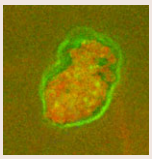
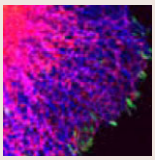
In this issue

By Jane Bradbury



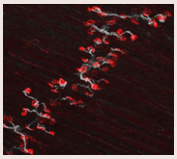
Pressure-driven bleb-based motility

Cell motility is required for many physiological processes (for example, cell movements during development) and is involved in several pathological processes. Benoît Maugis and colleagues have been investigating the motility of the human parasite *Entamoeba histolytica* and, on page 3884, they propose a new model for bleb-based motility, a poorly studied form of amoeboid locomotion. Blebs are spherical membrane protrusions that are seen in apoptotic, migrating and non-migrating cells, and in cells before they fully adhere to a substrate. The authors show first that *E. histolytica*, which encounters several environments as it passes through the human body, produces blebs in various microenvironments in vitro. Then, using reflection interference contrast microscopy, they elucidate the relationship between bleb formation and retraction, contact dynamics and net cell motion, and show that bleb-based motility involves the rapid formation of protrusions followed by their stabilisation or retraction. Finally, they use a novel local electroporation method to show that dynamic instability of intracellular pressure drives bleb-based motility. Together, these data establish *E. histolytica* as a unique model for studying the physical and biological aspects of amoeboid motility.



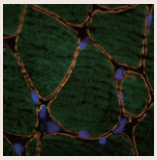
Focal adhesions: the ER connection

Cell shape control, spreading and migration – important cellular processes that underlie many physiological functions – are driven in part by the formation of focal adhesions (FAs) at the cell periphery. Many endoplasmic reticulum (ER) proteins colocalise with FAs. Here (p. 3901), Hanry Yu and colleagues provide new insights into the mechanism that drives this colocalisation and the ER's effect on FA dynamics. They show that the interaction between kinectin (an integral ER membrane protein that extends the ER along microtubules) and kinesin (the motor protein involved in plus-end-directed transport along microtubules) mediates ER extension into the cellular lamella and ER colocalisation with FAs in HeLa cells. Functional impairment of the kinectin–kinesin interaction reduces the number of FAs formed within the cellular lamella, and results in a morphological change to a rounded cell shape, and reduced cell spreading and migration. Finally, whereas microtubules alone facilitate FA disassembly, the authors show that ER localisation to FAs promotes FA growth, even in the presence of microtubules. Thus, they suggest, the kinectin–kinesin interaction supports FA growth by facilitating ER transport along microtubules.



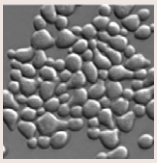
Agrin cleavage for NMJ maturation

Early in the development of neuromuscular junctions (NMJs) – specialised synapses between the axon terminals of motoneurons and a receptor-rich postsynaptic apparatus of the muscle fibre membrane – the nerve-derived proteoglycan agrin organises and stabilises plaque-like postsynaptic clusters of acetylcholine receptors. These plaques are subsequently converted into pretzel-like structures that contain central receptor-free areas. So, ask Peter Sonderegger and colleagues (p. 3944), does agrin's NMJ-promoting and stabilising function have to be reduced during NMJ maturation? The authors show that transgenic overexpression of neurotrypsin (a neuronal serine protease that cleaves agrin at two sites) in mouse motoneurons results in excessive reorganisation and dispersal of NMJs. By contrast, they report, expression of cleavage-resistant agrin in motoneurons slows down NMJ remodelling and maturation. The authors propose, therefore, that agrin-dependent stabilisation of the NMJ has to be relieved by the proteolytic degradation of agrin for the plaque-to-pretzel maturation of the NMJ to proceed. Notably, however, NMJ maturation is normal in neurotrypsin-dependent mice. Thus, an unidentified protease rather than neurotrypsin must be involved in endplate reorganisation during NMJ maturation.



