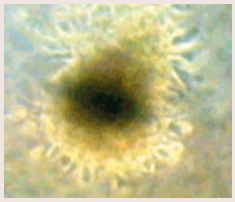
In this issue

Prohibitin' muscle differentiation

Muscle differentiation, like many aspects of development, is controlled by interplay between different signalling molecules and cell fate determinants. The MyoD and MEF2 transcription factors play key roles in the process, as does signalling by insulin-like growth factors (IGFs), which activate the kinases PI3K and Akt (also known as PKB). On p. 3021, Zhenguo Wu and co-workers establish a link between these myogenic regulators and along the way uncover a role for prohibitin 2 (PHB2) – a highly conserved protein whose function has so far remained elusive. Picking up PHB2 in two-hybrid screens for Akt-binding partners, the authors demonstrate that it is a transcriptional repressor that can inhibit MyoD- and MEF2-dependent transcription in C2C12 myoblasts and block muscle differentiation. They also show that it interacts with endogenous MyoD and MEF2 and inhibits transcription by recruiting the histone deacetylase HDAC1. Wu and co-workers go on to reveal that Akt promotes muscle differentiation by disrupting binding of PHB2 to MyoD, which allows the transcription factor to execute its function. Their findings therefore highlight a lesser-known aspect of Akt function: its kinase-independent effects.

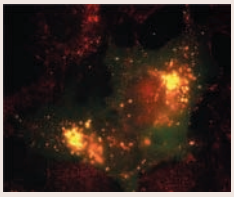


MIAMI cells: pluripotent progenitors with potential

Cell transplantation has immense potential as a therapy for inherited and degenerative diseases. Generating stem-cell-like donor populations that can develop into various different lineages but also maintain their proliferative capacity in culture has proven difficult, however. Paul Schiller and co-workers now unveil a human bone-marrow-derived cell type that might fit the bill: marrow-isolated adult multilineage inducibe (MIAMI) cells (see p. 2971). Starting with whole unfractionated bone marrow, they coculture adherent and non-adherent cells on a fibronectin substrate, using a specific combination of growth factors, vitamins, low oxygen tension and cell density to mimic the stem cell microenvironment. Their selection and expansion strategy yields cells that express embryonic stem (ES) cell markers such as Oct-4, as well as markers characteristic of mesodermal, endodermal and ectodermal lineages. These MIAMI cells have a greater potential for multilineage differentiation than cells previously isolated from marrow – they can differentiate into osteoblasts, adipocytes, pancreatic cells and neuronal cells. Moreover, in contrast to many previously described stem-cell-like populations, MIAMI cells continue to proliferate beyond 50 doublings, without any signs of senescence. They thus represent promising tools for cell transplantation to repair damaged, aged or diseased tissues.

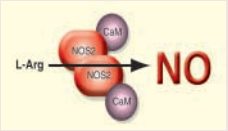
Synaptic role for retinoid

All-trans retinoic acid (RA) is one of several signalling molecules, including oestrogen, progesterone and vitamin D3, that exert their effects by binding to nuclear receptors that act as ligand-activated transcription factors. In this way, RA regulates gene expression programmes that control developmental processes such as limb morphogenesis, anterior-posterior patterning and neurite growth. Jau-Cheng Liou and co-workers now reveal that RA also controls synaptic activity and, surprisingly, does so without affecting gene expression (see p. 2917). They show that RA increases the frequency of release of the neurotransmitter acetylcholine from neuromuscular synapses in developing *Xenopus* neurons in culture. The authors demonstrate that the effect is specific and can be mimicked by agonists of the RA receptor (RAR) RARβ but not RARα/RARγ agonists. In addition, they find that it cannot be blocked by protein synthesis inhibitors. Liou and co-workers therefore conclude that RA acts through RARβ to modulate synaptic transmission by a novel, 'nongenomic' mechanism. Since RA and RARs are present at high levels in the embryo, and neuromuscular transmission at synapses is crucial at developing synapses, this could be an important aspect of its developmental role.



Classy endocytic proteins

Class E vacuolar protein sorting (Vps) mutations cause yeast to generate a novel organelle – the class E compartment – next to the vacuole. The proteins affected by these mutations function in endosomal trafficking and have relatives in mammals, including the AAA-type ATPase SKD1. To investigate SKD1 function further, Hideaki Fujita and co-workers have used two-hybrid screening to search for its binding partners. They now reveal two new mammalian class E Vps proteins that bind to SKD1: SBP1 and mVps2 (see p. 2997). Both have orthologues in yeast and are targeted to aberrant endosomal structures in cells expressing ATPase-deficient SKD1. The authors' studies indicate that mVps2 controls membrane association of SKD1 and that SKD1 regulates assembly of a large SBP1-containing complex. Interestingly, SBP1 turns out to be identical to a previously isolated protein that interacts with the lysosomal trafficking regulator Lyst, mutations in which cause Chediak-Higashi syndrome (CHS). Fujita and co-workers also provide evidence that SKD1 can regulate membrane association of Lyst and that it is recruited to membranes by SBP1. Their findings thus point the way for new studies into the molecular mechanisms underlying formation of giant lysosomes in CHS.



Thrice NO

Endogenously produced nitric oxide (NO) has numerous physiological roles. It is generated by three enzymes: eNOS, nNOS and iNOS. NO produced in endothelia by eNOS regulates blood vessel dilation by targeting vascular smooth muscle cells; NO produced in neurons by nNOS regulates synaptic signalling and plasticity in the brain; and NO produced in large quantities by iNOS in cells of the innate immune system can kill fungal and bacterial pathogens and inhibits viral replication. Over the past three issues, Cell Science at a Glance has featured a series of contributions covering the various roles of NO. In the last of these, Charles Lowenstein and Elizaveta Padalko tackle NO generated by iNOS (see p. 2865 + poster).

Development in press

To divide or differentiate: a neural question

In the developing mouse brain, the balance between self-renewal of neural precursor cells (NPCs) and their differentiation into neuronal and glial cells determines the final make-up of the brain. In a paper published in *Development*, Hirabayashi and co-workers propose that the Wnt (Wingless) signalling pathway directs neuronal differentiation in the developing mouse neocortex. They show that expression of Wnt7a or activated β-catenin inhibits NPC self-renewal and induces NPC differentiation by regulating the proneural transcription factor neurogenin 1. Hirabayashi et al. reconcile these results with previous studies in which Wnt signalling was found to promote NPC self-renewal by showing that activated β-catenin induces the differentiation only of NPCs taken from 11.5-day or older embryos and not those from younger embryos. They conclude that, as in the case of wing-disc development in *Drosophila*, Wnt signalling has stage-specific effects during vertebrate neural development.

Hirabayashi, Y., Itoh, Y., Tabata, H., Nakajima, K., Akiyama, T., Masuyama, N. and Gotoh, Y. (2004). The Wnt/β-catenin pathway directs neuronal differentiation of cortical neural precursor cells. *Development* **131**, 2791-2801.