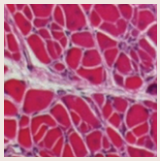
In this issue

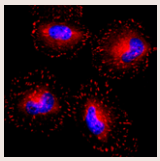
p120-catenin: acting between Wnt and Rac1

Canonical Wnt signalling is essential for embryo development, and is involved in the control of cell growth and differentiation of most mammalian cells. The activation of Wnt target genes in response to Wnt activation through its ligands such as Wnt3a involves nuclear β-catenin, which in unstimulated cells is degraded by a destruction complex. Wnt ligands inhibit the activity of this destructions complex, thereby stabilising β-catenin and allowing it to translocate to the nucleus. Previous studies have shown that Wnt signalling can activate Rac1, and that Rac1 activation is essential for the nuclear translocation of β-catenin. On page 5288, Duñach and colleagues build upon these data as well as their previous work showing that p120-catenin is involved in Wnt signalling, to address the role p120-catenin has in the activation of Rac1 by Wnt3a. Using the SW-480 cell line, which is unable to degrade β-catenin, and HEK-293 cells, they show that Rac1 activation through Wnt depends on p120-catenin and involves its direct binding to Rac1 and to the Rac1 activator Vav2. The authors then investigate the role of Rac1 in *Xenopus* p120-catenin deletion mutants that show gastrulation defects. They find that, in contrast to functional 120-catentin or constitutively active Rac1, expression of a p120-catenin mutant that cannot bind Rac1 and Vav2 does not rescue these defects, suggesting that failure of Rac1 activation in the absence of p120-catenin is the cause of these defects.



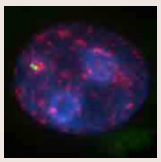
Dual role of Foxk1 in muscle progenitor cells

Owing to resident myogenic progenitor cells (MPCs), skeletal muscle has a remarkable regenerative capacity in response to severe injury. Some of the factors underlying this capability have been identified, among them the forkhead transcription factor Foxk1, but the molecular networks that govern the regeneration of MPCs are not well understood. On page 5329, Daniel Garry and colleagues perform experiments that involve the knockdown and overexpression of Foxk1 in order to identify thus far unknown downstream targets in the myogenic lineage. They find that Foxk1 directly interacts with another forkhead transcription factor, Foxo4, and represses its transcriptional activity, resulting in the dysregulation of its target genes (such as the cyclin dependent kinase inhibitor p21) and, consequently, promoting cellular proliferation. In addition, they show that the Mef2 target genes that are regulators of differentiation, are also affected by perturbed Foxk1 expression, suggesting that Mef2 activity is modulated by Foxk1. Indeed, the authors find that Foxk1 interacts with Mef2c, which precludes it from activating the myogenic differentiation program. Taken together, their work demonstrates a dual role for Foxk1: it promotes MPC proliferation by repressing Foxo4 transcriptional activity and inhibits myogenic differentiation through the repression of Mef2, providing new insights into the transcriptional networks that regulate MPCs and their regeneration.



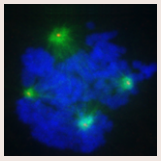
RIAM keeps focal adhesions in check

Focal adhesions link the extracellular matrix with the actin cytoskeleton and mediate integrin-dependent signalling to allow the cell to move in response to external cues. They consist of structural components (i.e. talin, paxillin and vinculin) and signalling molecules. The recruitment of talin to focal adhesions is mediated by Rap1-GTP-interacting adaptor molecule (RIAM), whose depletion leads to defects in migration and invasion of melanoma cells; however, the underlying mechanisms leading to these defects are not well understood. On page 5338, Joaquin Teixidó and colleagues set out to investigate the involvement of RIAM in focal adhesion turnover and dynamics. They find that RIAM-knockout melanoma and breast cancer cells have bigger and more-stable focal adhesions, suggesting that disassembly focal adhesion is impaired in these cells. The authors also observe that, in these cells, RIAM seems to be required for integrin-dependent MEK–Erk1/2 activation. Importantly, when MEK is overexpressed, focal adhesion disassembly and, subsequently, cell invasion is restored. Taken together, these data indicate that integrin-mediated, RIAM-dependent MEK activation represents a key feedback event required for efficient focal adhesion disassembly, which might explain how RIAM impacts on cell migration and invasion.



