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INSIDE LAB INVEST

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The epithelial-mesenchymal transition: keeping an eye on osteopontin

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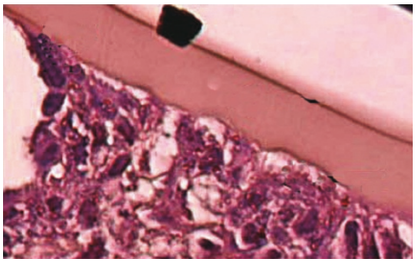
Lens epithelial cells undergo an epithelial-mesenchymal transition (EMT) in response to various forms of ocular injury. Although this can be an adaptive process that promotes healing, exuberant production



of mesenchymal elements damages the lens and impairs vision, as occurs in fibrous-type capsular opacification after cataract surgery. Prior work suggests that EMT of lens epithelium is meditated by the transforming growth factor β (TGFβ)/Smad signaling pathway and by extracellular matrix molecules. Osteopontin (OPN) is a matrix glycophosphoprotein that is highly expressed during inflammation and repair. Inside this issue, Saika *et al.* (p. 130) examine the role of osteopontin during the EMT in a murine model of lens injury. This group previously reported that osteopontin is upregulated during lens fibrosis in rodents and humans. In the current paper, molecular alterations of lens epithelium induced by needle puncture were studied in osteopontin knockout mice vs. wild-type controls. OPN-null mice showed reduced expression of collagen I, smooth muscle actin, and TGFβ with suppression of Smad signaling, which ultimately resulted in reduced EMT of lens epithelial cells. These findings provide a clearer view of osteopontin's role in promoting EMT in the injured lens. *ATY*

Paraptosis mediated by BK channels

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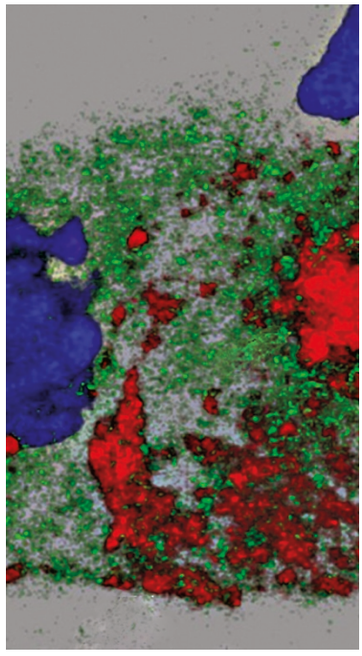
Monocytes kill glioma cells expressing membrane M-CSF by a process termed paraptosis, which is a programmed cell death involving vacuolization and culminating in necrosis. The paper in this issue by Hoa *et al.* (p. 115) shows that this process is initiated by reactive oxygen species (ROS) being released by monocytes upon contact of m-MCSF. They further show that ROS lead to the activation and opening of big potassium (BK) channels, an event that is necessary and sufficient for the induction of paraptosis. BK channels are widely expressed in glioma cells and yet seem to have little function. The underlying hypothesis of the study is that BK channels may be subject to modulation via cell stress signals and their subsequent activation may provide the impetus for the induction of paraptosis. From a more practical point of view, osmotic dysregulation of tumor cells induced by BK-channel activation provides a promising venue in which to develop therapeutic approaches of monocyte-mediated cytotoxicity. *LM*



