Missing Txnr1? Replicate as normal

The conversion of ribonucleotides to deoxyribonucleotides by ribonucleotide reductase (RNR) is essential for DNA replication. RNR obtains the electrons required for this reaction via a thioredoxin-reductase- or a glutathione-reductase-dependent route. Most forms of life can use both routes but yeast and plants that lack thioredoxin reductases grow slowly, which suggests that glutathione-reductase-dependent routes support DNA replication poorly in these organisms. Surprisingly, Edward Schmidt and colleagues (p. 2402) now report that mouse hepatocytes that lack thioredoxin reductase 1 (Txnr1) replicate normally during development and regeneration. They show that liver-growth rates during development and regeneration are similar in normal mice and in mice with Txnr1-deficient hepatocytes. Livers of either genotype have similar levels of proliferative, S- and M-phase hepatocytes, they report, and in chimeric mice whose livers contain both Txnr1-deficient and normal hepatocytes, the two cell types contribute equally to liver development and regeneration over many generations. These results suggest that a Txnr1-independent route for the supply of electrons to RNR can fully support DNA replication and normal proliferative growth, and has implications for the development of Txnr1 inhibitors as anti-cancer drugs.

Two-step regulation of NHE3 mobility

Epithelial tissue barriers in the intestine and kidneys are involved in essential absorptive processes. The brush-border (BB) Na⁺-H⁺ exchanger NHE3, which is largely responsible for intestinal and renal Na⁺ absorption, cycles between the plasma membrane and the endosomal recycling compartment under basal conditions, and its activity is regulated by changes in trafficking. But NHE3 is anchored to the actin cytoskeleton through interactions with the actin-membrane-linking protein ezrin and with NHE regulatory factors (NHERFs), which also bind ezrin. So how is NHE3 trafficking regulated? Mark Donowitz and colleagues investigate this question on page 2434 by examining how lysophosphatidic acid (LPA, an inflammatory mediator that stimulates NHE3 activity) affects NHE3 mobility in kidney epithelial cells. Their results indicate that the transient increase in NHE3 mobility, which is induced by LPA, occurs in two separately controlled parts. First, LPA regulates NHE3 exocytotic trafficking to the BB and, second, it controls the attachment of NHE3 to the BB cytoskeleton by regulating the NHE3-NHERF2 interaction. PI3K-dependent signalling controls the first of these processes, note the authors, but PI3K-independent signalling controlling the second – a result that provides an important new insight into NHE3 regulation.

Twinfilin-1 and miR-1 vie for hearts

The heart responds to physiological stimuli and tissue injury by undergoing hypertrophic growth to sustain cardiac output. Unfortunately, although cardiac hypertrophy is an adaptive response, it can lead to heart failure and sudden death if prolonged. MicroRNAs (miRNAs) – conserved, single-stranded non-coding RNAs that negatively regulate gene expression – have been implicated in cardiac hypertrophy. Now, Qing Jing and colleagues (p. 2444) report that downregulation of miRNA-1 (miR-1) by hypertrophic stimuli induces cardiac hypertrophy by increasing the expression of the cytoskeleton regulatory protein twinfilin-1 (TWF1). Using miRNA microarrays, the authors discover that miR-1 is the most abundant miRNA in the human heart. They identify TWF1 as a potential target of miR-1 using bioinformatics and show that overexpression of miR-1 suppresses endogenous expression of TWF1 in mouse fibroblasts. Further experiments indicate that miR-1 overexpression reduces the size of hypertrophic cardiomyocytes and attenuates the expression of hypertrophic markers. Conversely, TWF1 overexpression promotes cardiomyocyte hypertrophy. The authors suggest, therefore, that manipulation of TWF1 expression in cardiomyocytes helps to prevent the initiation and progression of cardiac hypertrophy.

Sorted! Charged amino acids in charge

The plasma membranes of the epithelial monolayers that line the body cavities are divided into two types of domain. These are the apical domains, which face the lumen of the cavities, and basolateral domains, which contact the other cells in the monolayers and underlying cells and connective tissues. Both domains contain unique sets of proteins – but how is polarized trafficking of epithelial proteins achieved? On page 2512, Robert Nicholas and colleagues define a new class of targeting signal in the P2Y₁ receptor that might provide a common mechanism for this process. P2Y receptors are nucleotide-activated, G-protein-coupled receptors. Four P2Y receptors, including P2Y₁, are localized to basolateral epithelial-cell membranes. The authors identify a 25-residue region within the C-terminal tail of the P2Y₁ receptor that directs basolateral sorting in MDCK epithelial cells. This region, which lacks previously established basolateral-sorting motifs, is functional even when its amino acids are scrambled. Notably, mutagenesis experiments indicate that the total number of charged residues (which can be either positive or negative) in the signal is the crucial determinant of basolateral targeting. This new class of non-sequence-specific sorting signal, suggest the authors, accounts for the basolateral sorting of a variety of epithelial proteins.

FORwards to ciliogenesis

Cilia are conserved, microtubule-based, hair-like organelles that extend from eukaryotic cells. In vertebrates, motile cilia on specialized epithelial cells generate fluid flow in the airways, oviduct and brain ventricles. In addition, a single, non-motile primary cilium, as present on many vertebrate cells, concentrates signalling machinery and acts as an antenna. Cilia grow from a modified centriole (the basal body) that docks at the cell membrane and provides a template for the elongation of the cytoskeletal core of the organelle. However, the details of ciliogenesis are unclear. Now, on page 2391, Olivier Rosnet and colleagues identify FOR20, a conserved protein that is required for primary cilia formation. FOR20, they report, is a self-interacting protein that is found in pericentriolar satellites, electron-dense granular structures that may transport cargoes to the centrosomes and basal bodies. The authors show that depletion of FOR20 in cultured epithelial cells decreases the length of the cilium on, and the percentage of, ciliated cells, and modifies pericentriolar satellite distribution. Together, these findings suggest that FOR20 helps to control ciliogenesis by regulating pericentriolar satellites.

Development in press

Integrin complexity at heart of angiogenesis

Integrin cell-adhesion receptors and their ligand fibronectin have important roles during disease-associated and developmental angiogenesis. However, there are many different integrins, each of which contains a specific β-subunit and a specific α-subunit, and it is not clear which α-subunits are involved in angiogenesis. Now, in a study published in Development, Arjan van der Flier and colleagues implicate both α5 integrins and αv integrins, the major endothelial fibronectin receptors, in vascular remodelling during mouse development. The researchers first show that, unexpectedly, the endothelial-specific knockout of α5 integrin has no obvious effect on developmental angiogenesis. They then test whether αv-integrins compensate for the absence of α5 integrins by generating endothelium-specific α5-αv-double-knockout mice. Vasculogenesis and angiogenesis are initially normal in these mice, but subsequent remodelling defects in the great vessels and the heart eventually cause embryonic death. Further investigations into the complex interplay among integrins during angiogenesis revealed here could lead to the development of effective anti-angiogenic drugs for cancer therapy.