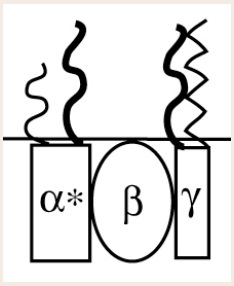
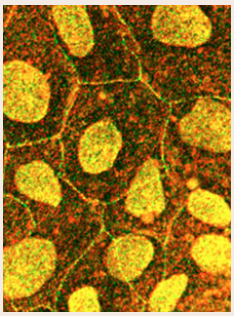
In this issue

by Jane Bradbury



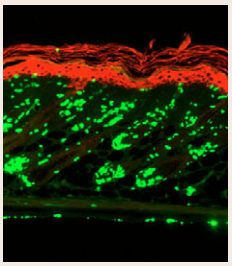
G-proteins go green…

Heterotrimeric G proteins are important signal transducers for 7-transmembrane-span receptors. In mammals, receptor activation leads to exchange of GDP bound to the G protein α subunit (Gα) for GTP. Gα and Gβγ then dissociate and activate various effectors. On p. 5087, Theodorus Gadella and co-workers provide the first evidence for a heterotrimeric G protein in a dicot plant. This, they reveal, behaves very differently from mammalian G proteins. Lipid modifications are important for the function of mammalian G proteins. To discover their role in the formation and localization of plant G protein heterotrimers, the authors used fluorescence resonance energy transfer (FRET) with fluorescence lifetime imaging microscopy (FLIM) to follow GFP-tagged *Arabidopsis* G-protein subunits in cowpea cells. Localization of Gα (GPα1) and the two Gγ subunits (AGG1 and AGG2) to the plasma membrane, they report, requires modification of two lipidation motifs in each subunit. More importantly, they show that GPα1-AGβ1-AGG1 heterotrimers exist at the plasma membrane but do not dissociate upon activation of GPα1; instead these may toggle between two conformations on GDP/GTP exchange.



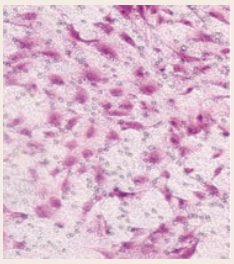
…tight junctions use nuclear power

The localization of several proteins to both epithelial tight junctions (TJs) and the nucleus suggests that TJs might participate in the regulation of gene expression. On p. 5098, Maria Balda, Karl Matter and co-authors provide compelling evidence that this is indeed the case. They report that two such proteins – the canine Y-box transcription factor ZONAB (DbpA in human cells) and the RNA-processing factor symplekin – cooperate in the regulation of transcription and promote epithelial proliferation. The authors show that ZONAB/DbpA and symplekin, both of which are found at TJs, form a complex in the nucleus of canine kidney and human intestinal cells. Using reporter gene assays they demonstrate that symplekin functionally interacts with ZONAB/DbpA to promote transcriptional repression. Finally, they show that RNAi-induced depletion of symplekin reduces the nuclear accumulation and transcriptional activity of ZONAB/DbpA in human colon adenocarcinoma cells, which inhibits proliferation and reduces expression of the ZONAB/DbpA target gene *cyclin D1*. Because DbpA is overexpressed in many human tumours, these insights into its regulation could help in the search for anti-cancer drugs.



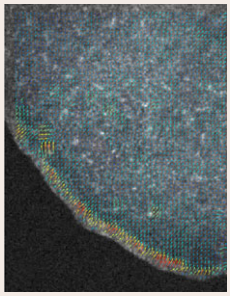
Keratin 10 – cancer in the end

Epithelial cells express many keratins, all of which may have specific roles. In the mammalian epidermis, the basal layer (which includes proliferating keratinocytes) expresses keratin 14 (K14), whereas post-mitotic suprabasal keratinocytes express keratin 10 (K10). Because K10 overexpression in the basal layer inhibits keratinocyte proliferation in transgenic mice, it has been proposed that K10 suppresses proliferation in the skin. On p. 5067, Peter Koch and colleagues overturn this idea by showing that expression of K10 end domains (which inhibit cell-cycle progression in vitro) at physiological levels does not inhibit basal keratinocyte proliferation in vivo. The authors have made transgenic mice whose basal keratinocytes express physiological amounts of a chimeric keratin that contains the K14 central domain and the K10 end domains. Skin development is normal in these mice but papillomas form after carcinogen treatment faster than in wild-type mice, partly because apoptosis is suppressed. The authors speculate that K10 normally suppresses cell death in suprabasal keratinocytes to allow them to differentiate, a physiological function missed in experiments in which K10 was overexpressed.



