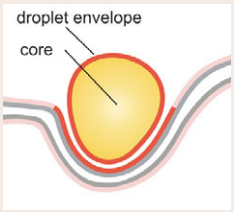
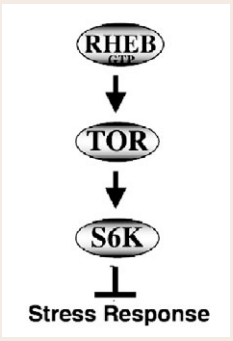
In this issue



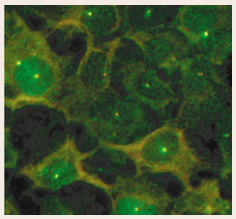
Rethinking lipid droplets

Once thought to be mere storage depots, lipid droplets are in fact active organelles that play key roles in signalling and membrane trafficking. The droplets contain a core of apolar lipids surrounded by a monolayer of phospholipids and associated proteins. Until now, the prevailing view has been that they form within the bilayer of the ER and bud off from its cytoplasmic leaflet. On p. 4215, however, Horst Robenek and co-workers show that this is not the case. They have followed the biogenesis of lipid droplets in the ER, using a combination of cryo-thin-section EM, confocal light microscopy and freeze-fracture EM to get a 3D perspective on the process. This approach reveals that a droplet forms alongside – not between – the ER membranes, which together form an 'egg cup' that holds the droplet. Their study also shows that adipophilin – a PAT-family protein present in lipid droplets – forms clusters in the cytoplasmic leaflet of the ER adjacent to nascent droplets. Since adipophilin may function as lipid transporter, the authors propose that these clusters represent sites for transfer of material from the ER to the droplet during its biogenesis.



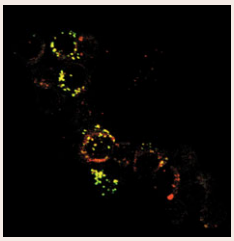
Ageing – ay, there's the Rheb

Stress – particularly oxidative stress – is probably a major contributing factor in ageing, cancer and neurodegenerative conditions. It damages DNA and other key macromolecules and must be combated by various cellular defence mechanisms. Another factor linked to ageing is target of rapamycin (TOR) signalling – a pathway in which insulin, the GTPase Rheb, the TOR protein and S6 kinase (S6K) regulate protein synthesis and cell growth. On p. 4285, Parthive Patel and Fuyuhiko Tamanoi demonstrate that the two are connected. By overexpressing Rheb, TOR or a constitutively active mutant of S6K, they show that increasing TOR signalling sensitizes flies to various stresses. When faced with oxidative stress caused by H_2O_2 or paraquat, for example, the flies become less mobile (through senescence of motor activity) and die prematurely. They are similarly sensitive to starvation-induced stress. The authors confirm this is due to TOR signalling by showing that an inactive S6K mutant can block the effects and that expression of TSC2 (a negative regulator of the pathway) confers resistance to stress. Since Rheb-TOR signalling is increased by elevated insulin levels and nutrient availability and in certain disease states, this link could be highly important in ageing and pathological conditions.



