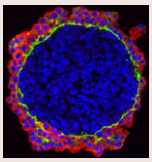
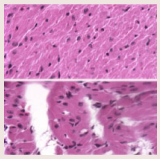
In this issue



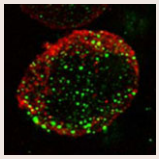
Early steps for integrins

It has been known for more than a decade that αβ1 integrins are essential for the formation of primitive germ layers from the inner cell mass (ICM), but how these integrins regulate ICM morphogenesis has been more difficult to decipher. Here, Shaohua Li, Reinhard Fässler and colleagues (p. 233) use the mouse embryonic-stem-cell-derived embryoid body (EB) to dissect the early stages of morphogenesis. By ablating β1 integrin in EBs, they show that αβ1 integrins are essential for the adhesion of endoderm cells to the basement membrane. Moreover, endoderm differentiation can be divided into two steps – lineage commitment and maturation – and β1 integrins are only required for maturation. In the absence of β1 integrins, the endoderm-specific transcription factor GATA4, which regulates laminin synthesis, is expressed, but does not translocate to the nucleus. Interestingly, β3 integrin can substitute for β1 integrin in the endoderm and, when transfected, causes correct localization of GATA4 to the nucleus and expression of laminin. Finally, the authors show that the mitogen-activated protein kinases ERK1/2 and p38 mediate integrin-dependent GATA4 nuclear translocation and endoderm maturation. These findings provide new mechanistic insights into how β1-mediated signalling regulates the differentiation of the visceral endoderm.



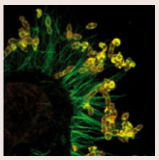
Keeping (TGFβ) active with integrins

Before its activation, the multipotent cytokine TGFβ is secreted from the cell in a latent complex with its inhibitory peptide LAP. Two integrin heterodimers, αvβ6 and αvβ8, activate the TGFβ isoforms TGFβ1 and TGFβ3 in vivo, dislodging LAP by interacting with an Arg-Gly-Asp (RGD) sequence on the latent complex. Six other integrin heterodimers are also known to bind to RGD sequences – but do they activate TGFβ1 and TGFβ3? To address this question, John Munger and colleagues (p. 227) explore the phenotype of mice that lack functional β6- and β8-integrins. The authors first show that double-knockout (*Itgb6*$^{-/-}$/*Itgb8*$^{-/-}$) mice mostly die at mid-gestation. Notably, however, those that survive develop cleft palates – as do *Tgfb3*$^{-/-}$ mice. To study the role of integrins αvβ6 and αvβ8 at later developmental stages, the authors next treat *Itgb8*$^{-/-}$ mice with an anti-αvβ6-integrin antibody after palate fusion. These mice develop severe systemic autoimmunity (indicated by mononuclear infiltrates in several organs) and also lack Langerhans cells, echoing the phenotype of mice that lack integrin-responsive TGFβ1. The authors propose, therefore, that the activity of integrins αvβ6 and αvβ8 (but not of other RGD-binding integrins) is required for the developmental effects of TGFβ1 and TGFβ3. Their data clarify the role of integrin-mediated TGFβ activation in vivo.



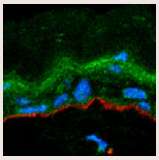
JAM-A – getting neutrophils unstuck

Early in the inflammatory response, neutrophils infiltrate tissues by migrating (extravasating) across the endothelium of blood vessels, then moving chemotactically towards the site of inflammation. The expression of the cell-surface adhesion protein JAM-A in endothelial cells is thought to affect neutrophil extravasation – but does JAM-A expressed in neutrophils also function in infiltration? On page 268, Elisabetta Dejana and colleagues show that it does. The authors have previously demonstrated that, in vitro, JAM-A expression in neutrophils is needed for their efficient directional migration; now, they show that the migration of leukocytes after extravasation is impaired in JAM-A-deficient mice. In activated HL60 neutrophils, they show, JAM-A is internalised into intracellular vesicles that also contain several integrins. Moreover, cell-surface JAM-A co-clusters with β1 integrin in the presence of fibronectin-coated beads or anti-integrin antibodies. Importantly, the internalisation of integrins by neutrophils derived from JAM-A-deficient mice in response to chemotactic signals is impaired, affecting both uropod retraction and cell motility. On the basis of these and other data, the authors propose that JAM-A promotes neutrophil chemotaxis by controlling integrin internalisation and recycling.



