIB) – that regulates mitochondrial fusion by interacting with mitofusins (Mfns), mitochondrial outer-membrane GTPases that are required for mitochondrial fusion (see p. 4913). The authors isolated MIB, which binds to mitochondrial membranes, from rat cytosol by using affinity purification with recombinant Mfn. Overexpression of MIB, they report, induces mitochondrial fragmentation in HeLa cells, whereas knocking it down by RNAi induces an expansion of mitochondrial network structures and inhibits cell growth. Knocking down both MIB and Mfn1, however, causes mitochondrial fragmentation, which indicates that MIB functions as a negative regulator of Mfn1-dependent mitochondrial fusion. The authors therefore conclude that MIB plays an essential role in cellular function by regulating mitochondrial dynamics in cooperation with Mfn proteins.

## *Development* in press

### Rab11 goes to (the) BEACH

Vesicle trafficking is essential for many developmental events in *Drosophila*, such as eye and bristle development and synaptic morphogenesis. In a paper appearing in *Development*, Khodosh and colleagues provide new information about the developmental regulation of this process by reporting that the *Drosophila* BEACH protein Blue cheese (Bchs) antagonizes Rab11, a small GTPase that is involved in vesicle trafficking. BEACH proteins – large proteins that contain a 'Beige and Chédiak-Higashi domain' – have been implicated in membrane trafficking, but how they regulate this process is a mystery. The researchers show that blocking Bchs function suppresses the effects of loss-of-function *rab11* mutations in bristle and eye development; it also suppresses changes in synapse morphology at the neuromuscular junction (NMJ) caused by a reduction in Rab11 function. Moreover, Bchs colocalizes with Rab11 at the NMJ in vesicles. The researchers conclude that Bchs antagonizes Rab11 during development and suggest that interactions between other BEACH proteins and small GTPases could also regulate vesicle trafficking.

**Khodosh, R., Augsburger, A., Schwarz, T. L. and Garrity, P. A.** (2006). Bchs, a BEACH domain protein, antagonizes Rab11 in synapse morphogenesis and other developmental events. *Development* **133**, 4655-4665.