NO limit to muscular dystrophy

Muscular dystrophies are untreatable, sometimes fatal, genetic diseases that are characterized by progressive wasting of skeletal muscle. Stem-cell-based therapies, such as the injection of mesoangioblasts (blood-vessel-associated myogenic stem cells), have usually stimulated only limited muscle repair in animal models of muscular dystrophy. But, on p. 5114, Giulio Cossu, Emilio Clementi and co-authors report that ex-vivo treatment of mesoangioblasts with nitric oxide (NO) donors increases their therapeutic efficacy in the α-sarcoglycan-null mouse model of Duchenne muscular dystrophy. NO treatment, they report, enhances the migration of mesoangioblasts to the dystrophic muscles of these mice and helps the mesoangioblasts resist the apoptogenic environment of these muscles and engraft. The authors replicate these beneficial effects of NO in vitro and show that all the effects are GMP-dependent. Finally, they report that NO switches on signalling pathways in the mesoangioblasts that are involved in myogenesis and muscle repair. Thus, the authors conclude, treatment with NO might be a simple way to improve the efficacy of stem-cell therapy for muscle-wasting disorders.



Cell migration: slip-sliding away

Cell migration involves the formation and stabilization of protrusions and the assembly/disassembly of adhesions between the cell and its substrate. Protrusion and adhesion are interconnected and controlled by the efficiency of the linkage between the substrate and the actin cytoskeleton. To investigate how this linkage is regulated during cell migration, Claire Brown and co-authors have used a powerful new technique known as STICS – spatio-temporal image correlation spectroscopy (see p. 5204). By analysing fluorescence image time series collected from migrating cells that contain fluorescent proteins, the authors have built detailed velocity maps for actin and various adhesion-related proteins, including α-actinin, α5-integrin and talin. Their results indicate that the efficiency of the linkage between integrin and actin varies between cell types and depends on the strength of the interaction with the substrate. Furthermore, given the correlations between the movement of different proteins, the authors propose that the linkage between immobile integrin and retrograde-flowing actin contains two slippage points: one between integrin and the cytoplasmic adhesion proteins, the other between these proteins and actin.

Development in press

Ldb1 changes partners for haematopoiesis

During haematopoiesis, coordinated changes in transcription drive the differentiation of haematopoietic stem cells. In a paper published in *Development*, Frank Grosveld and colleagues now suggest that the LIM-domain-binding protein Ldb1 facilitates these transcriptional changes by forming distinct complexes with different partners. Ldb1 is a co-factor for several DNA-binding proteins, including haematopoietic transcription factors. To find new Ldb1-binding partners, the researchers expressed biotin-tagged Ldb1 in C88 erythroleukaemic cells and pulled out interacting proteins with streptavidin-coated beads. New partners included the repressor protein Eto-2, the cyclin-dependent kinase Cdk9, and the bridging factor Lmo4. The researchers show that the composition of Ldb1 complexes changes during the differentiation of C88 cells. They also report that these Ldb1 partners are essential for definitive haematopoiesis in zebrafish and are coexpressed in pre-haematopoietic cells in mouse embryos. Finally, the researchers speculate that changes in Eto-2 and Lmo4 levels cause a shift from a large Ldb1-containing complex to a smaller complex that is required for haematopoiesis.

Meier, N., Krpic, S., Rodriguez, P., Strouboulis, J., Monti, M., Krijgsveld, J., Gering, M., Patient, R., Hostert, A. and Grosveld, F. (2006). Novel binding partners of Ldb1 are required for haematopoietic development. *Development* **133**, 4913-4923.