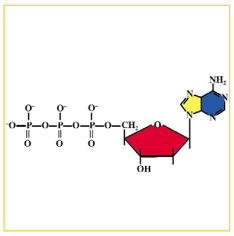
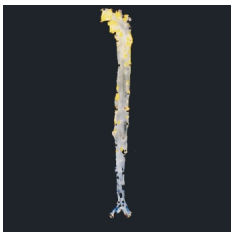
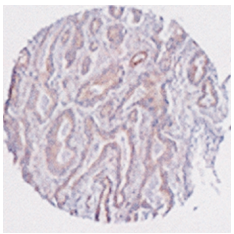


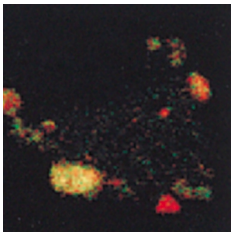
The toxic metabolite in ADA deficiency. Adenosine deaminase (ADA) deficiency leads to severe combined immunodeficiency. While the link between the loss of the enzyme and the disease has been known for over 30 years, and ADA deficiency has been the first target of human gene therapy for over 15 years, it is still unclear why this enzymatic deficiency has such profound effects on the immune system. Adenosine, deoxyadenosine, AMP, and dATP have all been suggested to be responsible for the lymphopenia seen in patients. Studying cultured fetal thymic organs from ADA-deficient mice, Linda Thompson and colleagues report now (pages 395–402) that normalization of dATP levels by inhibition of adenosine kinase abolishes the effects of ADA deficiency. The cultures can also be rescued by introduction of a *Bcl-2* transgene, suggesting that toxicity results from dATP-induced cytochrome *c* release from the mitochondria, which in turn triggers apoptosis of thymocytes past the double-negative stage.



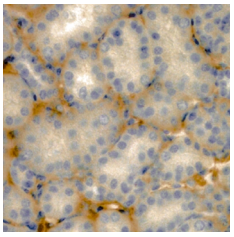
eNOS and atherosclerosis: Mind the details! NO produced by endothelial nitric oxide synthase (eNOS) is thought to protect against atherosclerosis. Ectopic expression of eNOS in blood vessels has been suggested as a therapeutic strategy in individuals at risk for atherosclerosis, and initial results from transient gene transfer studies in animals were encouraging. Seinosuke Kawashima and colleagues examined the long-term effects of eNOS overexpression in the endothelium. Their study beginning on page 331, revealed that eNOS expression did not prevent but accelerated atherosclerosis in *ApoE* knockout mice (which develop atherosclerotic lesions spontaneously). Supplementary treatment of the animals overexpressing eNOS with an NOS cofactor resulted in lesions comparable to those in *ApoE* knockout animals. This demonstrates that eNOS expression alone is not sufficient for proper function of the enzyme, and suggests that therapeutic approaches seeking to enhance NO levels in blood vessels will need to consider the many aspects of its complex biosynthesis and regulation.



HIP1 expression in prostate cancer. Huntingtin-interacting protein 1 (HIP1) is involved in clathrin-mediated cellular trafficking. Having previously found that HIP1 is involved in a leukemia-associated translocation and overexpressed in several cancer cell lines, Theodora Ross and colleagues report now (pages 351–360) that the gene is expressed in a large fraction of human prostate cancers but not in normal prostate tissue. Examining tissue microarrays from over 100 prostate cancer patients, they found that expression of HIP1 correlated with aggressive pathology and poor prognosis. HIP1 expression is also seen in over 50% of mouse prostate cancers induced by expression of SV40 early genes, suggesting that its expression is a common additional genetic event in tumorigenesis.



Cathepsin S and autoimmunity. Cathepsins are lysosomal cysteine proteases that were first discovered in the 1940s. Until recently, their role was thought to be that of non-specific scavengers, but targeted disruption of cathepsins in the mouse has revealed specific functions of several family members. Cathepsin F, L, and S, for example, are thought to be involved in the maturation of MHC class II molecules and antigen presentation. Having previously developed specific small molecule inhibitors against cathepsin B, L, and S, Yoshio Hayashi and colleagues analyzed the role of these proteases in autoimmune diseases. As they report beginning on page 361, inhibition of cathepsin S (but not B or L) prevented the development of autoimmune lesions in the salivary and lacrimal glands in a mouse model of Sjogren syndrome. Together with earlier findings that cathepsin S–deficient mice are less susceptible to collagen-induced arthritis, these results implicate cathepsin S as a critical player in autoimmunity and suggest a novel target for immune modulation in patients with autoimmune disorders.



Bradykinin protects against renal fibrosis. Angiotensin-converting enzyme (ACE) inhibitors are known to slow down the progression of various kidney diseases, including fibrosis. ACE converts angiotensin I to angiotensin II and degrades bradykinin. Jean-Loup Bascands and colleagues focused on bradykinin's G protein–coupled B2 receptor in their investigation of a possible role of bradykinin in renal fibrosis. As they report, beginning on page 371, mice lacking the receptor are more susceptible to experimentally induced tubulointerstitial fibrosis, and rats overexpressing endogenous bradykinin are less susceptible than control animals. Additional experiments suggest that bradykinin might exert its protective functions by increasing the activity of plasminogen activators and subsequent activation of matrix metalloproteinases.