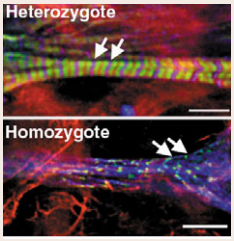
Checkpoint kinase checks out Cdc25B

Cdc25 is an essential phosphatase that triggers cell-cycle progression by dephosphorylating (and thus activating) the central mitotic regulator cyclin-dependent kinase 1 (CDK1). Cdc25B activates a centrosomal pool of CDK1 prior to mitosis. CDK1 is thought to be held in check until then by the checkpoint kinase Chk1, but how Chk1 accomplishes this has not been clear. On p. 4269, Bernard Ducommun and co-workers reveal it does so by phosphorylating Cdc25B. They demonstrate that Chk1 phosphorylates several sites on Cdc25 in vitro, including S230. They then show that S230 of Cdc25B is phosphorylated in vivo in a cell-cycle-dependent manner. Furthermore, they use a specific Chk1 inhibitor and RNAi to show that this depends on Chk1. Finally, the authors show a non-phosphorylatable S230A mutant of Cdc25B, which presumably cannot be inhibited by Chk1, promotes premature entry of cells into mitosis. Ducommun and co-workers therefore conclude that Chk1 plays a role beyond its well-known function in the DNA damage response, proposing that it also constitutively phosphorylates Cdc25B during interphase to prevent premature entry into mitosis.



Diabetes – β cells show their metal

Insulin is stored in pancreatic β cells as zinc-insulin crystals. In fact, the zinc levels in β cells are among the highest in the body and they may even regulate insulin secretion under some circumstances. But what controls zinc levels and how does this affect glucose homeostasis? Fabrice Chimienti and co-workers have recently identified a novel zinc transporter, ZnT8, which they now show is present in pancreatic islet cells in vivo (see p. 4199). The transporter is exclusively expressed in the insulin-producing β cells and colocalizes with insulin in secretory granules. Moreover, the authors find that overexpressing ZnT8 increases the amount of zinc in β cells and promotes the release of insulin in response to stimulation with high levels of glucose. It also protects them from zinc-depletion-induced cell death. Zinc, insulin and glucose homeostasis thus appear to be closely linked. Given that increasing insulin secretion is an effective way of combating the hyperglycaemia characteristic of conditions such as diabetes, manipulating zinc levels in this way represents a promising therapeutic approach.



Sarcomere formation – a titin-ic task

Titin is a massive filamentous protein expressed in cardiac and striated muscle. It functions as a 'molecular ruler' that binds numerous signalling/structural proteins and stretches ~1 μM from the Z-disc to the M-band of the muscle sarcomere. On p. 4322, Michelle Peckham and co-workers expose its critical role in the development of muscle fibres. To do this they have created embryonic stem (ES) cells in which titin is mutated and monitored their differentiation to form cardiomyocytes. They find that cells in which both alleles are mutated fail to differentiate properly. The cells do not beat; moreover, the striations characteristic of muscle do not form, and proteins such as myosin and α-actinin instead localize to disorganized filaments or primitive dot-like structures. Fully functional titin thus seems to be essential for myofibrillogenesis. The mutant protein expressed in the cells lacks the M-band region that contains the titin kinase (TK) domain and binding sites for various M-band proteins. Surprisingly, however, Z-disk maturation is also defective in the cells. Communication between the M-band region of titin and events at the other end of the sarcomere must therefore be important during myofibrillogenesis.

Development in press

Translational control gets a shunt

The green alga *Volvox carteri*, with its two distinct cell types – somatic and reproductive cells – is an ideal organism for studying the molecular basis of differentiation. Somatic cell terminal differentiation in *Volvox* is controlled by the transcriptional repressor RegA, which stops these cells from becoming reproductive cells. Now, in a paper published in *Development*, Babinger and colleagues report that, surprisingly, the translation of *regA* is controlled by ribosome shunting, a process in which the translation initiation complex dissociates from the mRNA at a stable secondary structure and then rebinds at a downstream 'landing site'. By a systematic mutational analysis of the *regA* 5′ untranslated region (UTR), which contains eight start codons, the researchers discounted leaky scanning, reinitiation and internal ribosome entry site mediated initiation as the mechanisms that control *regA* translation. Instead, their results indicate that *regA* translation is controlled by ribosome shunting, an unusual mechanism in eukaryotes for regulating translation that, the researchers suggest, might be used in other developmental situations.

Babinger, K., Hallmann, A. and Schmitt, R. (2006). Translational control of *regA*, a key gene controlling cell differentiation in *Volvox carteri*. *Development* **133**, 4045-4051.