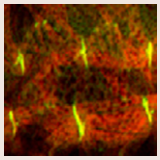
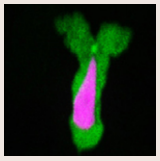
# In this issue



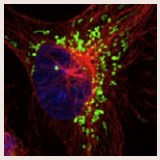
## Zasp and talin – working together to activate integrins

Integrins are heterodimeric adhesion receptors that link the extracellular matrix (ECM) to the cytoskeleton; they are activated by the binding of talin to the cytoplasmic tail of β-integrin, which results in a conformational change of the integrin extracellular domains and allows ligand binding. Additional factors regulate integrin activation, and either act through talin or directly on integrins, but the underlying mechanisms are not fully understood. On page 5647, Frieder Schöck, David Calderwood and colleagues investigate the role of Z-band alternatively spliced PDZ-motif-containing protein (Zasp) in the activation of β1-integrins. Zasp is known to localise to integrin adhesion sites, but was thought to function primarily in the assembly and maintenance of the muscle contractile machinery. Here, the authors report that co-expression of Zasp with the talin head domain potentiates α5β1 integrin activation in Chinese hamster ovary (CHO) cells, suggesting that Zasp cooperates with talin to activate integrins. They also show that, in *Drosophila*, Zasp deficiency leads to detachment of αPS2βPS integrins from the ECM, an indicator of perturbed integrin activation *in vivo*, without affecting talin localisation. Moreover, they find that Zasp specifically coactivates β1- and not β3-integrins, which are activated by kindlins. Taken together, these data identify Zasp as a new regulator of integrin activation, with a mode of action that is distinct from that of other known integrin coactivators.



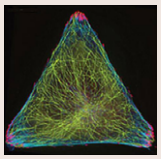
## Microtubules 'Rac and Rho' in migrating neutrophils

Microtubules contribute to directed cell migration by positively regulating cell polarity. Previous work on isolated neutrophils showed that disruption of microtubules enhances migration but impairs directionality – presumably through the activation of Rho – but little is known with regard to how microtubules regulate neutrophil migration in 3D tissue environments *in vivo*. Here (p. 5702), Anna Huttenlocher and colleagues used the zebrafish system to study the role of microtubules in neutrophil migration in 3D *in vivo*. Interestingly, in contrast to findings of *in vitro* studies, they show the microtubule-organising centre to be positioned in front of the nucleus in motile neutrophils. The authors have previously shown that phosphoinositide-3 kinase (PI3K) regulates neutrophil motility and, in this work, they addressed the molecular details of PI3K signaling in this process. They demonstrate that microtubule disassembly induces neutrophil motility, at least in part, through the activation of both Rho and Rac in a manner that is independent of PI3K activity. The involvement of Rac is unexpected as, in other cell types, it is activated by microtubule polymerisation and not depolymerisation. Taken together, these results provide new insights into the role of microtubules in neutrophil migration in a living vertebrate, and also show that the motility of these migratory cells follows different rules than those established for other cell types.



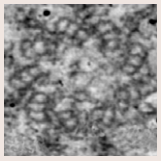
## Link between mitochondrial hyperfusion and genome stability

Mitochondria constantly undergo fusion and fission events that are integrated with the cell cycle. Mitochondrial remodeling throughout the cell cycle is thought to help meet the varying cellular energy demands of the cell and to ensure faithful inheritance of mitochondria during cell division. Dynamin-related protein 1 (Drp1) is essential for mitochondrial fission, and Drp1 deficiency results in a failure of mitophagy – the removal of damaged mitochondria – leading to ATP depletion and, ultimately, proliferation defects. However, some data suggest that Drp1 also has other effects on proliferation, which are independent of the mitochondrial energy metabolism. On page 5745, Bennett Van Houten and colleagues set out to investigate the molecular mechanisms that link mitochondrial dynamics to the cell cycle. They show that RNAi-mediated loss of Drp1 results in mitochondrial hyperfusion and, surprisingly, arrest of cells in G2/M phase of the cell cycle and in aneuploidy. Addressing the underlying basis of this arrest, they uncovered an untimely expression of cyclin E and the subsequent replication stress activating the G2/M checkpoint through Ataxia telangiectasia mutated (ATM) kinase to be the cause, and not defects in the generation of mitochondrial ATP. Taken together, their data indicate that genome instability that is associated with mitochondrial dysfunction and mediated by Drp1 has a different mechanistic basis, which is unrelated to mitochondrial energy metabolism.



