Breaking down barriers

On page 653, Nitta et al. show that removal of the tight junction component claudin-5 makes the murine blood–brain barrier (BBB) selectively permeable to small molecules. Although considerably more work is needed before this approach can be applied clinically, the finding could be a boon for drug delivery to the central nervous system.

Although it was first described over a century ago, it has been shown more recently that the BBB consists of intercellular tight junctions, which prevent most molecules in the bloodstream from reaching the brain. In the new work, the authors found that the tight junctions of the BBB are primarily composed of the membrane proteins claudin-5 and claudin-12. Mice with a homozygous deletion in the claudin-5 gene appear to develop normally, and do not show signs of bleeding or edema, but do exhibit a striking abnormality in tracer experiments. Although the BBB of the knockout animals still blocks large molecules, it permits molecules smaller than \( \sim 800 \) D to pass into the central nervous system.

Unfortunately, all of the claudin-5 knockout mice died within ten hours of birth for unknown reasons. The authors are now trying to generate conditional deletions to characterize the functions of claudin-5 and claudin-12 in more detail.

Getting a handle on centrosomes

Centrosomes are required for cytokinesis and are important in cell cycle progression—but how are centrosomes connected to these essential cellular functions at the molecular level? On page 535, Gromley et al. describe the maternal centriole protein centriolin, the first integral centrosome protein linked to both cytokinesis and cell cycle progression in vertebrate cells.

Overexpression, siRNA silencing, or antibody inhibition of centriolin causes an unusual cytokinesis defect, in which cells remain connected by long strands of cytoplasm and form syncytia. Some of the cells later undergo cell cycle arrest in G1/G0, and some undergo apoptosis. The cytokinesis defect is caused by a domain in centriolin that shares homology with yeast regulatory proteins in the MEN/SIN pathway, which controls yeast mitotic exit and cytokinesis.

The results suggest that centriolin links centrosomes to a critical cytokinesis regulatory system and possibly to a cell cycle checkpoint. Screening work is now uncovering additional members of the cytokinesis pathway. Centriolin also contains domains with homology to proteins implicated in human tumorigenesis. Since centrosome defects would cause aneuploidy, a hallmark of cancer, the authors are now trying to determine whether centriolin has oncogenic functions.

The neutrophil as firefighter

Severe bacterial infection or trauma frequently leads to a systemic inflammatory response, a self-reinforcing activation of neutrophils and vascular endothelial cells that can be deadly. On page 641, Cepinskas et al. describe a neutrophil-mediated signaling mechanism that inhibits inflammation. The findings demonstrate a novel function for neutrophils and a previously unknown form of immunological tolerance, and they identify a promising target for new anti-inflammatory drugs.

In systemic inflammation, circulating cytokines cause the transcription factor NF\( \kappa \)B to translocate from the cytoplasm to the nucleus of vascular endothelial cells, where it induces the transcription of pro-inflammatory genes. Using a cell culture model of inflammation, the authors found that the migration of neutrophils across a monolayer of cytokine-activated endothelial cells causes NF\( \kappa \)B levels in the endothelial cell nuclei to drop. Cross-linking the adhesion molecule PECAM-1 on the surface of the endothelial cells produces the same effect, suggesting that the neutrophils send anti-inflammatory signals to the endothelium through PECAM-1. Exposing the neutrophil-calmed endothelial cells to a second round of cytokine activation results in even further reduction of the pro-inflammatory response. The authors are now trying to determine what controls this novel type of induced tolerance at the molecular level.