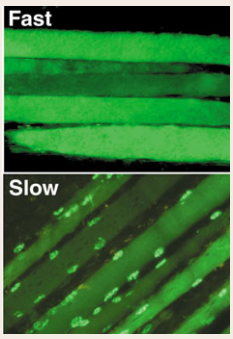
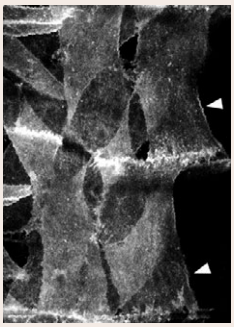
In this issue



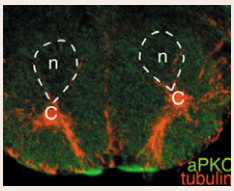
NFAT sets the pace

Skeletal muscles contain slow, fatigue-resistant fibres that depend on oxidative phosphorylation for energy and fast glycolytic fibres, which tire quickly. Individual muscle fibres can adapt, however, to changing functional demands. On p. 1604, Stefano Schiaffino and co-workers demonstrate that nerve activity can control fibre type in vivo by regulating nucleocytoplasmic shuttling of the transcription factor NFATc1. NFATc1 activity is controlled by Ca^{2+}-calcineurin signalling – calcineurin dephosphorylates NFATc1, which translocates to the nucleus and induces a gene expression program typical of slow oxidative muscle fibres. By transfecting fast (tibialis anterior) and slow (soleus) mouse muscles with a plasmid encoding NFATc1-GFP, Schiaffino's team show that NFATc1 is predominantly cytoplasmic in fast muscle but nuclear in slow muscle. Furthermore, they report, enforced inactivity causes nuclear export of NFATc1 in slow muscle, whereas electrostimulation of fast muscle to mimic the firing of slow motor neurons causes rapid nuclear import of NFATc1. These and other results lead the authors to conclude that NFATc1 is a nerve 'activity sensor' in skeletal muscle fibres in vivo.



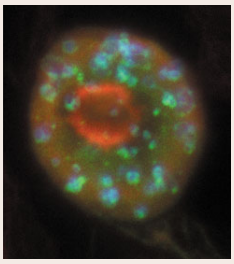
A talin(t) for adhesion

Adhesion of cells to the extracellular matrix is primarily mediated by integrins – transmembrane receptors composed of α and β subunits. Several cytoplasmic proteins link the cytoplasmic tail of integrin β to the cytoskeleton. Talin, in particular, is necessary for the formation of this link. Nicholas Brown and co-workers have examined talin-integrin interactions at muscle-attachment sites in *Drosophila* embryos, because integrins and associated cytoplasmic proteins are concentrated here and required for muscle function. They now report that multiple molecular interactions contribute to integrin-talin association in vivo (see p. 1632). For example, the authors show that the conserved N-terminal domain of talin is recruited to integrin adhesion sites through direct interaction with multiple residues in the cytoplasmic tail of integrin β, and that this must dimerize to recruit talin. Their results also indicate that recruitment of talin alone does not trigger the assembly of the whole protein complex that links integrins to the cytoskeleton but that other unidentified factors are needed to initiate this process.



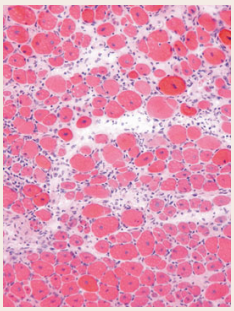
Centrosomes on PAR

During embryogenesis, asymmetric cell divisions establish distinct cell lineages by partitioning cell-fate determinants unequally in daughter cells. Conserved polarity proteins such as aPKC, PAR-6 and PAR-3 control these asymmetric divisions in worm, fly and mammal embryos. Now, on p. 1592, Janet Chenevert and colleagues report that a cell polarity complex containing these three proteins accumulates during asymmetric division in ascidian embryos at a structure known as the centrosome attracting body (CAB). The CAB – a mass of mRNA-containing cortical ER and electron-dense matrix – orchestrates three asymmetric divisions in early ascidian embryos. The authors show that the aPKC–PAR-6–PAR-3 complex localizes to the CAB and forms a thin layer between the plasma membrane and the mRNA-containing cortical ER. They also observe that astral microtubules from the proximal centrosome contact this area. Because the PAR complex localizes to the CAB just before and during the unequal cleavages in the ascidian embryo, the authors suggest that it is involved in centrosome attraction, during which capture of microtubules from one centrosome by the CAB positions the spindle so that unequal division can occur.



Lysosomes on the move

Organelles have unique peripheral membrane proteins that mediate interactions with the cytoskeleton and transport of vesicles between organelles. These proteins are recruited by activated GTPases or phospholipids that are specific to each type of organelle. On p. 1494, Irmgard Hofmann and Sean Munro identify the first GTPases that localize to mammalian lysosomes: two closely related human Arf-like GTPases called Arl8a and Arl8b. The authors show that, unusually, acetylation of the N-terminal methionine residue of Arl8b is required for its binding to membranes – most Arf and Arl proteins bind to membranes through an N-terminal myristoyl group. They also report that overexpression of Arl8a or Arl8b leads to microtubule-dependent redistribution of lysosomes towards the cell periphery and stimulates lysosomal motility. Hofmann and Munro therefore propose that these Arls – and probably their orthologs in other organisms – might function in some of the dynamic processes that depend on lysosomes, such as phagocytosis.



Dystrophin loses support

Mutations in dystrophin cause Duchenne muscular dystrophy, a severe muscle-wasting disorder. Dystrophin is the scaffold for the dystrophin-glycoprotein complex (DGC), which mechanically links the extracellular matrix to the cytoskeleton in muscle cells. The DGC also binds the enzyme nNOS, which produces the signalling molecule nitric oxide; so, in theory, loss of either the mechanical or the signalling function of the DGC could cause the myofibre degeneration in muscular dystrophy. On p. 1537 Jeffrey Chamberlain and colleagues reveal where the problem lies. They show that expression of a dystrophin isoform that contains the domains necessary for the signalling but not mechanical function of the DGC does not rescue the dystrophic phenotype in a mouse model of muscular dystrophy (*mdx* mice). Furthermore, they report, the expression of several other truncated dystrophin isoforms that cause mislocalization of nNOS does not correlate with disease severity. The authors therefore conclude that the loss of the mechanical function of the DGC – not signalling – mainly underlies the myofibre death that occurs in dystrophin-deficient muscle.

Development in press

Cloning: trophoblast fails to get with the program

Nearly ten years after the first cloned mammal was born, nuclear transfer into enucleated oocytes still rarely yields viable mammalian embryos: most cloned embryos implant normally but die after the blastocyst stage. Jouneau and co-workers now report that mouse embryos produced by the transplantation of embryonic stem cell nuclei into enucleated mouse oocytes (ES NT embryos) fail to develop primarily because of trophoblast defects that lead to placental abnormalities. The researchers use embryological studies, gene expression analyses and experiments with chimeric embryos to investigate why ES NT embryogenesis fails. They show that the peri-implantation death of ES NT embryos can be partly rescued through the injection of normal ES cells or inner cell mass cells. Based on their results, the researchers propose that ES NT embryos fail because of defective epigenetic reprogramming in the trophoblast lineage. The same could be true for clones produced by somatic cell nuclear transfer.

Jouneau, A., Zhou, Q., Camus, A., Brochard, V., Maulny, L., Collignon, J. and Renard, J.-P. (2006). Developmental abnormalities of NT mouse embryos appear early after implantation. *Development* **133**, 1597-1607.