Pneumococci take the integrin route

To promote its invasion into host cells, the Gram-positive bacterium *Streptococcus pneumoniae* (pneumococcus) interacts specifically with several host proteins, including cell-surface receptors and ECM components. For instance, pneumococci are known to bind to the ECM- and plasma-localised protein vitronectin, and Sven Hammerschmidt and colleagues (p. 256) now shed light on how this interaction affects pneumococcal uptake and host-cell signalling cascades. Using flow cytometry, the authors first show that pneumococci interact with the heparin-binding sites of multimeric (ECM-associated) vitronectin. Moreover, cell-associated multimeric vitronectin promotes pneumococcal adhesion to, and invasion of, human epithelial and endothelial cells. Notably, the authors show that αvβ3 integrin is required for vitronectin-dependent invasion – as is integrin-linked kinase (ILK), which is known to mediate several downstream effects of integrin activation (including actin-cytoskeleton reorganisation). In line with this observation, internalisation of pneumococci requires a dynamic actin cytoskeleton, and their interaction with the host cell causes the formation of microspike-like structures (see image) that are the sites of pneumococcal entrapment. The authors conclude that pneumococci exploit the dynamic processes of the host cell to enable invasion.



Integrin α3β1 runs interference

Wound healing in the skin requires migration and hyperproliferation of keratinocytes. Integrin α3β1, among other members of the integrin family, mediates the attachment of basal epidermal keratinocytes to the basement membrane, so its role in adult skin and wound healing is of interest. Complicating such studies, however, are α3-integrin-null mice, which die during the neonatal period. Controversially, integrin α3β1 has also been independently reported to promote and inhibit keratinocyte migration in vitro. Arnoud Sonnenberg and colleagues (p. 278) now generate epidermis-specific α3-integrin-knockout mice to investigate the function of integrin α3β1 in wound re-epithelialisation. These mice are viable, but display local inflammation, hair loss, basement-membrane duplication and microblistering at the dermal-epidermal junction; hemidesmosome assembly and keratinocyte differentiation are not impaired. In the absence of integrin α3β1 there is no change in keratinocyte proliferation, the distribution of other integrins and the deposition of basement-membrane proteins in the wound bed, but wound healing is faster, suggesting accelerated keratinocyte migration. Supporting in vitro evidence shows that α3-integrin-deficient keratinocytes migrate with increased velocity and persistence. The authors' results support a role for α3β1 integrin in inhibiting the directional migration of keratinocytes in vitro and wound re-epithelialisation in vivo.

Development in press

Cells cycle with *no poles*

In *Drosophila*, the nuclear divisions following fertilisation oscillate rapidly between S and M phases, with no growth phases or cytoplasmic cleavage. Metazoan development depends on correct cell-cycle control, but it remains unknown how DNA replication and mitosis are coordinated during such rapid divisions. In a paper published in *Development*, Laura Lee and co-workers reveal that *no poles* (*nopo*), a gene encoding a putative ubiquitin ligase, is essential for the preservation of genomic integrity during these early stages of *Drosophila* development. The researchers find that *nopo*-mutant flies have misshapen spindles and undergo mitotic arrest, and that a mutation in the gene encoding the DNA-checkpoint kinase *Chk2* partially rescues these defects. Thus, the *nopo* phenotype is probably caused by Chk2-mediated centrosome inactivation, a protective mechanism in flies that prevents nuclear division after DNA damage or incomplete replication. In addition, the authors demonstrate that NOPO interacts with BEN, a ubiquitin-conjugating enzyme, leading them to propose that NOPO and BEN form a ubiquitin ligase complex required to prevent DNA defects during *Drosophila* embryogenesis.

Merkle, J. A., Rickmyre, J. L., Garg, A., Loggins, E. B., Jodoin, J. N., Lee, E., Wu, L. P. and Lee, L. A. (2009). *no poles* encodes a predicted E3 ubiquitin ligase required for early embryonic development of *Drosophila*. *Development* **136**, 449-459.