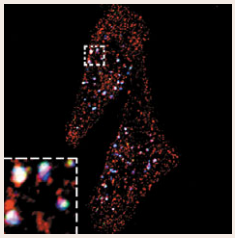
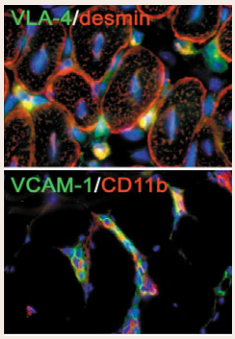
In this issue

by Jane Bradbury



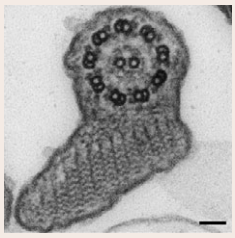
Clathrin not just a basket case

Clathrin is well known for forming 'baskets' that coat certain vesicles. However, 'flat' clathrin coats also exist. These are present on endosomes and contain Hrs, a ubiquitin-binding adaptor protein that sorts ubiquitylated membrane proteins for degradation. Harald Stenmark's team now report that these coats promote sorting of proteins for degradation by concentrating Hrs in dynamic microdomains (see p. 2414). The authors show that both clathrin and the clathrin-binding domain of Hrs are required to cluster Hrs into endosomal microdomains. These microdomains rapidly exchange both proteins with the cytoplasm and acquire components of the degradative protein sorting pathway. Finally, the recruitment of clathrin to endosomes by Hrs is required for degradation of epidermal growth factor receptor. The authors propose that, by concentrating Hrs in restricted microdomains, clathrin helps retain ubiquitylated cargoes; the dynamic nature of the coat then provides transient openings into which other proteins needed for degradative protein sorting can insert. These results provide the first evidence that clathrin can function in a trafficking pathway that does not involve coated vesicles.



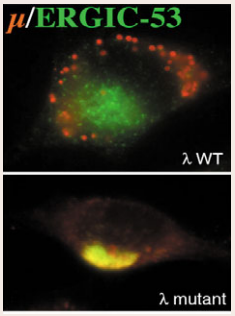
Macrophage contact soothes muscles

Stromal cells help specialized cells such as those in muscle to grow, develop and survive. This supportive role is poorly understood, however. Bénédicte Chazaud and co-workers have therefore been investigating how macrophages – a recognized stromal cell type – support post-injury muscle regeneration. They report on p. 2497 that macrophages use a set of pro-survival cell-cell adhesion systems to rescue myoblasts and myotubes from apoptosis during this process. The authors show that entry of macrophages into regenerating mouse muscle in vivo correlates with decreased apoptosis of myogenic cells. They then demonstrate that direct cell-cell contact with human macrophages rescues these cells from apoptosis in vitro. Array analysis indicates that macrophages and myogenic cells express the ligands and receptors, respectively, for four pro-survival cell-cell adhesion systems (VCAM-1–VLA-4, ICAM-1–LFA-1, PECAM-1–PECAM-1 and CX3CL1-CX3CR1); experiments with blocking antibodies demonstrate that macrophages use all these to prevent apoptosis of myogenic cells. These results provide new insights into how stromal cells support specialized cells during tissue repair and suggest ways to improve myoblast transfer therapy, which is currently limited by massive cell death.



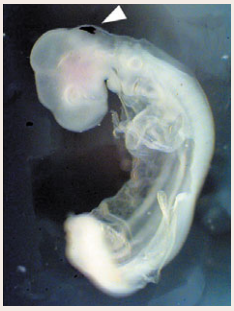
An off-beat flagella mechanism

Beating flagella power the movement of various eukaryotic cells. They are driven by the axoneme, a structure that usually comprises a central pair (CP) of singlet microtubules and nine surrounding doublets linked by dynein motors. Productive flagellar beating involves sequential activation and inactivation of these motors. Rotation of the CP is widely thought to regulate these changes but, on p. 2405, Keith Gull and colleagues reveal that the CP does not rotate in trypanosome axonemes. Using the paraflagellar rod as an external reference, the authors demonstrate that the CP axis in trypanosomes is kept constant relative to this extra-axonemal structure. They then show that the orientation of the CP is dependent on an intact basal body (which anchors the axoneme to the cell) and influenced by physical contacts made by the CP along its length by knocking down several flagellar and basal body proteins (e.g. δ-tubulin) by RNAi. The authors conclude that, although CP rotation might regulate dynein-driven flagellar beating in some species, flagellar beating can also be regulated by other means.



