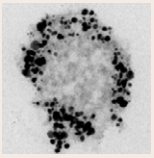
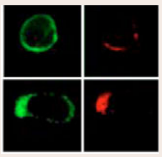
In this issue



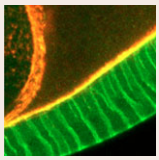
Compartmentalising the cilium

Defects in the primary cilium – which extends from the surface of most eukaryotic cells – can lead to several disorders, but little is known about how individual ciliary proteins function or how they are compartmentalised. For instance, mice that lack the cilium-localised protein inversin (Inv) have situs inversus (mirror-image rearrangement of the visceral organs) and develop multiple renal cysts, but have no apparent defects in ciliary structure. On page 44, Takahiko Yokoyama and colleagues use immuno-EM and confocal microscopy to explore the subciliary distribution of Inv. The authors first show that Inv-GFP and endogenous Inv localise to a region near the base of the cilium that is distinct from previously identified subciliary compartments – they term this region the Inv compartment. Next, they use truncated Inv-GFP constructs to identify a ninein-homologous sequence at the C-terminus of Inv that is essential for its localisation to the Inv compartment. Notably, mutations in this region – which is distinct from the Inv cilium-targeting sequence – have been associated with kidney disease in humans. Finally, the authors use FRAP to show that Inv is dynamic within the Inv compartment. They conclude that the Inv compartment is a novel region within the primary cilium that might be required to maintain normal renal architecture.



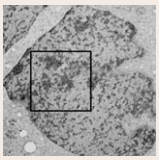
ERM – actin' in HIV-1 infection

Before HIV-1 can enter target cells, the viral envelope glycoprotein Env must first interact simultaneously with the cell-surface receptors CD4 and either CCR5 or CXCR4. Little is known about how HIV-1 induces CD4 and CXCR4 to redistribute and cluster together, although F-actin and its regulatory proteins are thought to have an important role. On page 103, Francisco Sánchez-Madrid and colleagues report on how ERM proteins – which link membrane-associated proteins and the actin cytoskeleton – function in HIV-1 attachment. The authors show that the ERM proteins ezrin and moesin are phosphorylated (and thereby activated) in response to viral particles or the envelope protein gp120. This phosphorylation is observed both in a $CD4^+$ $CXCR4^+$ T-cell line and in primary lymphocytes, and requires an interaction between gp120 and CD4 (but not CXCR4). The authors next report that activated moesin promotes CD4-CXCR4 interaction, as well as the redistribution of CD4-CXCR4 and F-actin to sites of contact between HIV-1 and target cells. Importantly, knocking down moesin or expressing a dominant-negative moesin mutant impedes F-actin reorganisation and HIV-1 infection. The authors conclude, therefore, that the activation of moesin is a key step in Env-mediated HIV-1 internalisation.



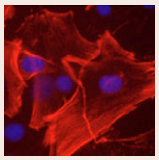
CME effectors – making the connection

The phosphoinositide PtdIns(4,5)P_2 and the small GTPase Rab5 both have key roles during the early stages of clathrin-mediated endocytosis (CME) – PtdIns(4,5)P_2 is important in clathrin-coated-vesicle (CCV) formation, whereas Rab5 promotes the budding and maturation of CCVs. Now, Antoine Guichet and colleagues (p. 25) explore how the roles of Rab5 and PtdIns(4,5)P_2 interconnect. The authors analyse early endocytic events during yolk-protein uptake in *Drosophila* oocytes, showing that oocytes that lack Rab5 cannot endocytose yolk proteins. Moreover, in wild-type oocytes, depletion of PtdIns(4,5)P_2 [through loss of function of the PtdIns(4,5)P_2-synthesising enzyme Skittles] impedes recruitment of Rab5 to a site below the plasma membrane, and diminishes the formation of early endocytic vesicles (EEVs). The authors next demonstrate that Rab5 mediates the removal of PtdIns(4,5)P_2 from EEVs; notably, oocytes that overexpress Skittles [and therefore overproduce PtdIns(4,5)P_2] fail to endocytose yolk proteins, and echo the phenotype of Rab5-deficient oocytes. The authors propose that the Rab5-dependent removal of PtdIns(4,5)P_2 from EEVs is necessary for CME to proceed. Their results shed light on the complex interplay between effectors of CME.



