In this issue

**Hearing through tight junctions**

The internal environment of multicellular organisms is split into specialized compartments containing different fluids. These compartments are surrounded by barriers made of epithelial cells, which are sealed together by tight junctions (TJs). On p. 5087, Shoichiro Tsukita and colleagues investigate how the establishment of the endolymph compartment of the mammalian cochlea is necessary for hearing. This compartment has a high K⁺ concentration and a positive endocochlear potential (EP). These characteristics, which are essential for transduction of acoustic signals to electrical signals by the cochlear hair cells, are thought to be generated by the stria vascularis, an adjacent compartment delineated by two epithelial cell layers. By making mice lacking claudin-11—a major component of TJs in the basal cell layer of the stria vascularis—the authors show that, although an intact stria vascularis is not needed to maintain endolymph K⁺ concentrations, it is indispensable for the generation/maintenance of EP and thus for hearing.

**Intraneuronal informatics**

Nuclear architecture is extremely complex. The nucleus contains numerous subcompartments in which regulatory factors concentrate; moreover, these are highly dynamic and reorganize as cells divide and differentiate. How such reorganization is linked to regulation of gene expression and other nuclear processes is not clear. Gary Stein and co-workers have therefore developed a systems biology strategy to tackle the problem (see p. 4889). They have combined fluorescence microscopy, image processing and statistical analysis to describe the subnuclear organization of Runx transcription factors. Key parameters in this intraneuronal informatics strategy include domain size, domain packing and spatial randomness. The approach reveals characteristic architectural signatures established by wild-type and mutant Runx proteins after mitosis. In addition, the authors are able to correlate these with the biological activities of the proteins and their involvement in disease. Stein and co-workers conclude that the organization of Runx factors within the nucleus is fundamental to their tissue-specific regulatory function. Furthermore, they suggest that intraneuronal informatics will be applicable to analysis of other spatially organized nuclear microenvironments.

**Rethinking rafts**

Polared epithelial cells generate their polarity by trafficking newly synthesised proteins to either the apical or basolateral plasma membrane. A long-standing hypothesis proposes that proteins are directed to the apical surface by associating with lipid rafts through glycosyl-phosphatidylinositol (GPI) anchors. Nigel Hooper and his colleagues challenge this dogma by showing that, in the case of porcine membrane dipeptidase (MDP), N-glycan sidechains rather than a GPI anchor direct apical targeting in kidney epithelial cells (see p. 5079). MDP contains a GPI anchor site and two N-glycosylation sites. The authors show that, although MDP lacking a GPI anchor site is secreted instead of being attached to the cell surface, it is still targeted to the apical surface. By contrast, when its N-glycosylation sites are removed, MDP localises to the basolateral membrane, even though it still associates with lipid rafts. Other proteins may use O-glycans instead of N-glycans as apical targeting signals, suggest the authors, and further studies should determine whether specific glycan sequences are required for targeting.

**Nuclear Velcro**

The nuclear envelope of eukaryotic cells is part of the endoplasmic reticulum (ER), a membrane system that intersects with several organelles. The best understood of these intersections is the budding yeast nucleus-vacuole (NV) junction. On p. 4959, Erik Kvam and David Goldfarb report that the yeast oxytetracycline-binding protein (OSBP) homolog Osh1p is targeted to NV junctions through a direct physical interaction with the Nvj1p protein on the nuclear envelope. During nutrient starvation, Nvj1p forms Velcro-like patches with Vac8p on vacuole membranes, through which nuclear fragments are pinched off for degradation in the vacuole—the process is called piecemeal microautophagy of the nucleus (PMN). Kvam and Goldfarb use a GFP-Osh1p fusion to show that recruitment of Osh1p to NV junctions and PMN structures is proportional to cellular Nvj1p levels. Although OSN1 is not needed for NV junction formation or PMN, yeast lacking the entire seven-member OSP family exhibit defective PMN. This leads the authors to suggest that an activity shared by the OSBs is involved in modification or transport of lipids that are required for PMN.

**Bridging the blood-brain barrier**

The blood-brain barrier (BBB) stops most peptides entering the CNS and represents a significant obstacle to therapies for neurological disorders. Identifying carriers that could transport peptide-based drugs across the endothelial cells of the BBB is therefore an important goal but so far largely unattained. Weihong Pan and co-workers now reveal that a chaperone protein called RAP that normally facilitates folding and trafficking of low-density lipoprotein (LDL) receptors might be the answer (see p. 5071). Using ¹²⁵I-labelled RAP, they show that the chaperone efficiently crosses the BBB both in brain-perfusion assays and in vivo when injected intravenously. They then dissect the transport mechanism, demonstrating that passage of RAP across epithelial monolayers in vitro is promoted by megalin—a protein implicated in transcytosis across several types of epithelial cell. At 39 KDa, RAP is large enough to serve as a transporter for smaller molecules. Moreover, its transport across the BBB is significantly more efficient than that of two other potential carriers, transferrin and melatonintransporter. RAP thus has exciting potential as a vehicle for peptide-based drugs that target the CNS.

**Development in press**

**Setting morphogen gradients**

Morphogen gradients provide cells in developing organisms with essential positional information. But do these gradients form through diffusion of extracellular morphogens alone or is intracellular trafficking also involved? Reporting in Development, Kruse and colleagues address this controversial issue and conclude that, in the fly wing epithelium, extracellular diffusion is not sufficient to establish a Decapentaplegic (Dpp) morphogen gradient. Transient ‘shadows’ of Dpp signalling occur behind clones of endocytosis-defective cells, and the researchers calculate that, if Dpp gradients were established through diffusion alone, the endocytosis-defective cells would have to upregulate Dpp receptor surface expression to cause these shadows. Yet, when Kruse et al. use specific antibodies to measure the levels of Dpp receptors on these cells, they find no receptor upregulation. According to the researchers, the next step is to determine the relative importance of different transport methods for Dpp spreading.