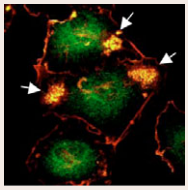
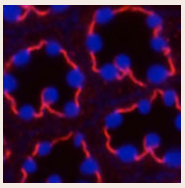
In this issue



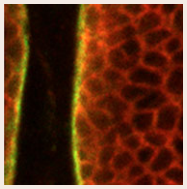
p190A and p190B: not created equal

Members of the Rho family of small GTPases, which facilitate cell migration, are negatively regulated by RhoGAP proteins, which include the closely related proteins p190A and p190B. These two proteins are ubiquitously expressed, share several binding partners and, in neurons, have partially overlapping functions – but do they have distinct roles in endothelial-cell migration? To address this question, Violaine Moreau and colleagues (p. 2054) use RNAi to knock down p190A and p190B individually in human umbilical vein endothelial cells (HUVECs). The authors show that, when p190B is absent, the total expression and cell-surface localisation of the matrix metalloproteinase MT1-MMP is decreased (although it is increased when p190A is knocked down), and that MMP2 – which is usually activated by MT1-MMP – is less active. Because both MMP proteins are associated with podosome-mediated degradation of the extracellular matrix, the authors induce the formation of podosomes and show that the number of podosomes per cell, as well as the amount of matrix degradation, increases in the absence of p190A. By contrast, knocking down p190B decreases podosome function. Thus, p190A and p190B have distinct, and possibly antagonistic, functions in endothelial-cell biology.



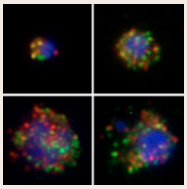
Crumbs and Stardust: it's complex

The *Drosophila* transmembrane protein Crumbs and its binding partner Stardust are members of a multiprotein complex that controls the morphogenesis of photoreceptor cells (PRCs). In adult PRCs, the Crumbs-Stardust complex localises to the stalk, a specialised apical membrane domain. Stardust contains numerous protein-protein-binding domains and is thought to act as a scaffold for other members of the Crumbs-Stardust complex – but what determines the localisation of Stardust and Crumbs? On page 2018, Elisabeth Knust and colleagues show that the domains of Stardust that are important for its localisation differ according to developmental stage. The authors show that, in the pupa (prior to the formation of the stalk), only the PDZ domain of Stardust is necessary for its apical localisation; by contrast, in the adult fly, multiple Stardust domains are required to target it to the stalk membrane. Notably, in pupal PRCs, Crumbs localises to the apical domain even when mutant Stardust does not but, in adult cells, Crumbs is unstable in the absence of stalk-associated Stardust. The authors also present data on the domains of Stardust that recruit other proteins of the Crumbs-Stardust complex. Their work highlights the intricate regulatory processes that govern PRC morphogenesis.



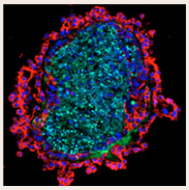
β-Synemin muscles in

In skeletal muscle, intermediate filaments (IFs) help to maintain muscle function by anchoring myofibrils to costameres – plasma-membrane-associated foci that include, among other proteins, the muscular-dystrophy-associated proteins dystrophin and α-dystrobrevin. The molecular basis of the link between costameres and IFs is poorly understood, although the crosslinker protein plectin 1 (which has binding sites for actin and the muscle IF protein desmin) is thought to have a central role. Now, Takao Hijikata and colleagues (p. 2062) show that β-synemin, which is best known as a muscle IF protein, interacts with plectin 1 both in vitro and in vivo. The authors identify three β-synemin-binding sites in the N-terminal domain of plectin 1 and show that β-synemin colocalises with plectin 1 and α-dystrobrevin at costameres. Using immuno-EM, they show that the costameric and IF-associated pools of β-synemin are distinct. In vitro, β-synemin can bind to F-actin and α-dystrobrevin, and plectin 1 binds to α-dystrobrevin, F-actin and β-synemin. On the basis of these data, the authors propose a new model of the IF-costamere linkage. Their results have implications for the treatment of muscular dystrophies.