β-Cell-specific aggregation of cellular prion protein

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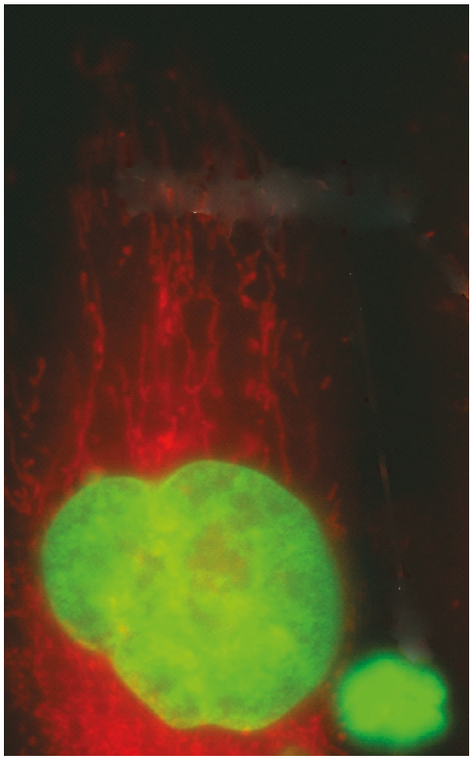
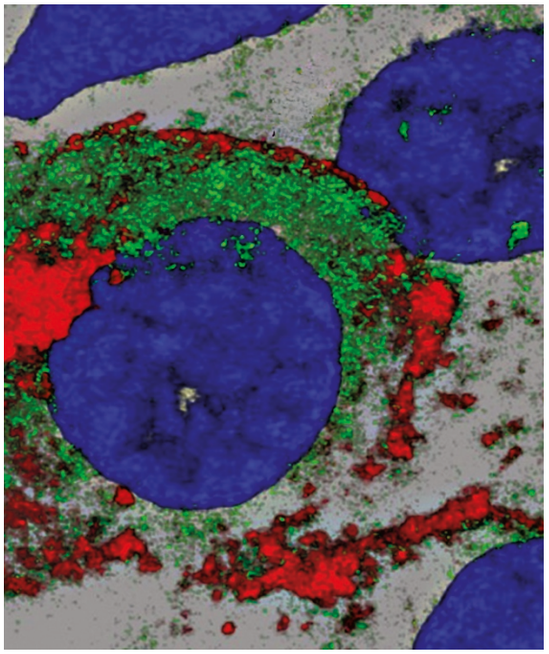
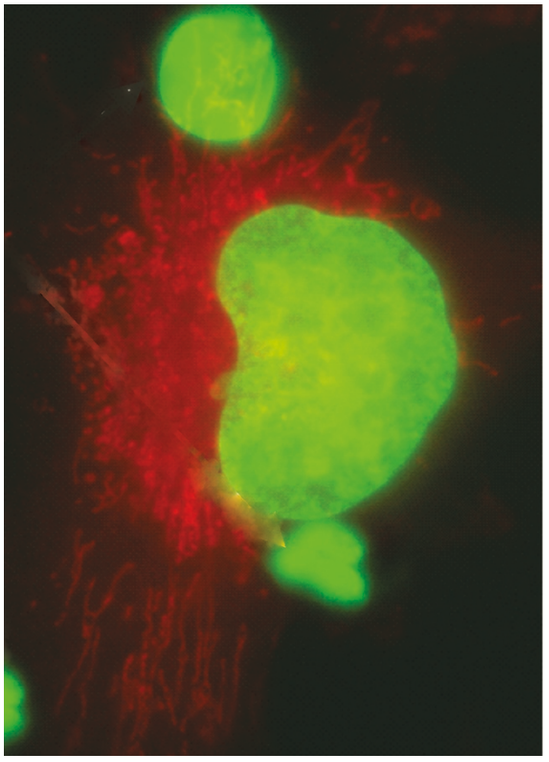
The function of cellular prion protein (PrP^C), which is expressed abundantly in non-neuronal tissues, is unknown. In this issue, Strom *et al.* (p. 139) hypothesized that PrP^C expression in the endocrine pancreas is related to the regulation of glucose homeostasis. By using both spontaneous and induced models of type 1 diabetes, these authors showed a distinctive accumulation of cytosolic PrP^C inclusions in a subset of insulin-producing β-cells. The frequency of β-cells with PrP^C inclusions was threefold greater in diabetic rats, suggesting that PrP^C accumulation plays a role in β-cell dysfunction. These observations open new venues for diabetes pathogenesis, and the one of the most pressing questions to address is the relationship between PrP^C accumulation and the autoimmune process; specifically, PrPC accumulation could be a primary cause of the disease, with PrP^C-damaged β-cells initiating the autoimmune process by release of neoantigens. Alternately, the PrP^C accumulation could be the consequence of autoimmune destruction of β-cells. *LM*