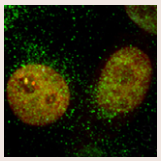
## Long-range microtubule guidance

In moving cells, dynamic microtubules (MTs) are targeted to focal adhesion (FA) sites, where their cargo mediates FA disassembly to allow the cell to detach from the substrate and propel itself forwards. Although MTs have been frequently observed at focal adhesions (FAs), their spatial overlap has thus far precluded the analysis of the mechanisms that guide the growing MTs through the cell to reach FAs at the cell periphery. On page 5790, Bartosz Grzybowski and colleagues controlled the cell geometry to remove this spatial overlap, in order to allow an unambiguous analysis of MT guidance to FAs. Specifically, these cells are confined to adhesive triangular microislands, which determine cell shape and ensure that FAs localise exclusively to the vertices of the triangles. Using a combination of high-resolution imaging and RNAi-mediated gene depletion, the authors show that initial MT nucleation occurs at the centrosome without any directional preference. However, with increasing distance from the centrosome, the trajectories of MTs that grow along F-actin bundles align with FAs at the vertices, suggesting that a non-random, active FA-mediated guiding mechanism is at play. Consequently, in the absence of FAs, MT growth is unguided. Furthermore, when either myosin IIA or myosin IIB is depleted, thereby removing F-actin bundles, MT growth also becomes random. These results suggest that MT guidance is controlled by a long-range mechanism that acts throughout the entire cell.



## Fly centriole cartwheels without Cep135

Centrioles are complex microtubule (MT)-based structures that form two important cell organelles, the centrosome and the cilium or flagellum, and the dysfunction of these organelles has been linked to several human diseases. Cep135 (also known as Bld10) is a conserved centriolar protein that in some species is required for the formation of the central cartwheel, which initiates centriole duplication. However, flies lacking Cep135 are viable, suggesting that either Cep135 is not essential for cartwheel formation, or the cartwheel is not essential for centriole assembly in flies. Here (p. 5881), Jordan Raff and colleagues address this question using electron tomography (ET) and super resolution 3D structured illumination microscopy (3D-SIM) of mature fly spermatocytes. They find that, initially, relatively normal cartwheels form in daughter centrioles when Cep135 is absent, but these deteriorate over time and become more disorganised in mother centrioles. Detailed analysis of the cartwheel structure in the absence of Cep135 revealed that the localisation of the inner centriole components Sas-6 and Ana2 is perturbed, as well as of outer centriole factors, such as As1. Furthermore, the authors show that in wild-type cartwheels, Cep135 localises to a region between these inner and outer centriole components, suggesting that, in *Drosophila*, Cep135 has a role in the stabilisation of the cartwheel, and not in its formation.



## New role for SUMO in death by UV

The small ubiquitin-like modifier (SUMO) ligase protein inhibitor of activated stat-1 (PIAS1) – one of the four mammalian PIAS proteins – is known to have a role in cellular stress response by SUMOylating several proteins that are involved in DNA repair, apoptosis and transcription. On page 5819, Raghavi Sudharsan and Yoshiaki Azuma expand upon these functions by demonstrating a previously unknown role for PIAS1 in UV-induced apoptosis. Using ectopic expression of PIAS1 in HeLa cells, they show that PIAS1 – but not the other PIAS members – induces UV-mediated apoptosis in these cells, which is mediated by the recruitment of the pro-apoptotic death-associated protein 6 (Daxx) to SUMOylated PIAS1 foci and depends on its SUMO-ligase activity. Furthermore, depletion of Daxx alleviates PIAS1-mediated UV-sensitivity. Analysing the protein domains responsible for this function, the authors show that the N-terminus of PIAS1 governs substrate specificity and regulates Daxx recruitment, and thus apoptosis, whereas recruitment of Daxx to SUMOylated foci depends on its C-terminal SUMO-interacting motif (SIM). Consequently, Daxx mutants lacking the SIM domain are unable to form SUMOylated foci and do not show an increased sensitivity to UV-irradiation in the presence of PIAS1. On the basis of these observations, the authors propose a new role for PIAS1-mediated SUMOylation in sensitising cells to UV damage through the recruitment of Daxx to PIAS1-specific SUMOylated substrates.