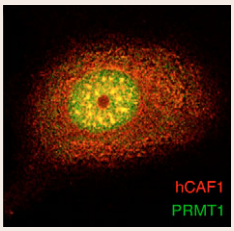
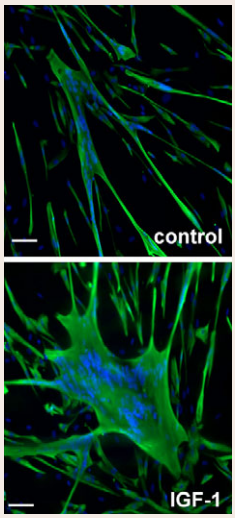
In this issue



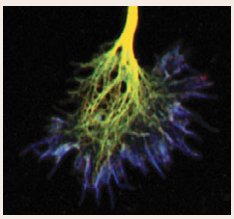
PRMTing histone methylation

Peptidylarginine methyltransferases (PRMTs) methylate arginine residues in polypeptides, increasing the structural and functional diversity of proteins involved in the regulation of numerous cellular processes, including histones. PRMT1 is the major PRMT in mammalian cells, responsible for more than 85% of all protein arginine methylation; yet surprisingly little is known about its own regulation. On p. 638, Yannis Robin-Lespinasse and colleagues report that human CCR4-associated factor 1 (hCAF1) regulates PRMT1 activity. They demonstrate that hCAF1 and PRMT1 directly interact in vivo and co-localise to the same sub-nuclear compartment. Furthermore, hCAF1 acts as a cofactor for PRMT1 and regulates its enzymatic activity in vitro in a substrate-specific manner. Loss-of-function studies show that hCAF1 modulates asymmetric methylation of endogenous PRMT1 substrates in vivo. Indeed, methylation of the nuclear RNA-binding protein Sam68 and histone H4, two PRMT1-specific substrates, increased following hCAF1 ablation. The authors thus identify hCAF1 as a novel regulator of PRMT1 function. They go on to speculate that regulation of methyltransferase activity by hCAF1 may contribute to the crosstalk between transcription and RNA processing.



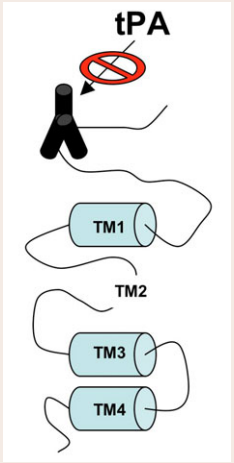
Recruiting muscle from the reserves

IGF-1 plays a major role in the control of skeletal muscle growth and regeneration. It increases skeletal muscle mass and has been touted as a potential therapy for muscle wasting and neuromuscular diseases. Therefore, understanding the mechanisms by which IGF-1 induces muscle hypertrophy is paramount. On p. 670, Virginie Jacquemin and colleagues reveal that IGF-1 signals exclusively to myotubes and not reserve cells, and that the myotubes then recruit reserve cells by a secondary mechanism. IGF-1 treatment of myoblasts induces expression of markers characteristic of myogenic differentiation and induces activation of the MAPK and Akt kinases specifically in myotubes. The authors hypothesised that the myotubes must secrete a soluble factor responsible for reserve cell recruitment. Using neutralising antibodies, they identified this factor as interleukin 13 (IL-13) and demonstrate that its induction is mediated by the NFATc2 transcription factor. In addition to increased cell fusion, IGF-1 treatment stimulates myotube protein metabolism via Akt, which activates mTOR signalling (a key growth pathway) and inhibits Foxo1-atrogin1 protein degradation pathways. The authors speculate that therapeutic strategies directed at specific IGF-1 metabolic targets rather than reserve cell recruitment could potentially prolong the regenerative capacity of muscle.



