Neutrophils choose the right direction

Two distinct signaling pathways operate sequentially, thus guiding neutrophils to bacterial invaders, according to Heit et al. on page 91. Although one pathway lures neutrophils in the right general direction, the other pathway dominates when the prey is within reach.

Neutrophils leave the bloodstream and migrate to infection sites by following intermediary chemokine signals (such as IL-8) that are generated by damaged host cells. End-target signals like fMLP or LPS, either released by the pathogen itself or by the body in response to the bacteria, also attract neutrophils. Since the blood cells prefer to pursue end-targets when both signals are present, the authors speculated, correctly, that different pathways controlled the two responses.

The authors speculate that migration may change depending on the chemokine that is recruited by p38 MAPK. The findings could explain why the leakage of bacterial products into the bloodstream can cause such severe problems, as these chemicals keep neutrophils from following intermediary signals into the surrounding tissue.

A GAP in COPI vesicle formation is filled

The effect of ARF1 GTPase-activating protein (ARFGAP1) on vesicle formation is making a turn-around. Contrary to previous theories, GAP does not antagonize COPI coat recruitment. As shown by Yang et al. on page 69, its newly discovered function reveals conservation among GAPs in anterograde and retrograde transport pathways.

COPI vesicle formation is initiated by the ADP-Ribosylation Factor (ARF) family of small GTPases, which recruits COPI coatomer subunits to Golgi membranes. ARFGAP1 inactivates ARF1 by stimulating GTP hydrolysis. Because COPI vesicles formed in vitro using nonhydrolyzable GTP (GTPγS) or GTP-bound ARF1 do not uncoat, it has been inferred that ARFGAP1 stimulates uncoating, and thus inhibits vesicle formation. But the new experiments, using hydrolyzable GTP, provide a clearer view of the ARFGAP1 function.

Yang et al. found that ARFGAP1 had the opposite effect of what was previously thought—it stimulated vesicle formation. ARFGAP1 was required for cargo sorting and was found on vesicles at levels exceeding even that of COPI. Thus, ARFGAP1 is actually a COPI coat component, similar to the GAP Sec23p on COPII vesicles. In the COPI case, GTP was required for ARF1 to bring ARFGAP1 to the site of vesicle formation. GTPγS blocked this recruitment, and thus blocked vesicle formation altogether. Additional shearing manipulations in previous in vitro experiments may have masked the requirement for ARFGAP1 in vesicle formation by releasing abnormal vesicles.

Everyone needs a home

An apoptosis-promoting factor leads cells to suicide by making them feel homeless. With their report on page 169, Wang et al. finally explain how a long-known death kinase initiates apoptosis.

The kinase in question is death-associated protein kinase (DAPK), a positive regulator of apoptosis induced by many stimuli, including c-myc and TGF-β. Although DAPK was cloned several years ago, its function in cell death has remained elusive. The new results reveal that DAPK has the unusual ability to initiate anoikis, a form of apoptosis induced in unattached cells, by interfering with integrin signaling.

Not one to dally with downstream signals, DAPK starts at the top—by altering integrin structure. Wang et al. found that DAPK locks integrin in an inactive state, thus suppressing epithelial cell adhesion to the extracellular matrix (ECM). As a result, the ECM survival pathway initiated by integrin and mediated by FAK was blocked, resulting in cell death. DAPK effects on adherence and survival were reversed by activating integrin or by expressing active FAK. Carcinoma cells, which are resistant to anoikis, were unaffected by DAPK. Wang et al. do not yet know whether DAPK binds to the cytoplasmic tails of integrin or how it might inactivate the receptor.