Orc1 takes on telomeres

Genes that are positioned close to the ends of chromosomes, near to telomeric repeats, are often silenced – a process that, in yeast, involves the histone deacetylase Sir2. In the malaria parasite *Plasmodium falciparum*, Sir2 mediates the silencing of the subtelomeric *var* genes, which encode key virulence factors and are expressed in a mutually exclusive manner. It has previously been shown that Sir2 silences some, but not all, of the *var* genes, which indicated that other proteins are involved in their regulation; here, Artur Scherf, Rosaura Hernandez-Rivas and colleagues (p. 2046) identify an additional *P. falciparum* telomeric protein, Orc1. The authors show that Orc1 localises both to telomeric foci at the nuclear periphery and to the nucleolus – a pattern that is similar to Sir2 localisation. In addition, both proteins bind specifically to the telomere and to subtelomeric repeats, although the pattern of binding is not identical. Strikingly, both Sir2 and Orc1 relocate before DNA replication begins during the *P. falciparum* blood-stage cycle, and exhibit a more diffuse nuclear and cytoplasmic localisation – this is accompanied by a partial breakdown of telomeric clustering. Orc1 might, the authors suggest, have a similar role to Sir2 in the silencing of subtelomeric genes in *P. falciparum*.



Con-nectin' adhesion and survival

Nectins, which are a family of immunoglobulin-like transmembrane proteins, participate in intercellular adhesion, and help to form tight junctions (TJs) and adherens junctions (AJs). The cytoplasmic region of nectins is connected to the cytoskeleton by the actin-binding protein afadin. Mice that lack afadin die during embryogenesis and have disorganised TJs and AJs; however, it was not previously known whether developmental mechanisms such as apoptosis are affected by the absence of afadin. Yoshimi Takai and colleagues (p. 2008) now show that embryoid bodies that are derived from afadin$^{-/-}$ embryonic stem cells contain many more apoptotic cells than those that are derived from wild-type cells. In addition, apoptosis (whether induced by the intrinsic or extrinsic pathway) is stimulated in NIH3T3 cells when afadin or nectin-3 is knocked down. Using the same cell line, the authors show that PDGF-dependent signalling through PI3K-Akt – a key pro-survival pathway – is substantially inhibited in the absence of afadin or nectin-3. Moreover, the nectin-afadin complex associates with the PDGF receptor at cell-cell boundaries. The authors conclude that the nectin-3–afadin complex has a role in PDGF-induced cell survival.

Development in press

Angiogenesis and β1 integrin stick together

Integrins – heterodimeric cell-surface receptors that bind to laminin, collagen and other ligands in the extracellular matrix (ECM) – propagate many intracellular signals during development. For example, integrin-ECM interactions regulate angiogenesis, the formation of new blood vessels. But which integrin-ligand pairs are required in endothelial cells (ECs) to mediate this process? In a article published in *Development*, Rong Wang and colleagues report that β1 integrin is needed for EC adhesion, migration and survival during angiogenesis in mice. The authors report that lineage-specific deletion of the *Itgb1* gene (which encodes β1 integrin) in ECs in mouse embryos causes embryonic-lethal vascular defects, including the formation of a discontinuous endothelium in blood vessels. Furthermore, isolated *Itgb1*-null ECs behave in a disorganised manner, fail to adhere to or migrate on laminin or collagen substrata, and have reduced survival. These findings highlight the essential role that β1 integrin has during angiogenesis, and suggest that targeted therapies that block the function of β1 integrins in ECs could control the growth and survival of cancers by preventing neovascularisation.

Carlson, T. R., Hu, H., Braren, R., Kim, Y. H. and Wang, R. A. (2008). Cell-autonomous requirement for β1 integrin in endothelial cell adhesion, migration and survival during angiogenesis in mice. *Development* **135**, 2193-2202.