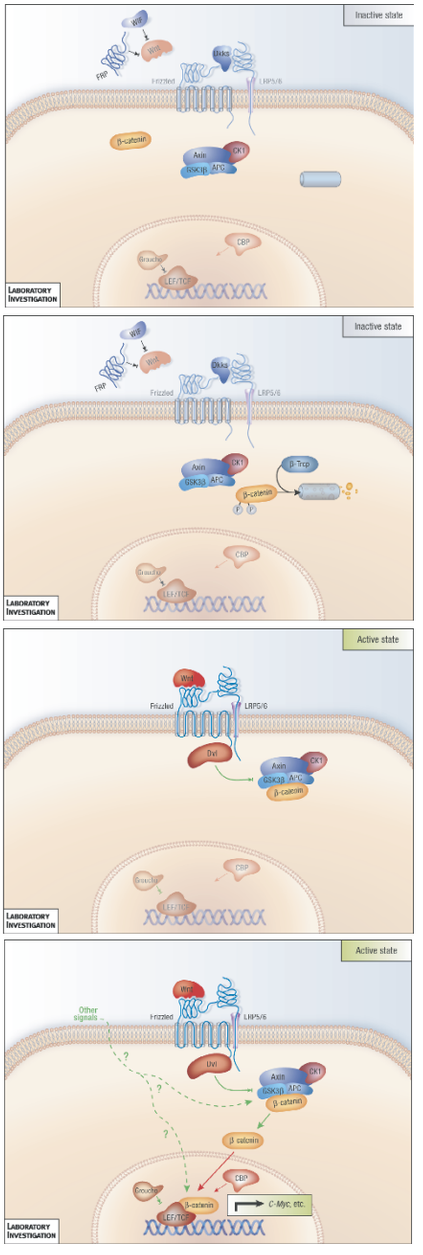






Pathobiology in Focus

Download free PowerPoint slides when you read this series online. This month, He *et al.* discuss the therapeutic implications of Wnt signaling and human diseases.



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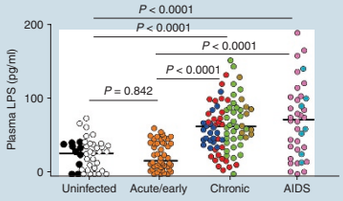
nature.com/pathology

HIV: microbial translocation causes immune activation Chronic immune activation is characteristic of progressive HIV disease. New findings, published in *Nature Medicine*, point to the increased translocation of gastrointestinal microbial products as the cause of HIV-related systemic immune activation. Among other evidence, researchers found increased levels of plasma lipopolysaccharide (LPS) both in patients with chronic HIV and in those with AIDS. Researchers also reported an association between raised plasma LPS and measures of immune activation.
Nature Medicine, published online 19 November 2006; doi:10.1038/nm1511



Gene m utations cause a nephritic syndrome variant A recent article in *Nature Genetics* reports the identification of mutations in the phospholipase C epsilon gene (*PLCE1*) as the cause of early-onset nephritic syndrome with end-stage kidney disease. Kidney histology of individuals with homozygous truncating mutations in *PLCE1* showed diffuse mesangial sclerosis, which was shown to indicate an arrest in normal glomerular development. The identification of this mutation represents the first molecular cause of nephritic syndrome variant that resolved after therapy in some individuals.
Nature Genetics 38, 1397–1405 (2006), doi:10.1038/ng1918

Amyloid plaque formation in Alzheimer's disease Amyloid plaque formation is the primary cause of Alzheimer's disease. In *Nature Medicine*, researchers recently reported that the activation of either β_2-adrenergic receptors (β_2-AR) or δ-opioid receptors (DORs) stimulates γ-secretase activity, which in turn accelerates amyloid plaque formation. β_2-ARs and DORs, among other receptors, are activated by environmental factors such as stress. Researchers further demonstrated that in the mouse model of Alzheimer's disease, a β_2-AR-selective agonist increased cerebral amyloid plaques, while a β_2-AR-selective antagonist reduced cerebral amyloid plaques.
Nature Medicine, published online 19 November 2006; doi:10.1038/nm1485