P marks the spot in myopathy

Mutations in *LMNA*, which encodes A-type nuclear lamins, cause at least 13 human hereditary diseases. These 'laminopathies' include several myopathies, lipodystrophy and progeria, but how do mutations in one gene cause all these disorders? On page 3893, Yukiko Hayashi and colleagues identify a disease-related phosphorylation site in A-type lamins that throws some light on this puzzle. Human A-type lamins contain more than 30 phosphorylation sites. To investigate the physiological importance of these sites, the authors made site- and phosphorylation-state-specific antibodies against human A-type lamins. An antibody that recognises phosphorylated Ser458 reacts with nuclei in muscle biopsies from patients with myopathy caused by mutations in the immunoglobulin-like fold motif of A-type lamins, they report, but not with biopsies from patients with other neuromuscular diseases. Furthermore, myopathy-related *LMNA* mutations induce Ser458 phosphorylation by Akt1 in vitro, but *LMNA* mutations related to lipodystrophy or progeria do not induce Ser458 phosphorylation. The authors propose, therefore, that Ser458 phosphorylation of A-type lamins contributes to the striated-muscle laminopathies caused by *LMNA* mutations, a finding that might facilitate early diagnosis of these myopathies.



Licensed to replicate

Replication licensing ensures that DNA replication occurs exactly once per eukaryotic cell cycle. Licensing is achieved by sequentially loading replication-initiation proteins onto replication origins to form pre-replicative complexes (pre-RCs). Phosphorylation of initiation proteins by cyclin-dependent kinases (CDKs) prevents unscheduled replication licensing, but it is unclear whether phosphatases help to reset replication competency. Now, Chun Liang and colleagues (p. 3933) show that cell division cycle protein 14 (Cdc14p) – a phosphatase that helps to orchestrate mitotic exit – dephosphorylates several replication-initiation proteins to restore their competence for pre-RC assembly in budding yeast. Cells without functional Cdc14p, the authors report, fail to dephosphorylate initiation proteins, form pre-RCs or replicate DNA in mitotic rereplication systems. Conversely, pulsed ectopic expression of Cdc14p in mitotic cells results in efficient pre-RC assembly and DNA replication. Finally, mitotic cells containing non-phosphorylatable and/or phosphorylation-insensitive alleles of initiation proteins do not require Cdc14p for DNA rereplication. These data clarify Cdc14p's role in DNA replication, and provide new insights into how the interplay between phosphorylation and dephosphorylation regulates DNA replication.

Development in press

Grainyhead heads up apical junction formation

Epithelial-cell differentiation requires the formation of the apical junctional complex, a membrane-associated structure that includes adherens junctions (which mediate stable adhesion between epithelial cells) and tight junctions (which regulate the movement of water and solutes between epithelial cells). In *Development*, Kai Schmidt-Ott and colleagues report that the mammalian transcription factor grainyhead-like 2 (Grhl2), an epithelium-specific homologue of *Drosophila* Grainyhead, regulates the molecular composition of the apical junctional complex. Grhl2, they report, determines the expression levels of E-cadherin and claudin 4 (Cldn4) – key components of adherens junctions and tight junctions, respectively – in several types of epithelia. Other experiments reveal that Grhl2 regulates epithelial differentiation in vitro and in vivo, that Grhl2 deficiency in mice results in defective neural tube closure, and that Grhl2 associates with conserved *cis*-regulatory elements in the Cldn4 and E-cadherin genes. Together, these data suggest that Grhl2 is a transcriptional activator of apical junctional complex components and is, therefore, a crucial participant in epithelial differentiation.

Werth, M., Walentin, K., Aue, A., Schönheit, J., Wuebken, A., Pode-Shakked, N., Vilianovitch, L., Erdmann, B., Dekel, B., Bader, M., Barasch, J., Rosenbauer, F., Luft, F. C. and Schmidt-Ott, K. M. (2010). The transcription factor grainyhead-like 2 regulates the molecular composition of the epithelial apical junctional complex. *Development*, **137**, 3838-3843.