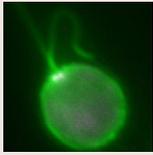
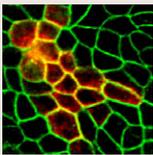


In this issue



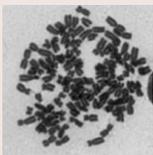
CRC70 starts off new centrioles

Centrioles are made up of nine triplet microtubules that are arranged in a characteristic pattern. Their duplication and assembly during cell division has been the subject of numerous studies. These investigations revealed that the new organelle originates from an amorphous assembly that goes on to form a cartwheel structure (composed of a central hub and nine spokes). Microtubule extension from the cartwheel then leads to formation of the procentriole. Although recent work revealed several proteins that are involved in centriole assembly, procentriole formation is still not well understood. On page 2964, Masafumi Hirono and colleagues now identify *Chlamydomonas* CRC70, a member of the Cep70 protein family, as a scaffold for centriole assembly. Using immunostaining approaches, they show that CRC70 is recruited to the procentriole before cartwheel assembly and is lost during centriole maturation. CRC70 depletion results in aberrant centriole formation and mitotic defects. By contrast, overexpression of CRC70 causes accumulation of centriole proteins in discrete cytoplasmic spots and induces the formation of centriole-like structures in mouse cells. Thus, the authors conclude, this new member of the Cep70 family has an important role in recruiting centriole proteins to the assembly site and members of this family might perform similar functions in other organisms.



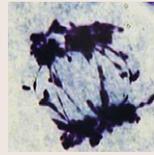
Putting eyesight to the BEST1

Vitelliform macular dystrophy is an eye disorder that leads to the progressive loss of central vision. The early-onset form of the disease – known as Best vitelliform macular dystrophy (BMD) – is caused by mutations in *BEST1*. Bestrophin-1, the protein encoded by this gene, is highly expressed in the retinal pigment epithelium (RPE) and has been implicated with a function in anion transport, intracellular Ca^{2+} homeostasis and ion transport across organelle membranes. However, the molecular mechanisms underlying BMD pathology are still unclear. Olaf Strauss, Bernhard Weber and colleagues (p. 2988) now show that disease-associated missense mutations in bestrophin-1 affect its cellular localisation and alter cellular anion permeability. Using polarised MDCK II cells, the authors show that wild-type bestrophin-1 localises to the basolateral membrane. By contrast, nine of the 13 mutant proteins investigated are primarily found in the cytoplasm and four others show reduced membrane localisation. In addition, all mutants result in reduced anion permeability of the plasma membrane when compared with wild-type bestrophin-1. For these reasons, the authors propose that missense mutations in bestrophin-1 result in altered Cl^- and H_2O transport across the RPE epithelium and impair regulation of the cell volume. This disruption of RPE function – which is essential for photoreceptor viability – might, therefore, be involved in causing BMD.



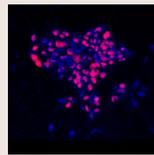
Sororin: cohesive on-off switch

Aneuploidy is the result of faulty DNA separation during cell division and can contribute to tumour progression and drug resistance. Therefore, it is of particular interest to understand the mechanisms that regulate correct chromatid linkage and separation during mitosis. Sister chromatid adhesion is mediated by the multi-protein cohesin complex. The protein sororin is recruited to this complex and stabilises chromatid adhesion during S phase. But how is this additional stability overcome during mitosis in order to allow separation of the chromatids? William Taylor and co-workers (p. 2976) now provide an answer by showing that the release of sororin from chromatin is regulated in a phosphorylation-dependent manner. Cdk1 is able to phosphorylate sororin, and this is sufficient and necessary to remove the protein from chromatin during mitosis. The mutation of nine potential Cdk1 phosphorylation sites on sororin increases sister chromatid cohesion. Furthermore, this mutant protein fails to redistribute to the cytoplasm during mitosis. Using additional sororin mutants, the authors find that multiple phosphorylation events act additively to cause its release. These observations suggest that the protein is required for the establishment and maintenance of cohesion until mitotic entry and must be removed from chromatids through Cdk1-dependent phosphorylation.



