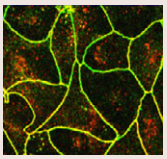
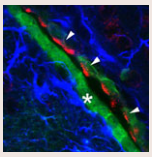
In this issue

By Jane Bradbury



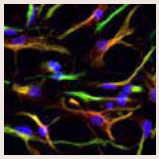
Paracellular claudin-2 water channels

Ions cross leaky epithelia such as the kidney proximal tubule both through the cells (transcellular route) and through the tight junctions (TJs) between cells (paracellular route) – but how does water cross leaky epithelia? Aquaporin water channels mediate the transcellular passage of water, but is there a significant paracellular water flux across these epithelia? On page 1913, Michael Fromm and colleagues report that the answer to this long-standing question is yes. The authors stably transfect MDCK C7 cells (a renal epithelial cell line with water-impermeable TJs) with either claudin-2 (a cation-channel-forming TJ protein expressed in leaky epithelia) or claudin-10b (also cation-channel forming, but present in the water-impermeable segments of Henle's loop) and measure the transepithelial water flux, through layers of the transfected cells, induced by an osmotic and/or Na^+ gradient. Both claudins increase the cation permeability of the cells. However, the water flux in claudin-2-transfected cells is higher than in vector controls, whereas claudin-10b transfection does not alter water flux. Therefore, conclude the authors, the water permeability of TJs depends on their molecular composition, as claudin-2 but not claudin-10b forms a paracellular water channel.



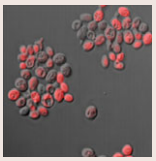
LRP2 regulates adult neurogenesis

Neurons are continuously generated in adult mammalian brains in two germinal niches: the subependymal zone (SEZ) of the lateral ventricles and the subgranular zone of the hippocampus. In the SEZ, as in the embryonic neural tube, bone morphogenetic proteins (BMPs) regulate neural stem cell proliferation; what controls BMP signalling in the SEZ, however, is poorly defined. Now, Thomas Willnow and colleagues report that low-density lipoprotein receptor-related protein 2 (LRP2), a clearance receptor that modulates BMP signalling during embryonic neurogenesis, also regulates BMP signalling in the SEZ of adult mouse brain (p. 1922). The authors show that LRP2 is expressed in the ependymal cells of adult mouse lateral ventricles. Notably, LRP2 expression is restricted to the ependyma that faces the SEZ. Lack of LRP2 expression, they report, impairs neural precursor cell proliferation in the SEZ and reduces the number of neuroblasts that reach the olfactory bulb; this reduction in neurogenesis coincides with an increase in the activity of the BMP2/4 pathway. The authors propose, therefore, that LRP2 modulates the microenvironment of the SEZ through catabolism of BMP in the ependyma, thereby enabling adult neurogenesis to proceed.



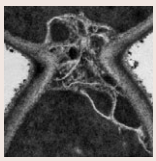
Meteorin: regulating the STATus of glia

The orphan ligand meteorin is thought to be involved in neuritogenesis, angiogenesis and gliogenesis, but its precise function in CNS development and the signalling pathways that mediate this function are poorly understood. Now, Kyu-Won Kim and colleagues report that meteorin promotes the differentiation of glial fibrillary acidic protein (GFAP)-positive glial cells through activation of the Jak-STAT signalling pathway (p. 1959). The authors show that meteorin is highly expressed in neural stem cells and radial glial cells during early mouse embryonic brain development but that its expression disappears as development proceeds, except in GFAP-positive astrocytes. In addition, they report that treatment of mouse neurospheres in vitro with recombinant meteorin induces tyrosine phosphorylation of STAT3, GFAP expression and glial differentiation. Furthermore, treatment of neurospheres with a Jak inhibitor or with *STAT3* siRNA blocks meteorin-induced glial differentiation. Finally, the authors show that meteorin also increases GFAP expression in Müller glia in mouse retina explants. Together, these results suggest that meteorin plays an important role in determining the fate of neural progenitor cells during CNS development.



