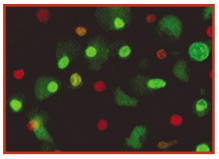
In this issue

By John Ashkenas, Science Editor

CNS cell death in bacterial meningitis

(See article on pages 19–27.)

Bacterial infection of the CNS is hazardous not only because of its often-lethal acute effects, but also because it leads to the death of irreplaceable neurons and glia. Braun et al. have established microglial and neuronal cell culture systems in which to study the mechanisms by which Pneumococcus bacteria induce cell death.



In a recent paper in the *Journal of Infectious Disease*, these same authors showed that exposure to these bacteria induces a caspase-independent cell death pathway. In this response, the mitochondrial protein apoptosis-inducing factor (AIF) translocates to the nucleus, where it activates some of the early events in apoptosis, including chromosomal condensation, DNA cleavage, and translocation of phosphatidylserine to the cell surface. Here, Braun et al. show that AIF activation and cell death can be induced by either of two secreted bacterial factors: hydrogen peroxide and the toxic protein pneumolysin, which forms pores in animal cell membranes. The authors inactivated both of these factors, first by using bacterial strains with specific mutations that block their production, and second by adding exogenous inhibitors. Simultaneous inhibition of pneumolysin and peroxide protects the cells from bacteria-induced killing, both in culture and in vivo. However, even when the bacteria fail to produce peroxide, host cells exposed to the bacteria generate it endogenously and are still subject to apoptotic death, albeit with lower efficiency. Most likely, inflammation caused by some additional bacterial factor is responsible for this residual pro-apoptotic effect.

The anti-inflammatory effect of apoptotic bodies

(See article on pages 41–50.)

The ubiquitous process of apoptotic cell death escaped the notice of cell biologists for decades, largely because cells that die by this mechanism are efficiently removed by phagocytosis in a process that provokes no local inflammation. Indeed, as Henson and collaborators have argued, the clearance of apoptotic debris is not merely silent, but actually suppresses inflammation. These authors previously identified a major phagocytic receptor for apoptotic cells, the phosphatidylserine (PS) receptor (PSR), which binds a phospholipid that is usually restricted to the inner leaflet of the plasma membrane but that accumulates on the cell surface during apoptosis. Exogenous apoptotic cells introduced into inflamed lung tissue in vivo are taken up by local macrophages, which then release active TGF-β1 and suppress the effects of inflammatory cytokines. Ligation of the PSR appears to be critical for this effect, since instillation of PS vesicles alone confers a similar effect, and live cells—or even apoptotic cells that lack extracellular PS—do not. Crucially, when the apoptotic cells are treated so that they can bind a different phagocytic receptor, the anti-inflammatory effect is also lost, confirming that the interaction with the PSR, rather than phagocytosis per se, helps terminate inflammation in this tissue.

Monitoring epithelial plasticity, one cell at a time

(See article on pages 89–99.)

The kidneys maintain plasma volume and composition by adapting to shifts in the concentration of ions and other solutes. Some years ago, Schwartz and colleagues identified one such homeostatic mechanism, in which acidosis alters the cellular population within the cortical collecting duct (CCD) of the kidney. Over a period of days, acidosis induces one epithelial cell type in the CCD, the so called β-intercalated cells, to adopt the characteristics of another cell type, the α-intercalated cells. Intercalated cells of both types employ a proton ATPase and an anion antiporter system to transport H^+ and HCO_3^- ions across the epithelium. However, because they differ in the distribution of these proteins on their apical and basolateral surfaces, these two cell types affect plasma pH in opposing directions: β cells secrete HCO_3^- toward the lumen, acidifying the plasma, whereas α cells reabsorb HCO_3^-, helping to neutralize plasma pH. Now, Schwartz et al. have revisited the β-to-α shift, this time using CCDs cultured ex vivo, a system that allowed them to observe the fates of individual cells over several hours following reduction of external pH. Just as is seen in the living kidney following a period of acidosis, CCD cells undergo a morphological change and shift their polarity to favor HCO_3^- reabsorption. Building on their earlier identification of the ECM protein hensin as a key factor in epithelial differentiation, the authors examined the effect of a hensin blocking antibody in their ex vivo system. They confirm that this antibody specifically inhibits the conversion to the α cell phenotype. Hensin is ubiquitously expressed, generally in a soluble form that has no effect on the intercalated cell polarity. Interestingly, however, the hensin binding protein galectin-3 is expressed by α but not β cells and appears to favor the formation of insoluble, ECM-bound hensin, which is biologically active. With the ability to monitor individual cells in real time, it should be possible to tease apart the changes in mRNA and protein expression, cellular morphology, and adhesive interactions that drive this dramatic shift in cellular phenotype.