NER takes shape in the nucleus

The cell nucleus is highly ordered, and contains several distinct structural and functional compartments. For instance, most DNA replication and transcription takes place in the perichromatin region – a compartment that contains partially condensed chromatin and surrounds domains in which chromatin is densely packed. Now, Roel van Driel and colleagues (p. 83) ask whether nucleotide excision repair (NER) of DNA is compartmentalised in a similar way. Using EM in combination with immunogold labelling, the authors show that UV-induced DNA damage can be detected both in the chromatin-dense domains and the perichromatin region. They next study the spatial dynamics of the NER proteins XPC (which detects DNA damage) and XPA (a component of the chromatin-associated NER complex), and demonstrate that both proteins accumulate rapidly in the perichromatin region after UV irradiation. Notably, however, only XPC is enriched in chromatin-dense domains. They go on to show that chromatin domains undergo transient expansion in response to UV damage. Thus, they propose, UV-damaged DNA might be detected by XPC within condensed chromatin, then translocated to the perichromatin region for repair. These data provide insight into the spatial organisation of nuclear processes.



MT1-MMP makes migratory muscle

When blood vessels are injured, vascular smooth muscle cells (VSMCs) contribute to lesion formation by de-differentiating, becoming invasive and migrating into the blood-vessel wall. The matrix metalloproteinase MT1-MMP is known to promote the invasion of VSMCs, and Kaisa Lehti and colleagues (p. 126) now uncover a role for MT1-MMP in the de-differentiation process itself. The authors observe that, in cultured VSMCs, MT1-MMP is dramatically upregulated during de-differentiation (which is measured as the repression of contractile-protein expression). Moreover, de-differentiation is attenuated when MMP inhibitors are present and in *MT1-MMP*$^{-/-}$ VSMCs. Growth factors have previously been proposed to promote de-differentiation of VSMCs, and the authors now show that MT1-MMP-dependent de-differentiation requires both PDGF-BB and its receptor, PDGFRβ. In addition, they show that MT1-MMP promotes processing of the receptor LRP1, as well as formation and internalisation of a multiprotein complex containing LRP1, β3 integrin, MT1-MMP and PDGFRβ. Finally, they demonstrate that de-differentiation does not require MT1-MMP when LRP1 is silenced. On the basis of these results, the authors propose a new MT1-MMP-dependent mechanism for VSMC de-differentiation.

Development in press

Branching out – a new mode of neuronal migration

Many migrating neurons and growing axons reach their correct targets during brain development by adjusting the growth of their leading process in response to guidance cues. Now, in a paper published in *Development*, Oscar Marín and colleagues propose that the dynamic regulation of leading-process branching represents a novel guidance mechanism for migrating neurons. The researchers use time-lapse videomicroscopy to analyse the dynamic behaviour of individual neurons migrating tangentially in mouse telencephalic slices. Cortical interneurons (and other populations of GABAergic neurons) consistently form branched processes during their migration, the authors report, and respond to chemoattractant signals by generating branches that are better aligned with the source of the signal, rather than by re-orienting existing branches. In addition, guidance cues influence the angle at which new branches emerge, and chemotaxis is blocked when cells are treated with an inhibitor of ROCK (to suppress branching). Thus, the researchers suggest that the directional migration of neurons that have branched leading processes is achieved by stabilising the most suitable branch.

Martini, F. J., Valiente, M., López Bendito, G., Szabó, G., Moya, F., Valdeolmillos, M. and Marín, O. (2009). Biased selection of leading process branches mediates chemotaxis during tangential neuronal migration. *Development* **136**, 41-50.