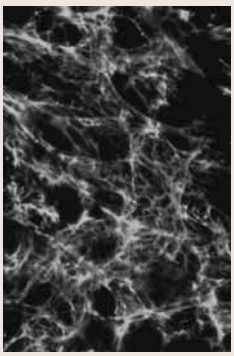
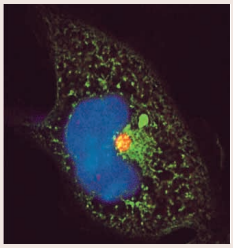
In this issue



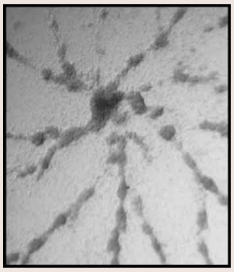
Making a matrix

The extracellular matrix protein fibronectin has important roles in cell adhesion, migration, growth and differentiation. It is secreted as a soluble dimer but subsequently assembles to form insoluble, multimeric fibrils. The assembly process depends on interactions between fibronectin and cell surface integrins and is regulated by several signalling pathways. In a Commentary on p. 3269, Iwona Wierzbicka-Patynowski and Jean Schwarzbauer discuss work that is shedding light on this complex mechanism. It is usually initiated by binding of α5β1 integrin to the RGD motif of fibronectin. Since fibronectin is a dimer, this promotes integrin clustering, fibronectin-fibronectin interactions and formation of fibrils. Another consequence of integrin binding is an opening up of the fibronectin molecule to expose hidden multimerization motifs. Recent studies indicate that partial unfolding of the molecule imparts elasticity on fibrils and allows them to remain under tension. This could increase the pliability of the matrix and is probably regulated by signals that control actomyosin contractility. Other signalling molecules that regulate fibronectin assembly include FAK and Src; these tyrosine kinases lie downstream of integrins and appear to participate in feedback loops that target the fibronectin ligand. Indeed perturbation of fibronectin assembly by Src and other oncogene products probably has a significant impact on tumor cell phenotype.



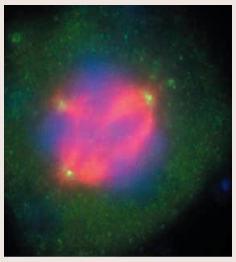
Retrovirus trafficking: gagged and dynein-bound

Once inside cells, intracellular pathogens must hijack cellular machinery to move around. *Listeria*, for example, makes use of the actin cytoskeleton, whereas adenovirus travels on microtubules; vaccinia virus can do both. So how do retroviruses get about? The foamy virus (a complex animal retroviruses) has been shown to travel from its site of entry to the nucleus via microtubule-organizing centres (MTOCs). Ali Saïb and co-workers now reveal how it does this (see p. 3433). They observe that transport of the incoming virus requires microtubules and can be blocked by a dominant negative inhibitor of the retrograde motor cytoplasmic dynein. Furthermore, they find that the Gag protein (a structural component of the viral capsid) is the only viral protein necessary for trafficking, pinning down the region of the protein responsible to a 30-residue coiled-coil motif at the N-terminus. The authors then demonstrate that Gag directly interacts with dynein light chain 8 (LC8) within the dynein motor complex. Finally, they follow the effect of a Gag point mutant that cannot interact with LC8 (GagL171G) on the viral life cycle, revealing that this interaction is critical for efficient viral infection. Saïb and co-workers conclude that the cytoplasmic dynein motor transports foamy virus along microtubules, speculating that helical coiled-coil motifs similar to that in Gag might be responsible for interaction of the motor with other cargos.



Superoxide: the route to multi-cellularity?

Generation of reactive oxygen species (ROS) such as superoxide ions is an important signalling mechanism in mammals and plants. Yeast and bacteria possess systems that allow them to respond to ROS produced during oxidative stress but do not actively produce them as messengers. So when did ROS generation become a signalling mechanism and why? Gareth Bloomfield and Catherine Pears suggest the answer lies at the advent of multicellularity (see p. 3387). They show that the social amoeba *Dictyostelium*, which straddles the boundary between unicellular and multicellular life (since it can exist in either form), can generate superoxide. The ROS is produced in response to a secreted factor early in development during the transition to multicellularity, which occurs when the organism runs out of food. The authors show that low-molecular-weight superoxide scavengers or overexpression of the superoxide-scavenging enzyme superoxide dismutase can block *Dictyostelium* aggregation during the transition to multicellularity; in addition, they find that it significantly reduces expression of genes important for early development. Bloomfield and Pears therefore conclude that a superoxide-dependent signal is critical for initiation of development in *Dictyostelium*. They also note that ROS play important developmental roles in animals and plants, suggesting that this mechanism might have arisen to provide the signalling diversity that multicellularity demands.



Ran splits the centrosome

The Ran GTPase regulates nucleocytoplasmic transport, mitotic spindle formation and nuclear envelope assembly. During interphase, Ran-GTP dissociates nuclear import complexes, releasing cargo molecules from their importin carriers. Studies in oocyte extracts indicate that it might function similarly at mitosis: it appears to release aster-promoting factors such as TPX2 from inhibitory importin complexes and thereby stimulate spindle assembly. Patrizia Lavia and co-workers have examined its role during spindle assembly in mammalian somatic cells, focusing on the involvement of centrosomes – an important difference between somatic cells and meiotic extracts. They have found that overexpression of the Ran-binding protein RanBP1, which reduces Ran-GTP levels, induces formation of multipolar spindles. They show that this is because the mother and daughter centrioles separate at spindle poles and go on to anchor distinct, functional microtubule arrays (see p. 3399). The authors use inhibitors to demonstrate that this 'centrosome splitting' depends on microtubule integrity and Eg5 – a kinesin motor that controls centrosome separation at the onset of mitosis. Moreover, they demonstrate that a fraction of endogenous RanBP1 is stably associated with centrosomes. Their findings thus indicate that the Ran network has a novel role in centrosome organization in which microtubule dynamics and/or transport mechanisms play a part.

Development in press

A novel EGF-R antagonist

Epidermal growth factor receptor (EGF-R) signalling is a commonly deployed pathway during development and must be tightly regulated to prevent inappropriate inductive events. Reporting in *Development*, two groups have now identified a novel antagonist of EGF-R signalling, adding to the negative regulators of this pathway that are already known. Their findings show that the *Drosophila* L1-type transmembrane molecule Echinoid (ED) acts as an EGF-R antagonist during fly retinal development and is required for the proper spatial development of R8 photoreceptor cells; in the absence of ED, EGF-R signalling is increased during R8 formation, causing isolated R8 photoreceptors to be replaced by groups of 2-3 cells. Studies by Spencer and Cagan shed light on how ED might do this: ED co-precipitates with EGF-R from cultured cells and eye imaginal discs, which indicates that it might downregulate EGF-R by directly binding to it. The new work also shows that EGF-R activation promotes phosphorylation of ED. These results, together with those of Rawlins et al., indicate that ED might mediate short-range repression of EGF-R in the developing eye and advance our understanding of the regulation of this important pathway.

Rawlins, E. L., White, N. M. and Jarman, A. P. (2003). Echinoid limits R8 photoreceptor specification by inhibiting inappropriate EGF receptor signalling within R8 equivalence groups. *Development* **130**, 3715-3724.
Spencer, S. A. and Cagan, R. L. (2003). Echinoid is essential for regulation of Egfr signaling and R8 formation during *Drosophila* eye development. *Development* **130**, 3725-3733.