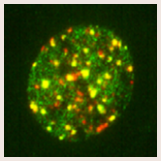
APC/C and premature centriole disengagement

To maintain genome stability, centrosome duplication has to be tightly coupled to the cell cycle, as loss of this coupling can lead to centrosome amplification – a common hallmark of cancer cells. Centrosome duplication and DNA replication are controlled by cyclin-dependent kinase 2 (Cdk2), which ensures these processes are only initiated upon S phase entry, i.e. when Cdk2 is active. Centrosome duplication is also regulated in mitosis; here, the disengagement of centrioles that occurs after anaphase onset and licenses them for the next round of replication is controlled by the cysteine protease separase and the mitotic kinase Plk1. On page 5353, Andrew Fry, Suzanna Prosser and colleagues set out to explore the underlying mechanisms behind this control, by arresting cells in G2. They find that G2 arrest promotes premature centriole disengagement, which, as they show, is dependent on Plk1 and separase. Activation of separase is caused by the untimely activation of the anaphase promoting complex (APC/C) in these cells that results from Plk1-mediated loss of the APC/C inhibitor Emi1. Their data also suggest that Plk1 has a second, more direct role in promoting centriole disengagement independent of APC/C. Taken together, these findings suggest that oscillation of APC/C activity in response to cell cycle arrest promotes centrosome amplification and can impact on genome stability.



Exploiting acentrosomal spindle assembly in cancer

In animal somatic cells, centrosomes are the main microtubule organizing centres (MTOCs) and orchestrate bipolar spindle assembly during mitotic cell division. In meiotic cells, their role is taken on by the kinesin HSET that focuses acentrosomal MTOCs into two spindle poles. HSET is also essential for bipolar mitosis in cancer cells and required for the survival of cancer cells with supernumerary centrosomes; however, the underlying molecular mechanisms have remained elusive. Here (p. 5391), Julia Kleylein-Sohn and co-workers show that HSET-mediated acentrosomal MT organisation is required for bipolar spindle formation in melanoma and breast cancer cell lines, irrespective of the number of centrosomes. Spindle formation here can be characterised by the formation and subsequent incorporation of acentrosomal MTOCs into the assembling spindle structure. The authors then show that, when HSET is depleted in these cells, spindle poles are unable to focus and fragment into multipolar spindles. In addition, they find that in spindle-checkpoint-defective cancer cells, acentrosomal spindle formation and HSET-dependence correlates with the activation of the DNA damage response. Taken together, their data suggest that HSET, as a key driver for acentrosomal spindle organisation, which is hyperactivated in cancer cells, represents an attractive target for cancer therapy.



New role for LSH in DNA repair

The widely expressed lymphoid-specific helicase (LSH) is related to members of the SNF2 family of chromatin-remodelling ATPases, and essential for the correct establishment of DNA methylation levels and patterns in mammalian cells and plants. LSH is thought to render DNA accessible to DNA methyltransferase enzymes, therefore supporting *de novo* DNA methylation and stable gene silencing. However, some of the phenotypes caused by LSH deficiency cannot be easily explained by aberrations of DNA methylation patterns, suggesting it also has other yet-unknown functions. On page 5524, Irina Stancheva and colleagues set out to elucidate such other roles by investigating the response of LSH-deficient mouse and human cells to DNA damage induced by ionizing radiation (IR). They find that LSH deficiency results in a reduced viability of these cells after exposure to IR and less efficient repair of DNA double-strand breaks. The authors show that the underlying basis for this is reduced phosphorylation of the histone variant H2AX, which, in turn, impairs the recruitment of the DNA-repair proteins MDC1 and 53BP1 to the DNA break, and also compromises phosphorylation and activation of the checkpoint kinase CHK2. Taken together, their data reveal a previously unsuspected role of LSH in double-strand DNA repair, which is independent of its function in *de novo* DNA methylation during development.