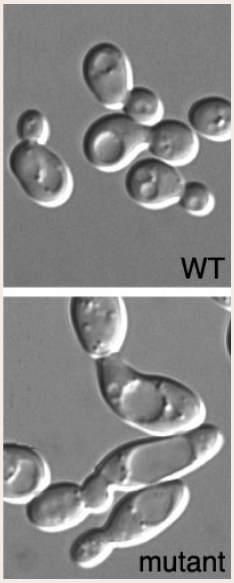
A new IQGAP

The Rho family GTPases control diverse cellular processes through a large group of effector molecules, which elicit specific physiological responses. On p. 567, Kozo Kaibuchi's group identify a novel member of the IQGAP family of Rho family effectors, IQGAP3. They demonstrate that it interacts with and functions as an effector for the activated Rho GTPases Rac1 and Cdc42. Furthermore, they show that it directly associates with actin filaments in vivo through its N-terminal calponin homology domain (CHD). IQGAP3 is highly expressed in the brain and localises to the distal tips of axons in hippocampal neurons. Using an siRNA approach the authors demonstrate that IQGAP3, unlike IQGAP1, is necessary for neurite outgrowth in PC12 cells in response to nerve growth factor (NGF) and show that this functional difference between IQGAP1 and IQGAP3 resides within the C-teminal region. Furthermore, they establish that IQGAP3 is vital for Rac1/Cdc42-directed hippocampal axon outgrowth. This study reveals that IQGAPs regulate neuronal cell morphology via their ability to organise the cytoskeleton and stabilise activated Rac1 and Cdc42 and identifies a specific role for IQGAP3 in axonal elongation.



Behavioural cues from tPA

Various ligands and modulators are involved in NMDA-receptor signalling, which controls crucial brain functions. Tissue-type plasminogen activator (tPA), for example, interacts with and then cleaves the NR1 subunit of the NMDA receptor, increasing receptor-mediated Ca^{2+} influx; however, the contribution this interaction makes to brain function and dysfunction is currently a matter of debate. Now, Karim Benchenane and co-workers demonstrate that tPA controls NMDA-receptor-mediated neurotoxicity and spatial memory (see p. 578). They developed an immunological strategy to selectively prevent tPA-NR1 interaction and NR1 cleavage to reveal the role it plays in neuronal death or survival and in behaviour. Blocking the tPA-NR1 interaction prevented permanent cerebral ischemia and reduced the severity of excitotoxic neuronal death in mouse brains. Cognitive function was also altered in some but not all behavioural tasks, indicating the tPA-NR1 interaction is not involved in all tPA-driven functions. The authors speculate that using antibody-based therapies that prevent the tPA-NR1 interaction may improve acute management of stroke patients.



Cyclin different places

In yeast, the mitotic cyclin Clb2 plays a fundamental role in anaphase initiation and in the maintenance of cell shape throughout G1 phase of the cell cycle. The mechanisms by which Clb2 regulates these processes remain unclear. On p. 702, Raïssa Eluère and others demonstrate that subcellular localisation of Clb2 is a key determinant of its biological function. To investigate the relevance of Clb2 compartmentalisation the authors generated mutant versions of Clb2 that exhibit impaired nuclear import or export and analysed two Clb2-dependent processes: G2-M phase progression and the switch from apical to isotropic growth. They show that nuclear Clb2 is required for timely entry into anaphase whereas the cytoplasmic pool is required for bud morphogenesis. Furthermore, they demonstrate that degradation of Clb2 is also regulated by its localisation, the cytoplasmic form being stabilised during anaphase but not during mitotic exit. The authors propose a model whereby the switch from polarised to isotropic growth occurs when the cytoplasmic pool of Clb2 reaches an appropriate level and this is independent of cell cycle progression.

Development in press

Prostates get into shape with FGFR2

The adult prostate depends on androgen for its growth and function – its epithelium regresses when androgens are depleted. FGF signalling, through the FGF receptor FGFR2, has been implicated in mouse prostate development, but studies of FGFR2's role in prostate organogenesis have been hampered by the early embryonic death of *Fgfr2*-null mutants. In an article appearing in the journal *Development*, Fen Wang's group report, from their studies of conditional *Fgfr2* mutant embryos, that FGFR2 is required for prostate growth and morphogenesis, and for certain aspects of this organ's androgen dependency. Branching morphogenesis is particularly affected in these mutants, and despite the continued ability of *Fgfr2* conditional mutant prostates to secrete proteins in response to androgen, their ability to regulate tissue maintenance in an androgen-dependent manner is compromised. As advanced prostate tumours can often grow independently of androgen, further studies into the molecular mechanisms that define how FGFR2 regulates the prostate's maintenance and growth in an androgen-dependent manner could yield new therapeutic targets for the treatment of these aggressive cancers.

Lin, Y., Liu, G., Zhang, Y., Hu, Y.-P., Yu, Y., Lin, C., McKeehan, K., Xuan, J. W., Ornitz, D., Shen, M. M., Greenberg, N., McKeehan, W. L. and Wang, F. (2007). Fibroblast growth factor receptor 2 tyrosine kinase is required for prostatic morphogenesis and the acquisition of strict androgen dependency for adult tissue homeostasis. *Development* **134**, 723-734.