Russell-ing through ER storage diseases

Secretory and membrane proteins normally fold and assemble in the endoplasmic reticulum (ER) before moving to the Golgi. Mutant proteins that fail to fold properly are mainly dispatched to the cytoplasm for degradation but some get stuck in the ER and cause ER storage diseases. On p. 2532, Roberto Sitia and co-authors provide new insights into these diseases by investigating the biogenesis of Russell bodies, dilated ER cisternae containing mutant immunoglobulins that are often seen in multiple myeloma. The authors show that immunoglobulin-μ heavy chains that lack the first constant domain (μΔCH1) accumulate as detergent-insoluble aggregates in Russell bodies when their synthesis rate exceeds their degradation rate. Where μΔCH1 chains aggregate, however, depends on the proteins they interact with. If immunoglobulin light chains are present, they condense in large ribosome-coated structures; in their absence, they aggregate in smooth tubular vesicles with ERGIC-53, a marker of the ER-Golgi intermediate compartment (ERGIC). These results reveal a new role for ERGIC-53 and indicate that a disruption of the equilibrium between synthesis, processing and degradation of aberrant proteins causes ER storage diseases.



INKlings about senescence

Replicative senescence limits the proliferative potential of cells and protects them against oncogenic signals. In mammalian cells, the proteins encoded by the *INK4a-ARF* locus play central roles in senescence. INK4a is a cyclin-dependent kinase (CDK) inhibitor whereas ARF stabilizes the tumour suppressor p53. Gordon Peters and colleagues have found that chicken cells do not encode INK4a and now report that the adjacent and closely related *INK4b* gene instead adopts the central role in senescence in these cells (see p. 2435). The authors show that INK4b mRNA and protein accumulate in senescent chicken embryo fibroblasts (CEFs) and that *INK4b* is transcriptionally silenced in two immortal chicken cell lines whereas *ARF* expression is unaffected. The authors also show that knocking down INK4b or ARF by RNAi in CEFs produces only a modest increase in life span – additional factors must therefore contribute to senescence. These observations thus underscore the importance of the *INK4b-ARF-INK4a* locus in senescence but also reveal that the relative contribution of each gene product varies between species.

Development in press

Talin(t) for tracheal branching

Although the formation of the *Drosophila* tracheal system is partly understood, little is known about how the terminal branches of this network of epithelial tubes are maintained. In a paper published in *Development*, Levi, Ghabrial and Krasnow now reveal that integrin-talin adhesion complexes maintain these branches and their luminal organization. Tracheal terminal cells form hollow terminal branches, which adhere tightly to target tissues to supply them with oxygen. In a genetic screen, the researchers isolated *tendrils* mutants, which have fewer terminal tracheal branches than normal and multiple, convoluted lumens. This phenotype arises late in development from loss of branches but not their lumens. It is caused by mutations in the gene encoding talin, which links integrin cell-adhesion molecules to the cytoskeleton. Terminal cells that have mutant β-integrins have a similar phenotype. The researchers therefore conclude that integrin-talin adhesion complexes anchor mature terminal branches to their target tissues and maintain their luminal organization. Similar complexes could stabilize other tubular networks.

Levi, B. P., Ghabrial, A. S. and Krasnow, M. A. (2006). *Drosophila* talin and integrin genes are required for maintenance of tracheal terminal branches and luminal organization. *Development* **133**, 2383-2393.