To H2B or not H2B: apoptosis regulation

Apoptosis plays a central role in development and cellular homeostasis in higher eukaryotes. Recently, yeast has been established as a model system for studies into apoptosis and, on page 1931, Birthe Fahrenkrog and colleagues provide new insights into the epigenetic control of apoptosis in *Saccharomyces cerevisiae*. Ubiquitylation of histone H2B is implicated in DNA repair and checkpoint activation after DNA damage, and the DNA damage response machinery is closely linked to apoptosis. So, could histone H2B ubiquitylation regulate apoptosis? To address this question, the authors manipulate the expression of Bre1p – an E3 ubiquitin protein ligase that ubiquitylates histone H2B – in *S. cerevisiae*. Increased Bre1p expression protects yeast cells from hydrogen-peroxide-induced cell death, they report, whereas deletion of *BRE1* enhances cell death and reduces the lifespan of cells during chronological aging, which is a physiological condition that involves apoptosis. Furthermore, the anti-apoptotic activity of Bre1p requires its E3 ubiquitin ligase activity, and apoptosis increases in cells carrying a histone H2B mutant that cannot be ubiquitylated. Therefore, the authors suggest that Bre1p-mediated histone H2B ubiquitylation, an epigenetic change that influences transcription, regulates apoptosis in yeast.



Mitotic-exit networks with cytokinesis

Cytokinesis is the highly regulated process that physically separates daughter and mother cells in late mitosis. In *Saccharomyces cerevisiae*, cytokinesis involves constriction of an actomyosin ring and formation of a chitin-rich primary septum, which are processes that must be coordinated with mitotic exit to ensure that cytokinesis only occurs after chromosome segregation. Gislene Pereira and colleagues now report that the mitotic-exit network (MEN), the signalling pathway that drives mitotic exit, directly regulates cytokinesis by targeting components that are involved in septum formation to the bud-neck region (p. 1851). The authors show, for example, that Cyk3, Inn1 and Chs2 – three regulatory components of the primary septum – fail to localise normally to the bud neck in MEN-deficient mutants that have been forced to exit mitosis through inactivation of the mitotic cyclin-dependent kinase Cdk1. Consistent with this observation, ultrastructural studies indicate that septum formation in MEN-deficient mutants is abnormal. On the basis of these and other results, the authors propose that the MEN coordinates cytokinesis in budding yeast by bringing together components involved in actomyosin-ring contraction and septum formation after mitotic exit.

Development in press

Acid test for endosomal Notch activation

Cell-cell signalling through Notch regulates multiple cell behaviours during development, and inappropriate Notch activation is a hallmark of many cancers. Consequently, it is important to understand exactly how Notch signalling is regulated. In a study published in *Development*, Thomas Vaccari and colleagues bring this goal a step closer by reporting that the vacuolar ATPase (V-ATPase) proton pump, which acidifies endosomal compartments, is required for physiological and pathological Notch-receptor activation in *Drosophila*. Once it is ligand bound, Notch is activated by γ-secretase-mediated cleavage, but mounting evidence suggests that the entry of Notch into endosomes promotes its signalling. In a search for factors that regulate Notch activation in endosomes, the researchers isolated mutants in the *Drosophila* genes that encode V-ATPase subunits. Their characterisation of these mutants indicates that V-ATPase, probably through the acidification of early endosomes, promotes not only the lysosomal degradation of Notch to prevent excess signalling, but also the endosomal activation of Notch signalling. Therefore, it might be possible to curtail Notch overactivation in tumours by using V-ATPase inhibitors.

Vaccari, T., Duchi, S., Cortese, K., Tacchetti, C. and Bilder, D. (2010). The vacuolar ATPase is required for physiological as well as pathological activation of the Notch receptor. *Development* **137**, 1825-1832.