Apoptosis follows catastrophic DNA breaks

The cell cycle is a complex process whose integrity is tightly regulated by a number of checkpoints. When these controls fail, the cell can enter mitosis before DNA repair is completed. In such an event, the dysregulation of mitosis can result in mitotic catastrophe, followed by apoptotic or necrotic cell death. Until now, the signals that determine and trigger these different modes of cell death remained unclear. Here, Boris Zhivotovsky and co-workers (p. 2951) describe a new mechanism that leads to p53-dependent apoptosis following DNA damage induced through mitotic catastrophe. They show that, in an attempt to exit from defective mitosis as a result of unrepaired DNA damage, cells create anaphase bridges, which leads to the formation of additional DNA breaks during the progression from anaphase to telophase. Subsequently, these breakage–fusion–bridge cycles result in increased γ H2AX phosphorylation, which then triggers an apoptotic death signal that involves ATM (ataxia telangiectasia mutated) and p53. In the absence of ATM or p53, cells are not eliminated through an apoptotic pathway but, instead, undergo necrosis. The authors conclude that additional DNA damage during mitotic catastrophe and subsequent activation of a p53-dependent apoptotic pathway leads to the elimination of chromosomally unstable cells.



Stem cell therapy: lose HLA I

The ability of stem cells to differentiate into any given cell type makes them highly suitable for therapeutical approaches to tissue injury. However, successful transplantation of human embryonic stem cell (hESC)-derived tissues is hindered by the immunological rejection by the host. Here, Sonja Schrepfer and colleagues (p. 3029) find that knocking down HLA class I (HLA I) in hESCs substantially reduces this immune response. They show that transplantation of regular hESCs into immunocompetent Balb/c mice results in strong Th1 and Th2 immune responses that involve the release of interferon γ and interleukin 4, respectively. This is accompanied by the formation of antibodies against the HLA I molecules that are expressed on the surface of hESCs within 5 days after transplantation and the rejection of the transplanted cells within the same period. Histological analysis reveals that the immune response primarily involves macrophages and T cells, whereas NK cells are less involved. Reducing the expression of HLA I by using RNAi results in decreased T cell activation and does not induce production of anti-HLA I antibodies. Additionally, the authors report, 40% of the knockdown hESCs survive in the host environment for more than 42 days. These observations provide an important basis for the future development of effective hESC therapies that are not associated with immune rejection and tumour formation.

In Development

Pushing the nuclear envelope

Not all nuclei are regular spheres as is often shown in textbooks. For example, in *Drosophila* embryos, nuclei are initially spherical but they elongate and acquire an irregular, lobulated morphology during cellularisation. These morphological changes coincide with transcriptional activation of the zygotic genome and reflect poorly understood changes in nuclear envelope mechanics. In *Development*, Thomas Lecuit and co-workers now provide new insights into nuclear envelope morphogenesis in early *Drosophila* embryos. Microtubule (MT) polymerisation events produce the forces necessary for nuclear envelope dynamics, they report, and the large-scale nuclear envelope deformations associated with lobulation require both a concentration of MT polymerisation in bundles that are organised by dynein and the presence of the farnesylated inner nuclear membrane protein Kugelkern. The researchers also show that MT-induced nuclear envelope deformations control the dynamics of chromatin and its organisation at steady state. They suggest, therefore, that the mechanical regulation of chromatin dynamics by MT-induced nuclear envelope fluctuations are important for gene regulation in *Drosophila* embryos.

Hampoez, B., Azou-Gros, Y., Fabre, R., Markova, O., Puech, P.-H. and Lecuit, T. (2011). Microtubule-induced nuclear envelope fluctuations control chromatin dynamics in *Drosophila* embryos. *Development* **138**, 3377–3386.