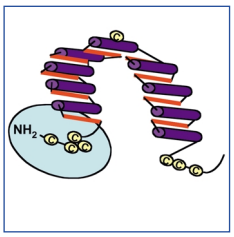
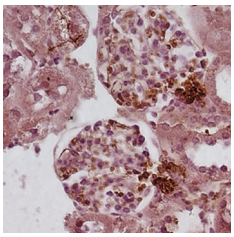
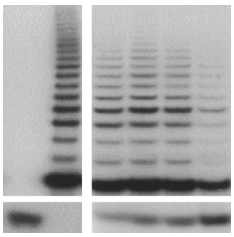


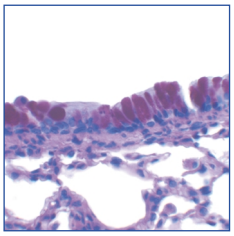
Molecular etiology of Graves disease. Unlike in other autoimmune diseases — where autoantibodies cause tissue damage — the autoantibodies in Graves disease activate the thyrotropin receptor and stimulate thyroid function. Studying recognition of the receptor by different antibodies, Basil Rapoport and colleagues found that the epitopes recognized by thyroid-stimulating antibodies are poorly accessible when the holoreceptor is present on the cell surface (see pages 209–217). Such antibodies preferentially recognize the free A subunit of the receptor, suggesting that shed subunits either initiate or amplify the autoimmune response to the thyrotropin receptor. The gonadotropin receptor is a close relative of the thyrotropin receptor, but it doesn't undergo cleavage and subunit shedding. Consistent with a critical role of the free subunit in generation and affinity maturation of activating antibodies, no such antibodies against the gonadotropin receptor have ever been found.



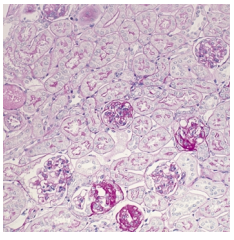
Vitamin D control of blood pressure. Clinical studies have long found an inverse correlation between plasma levels of vitamin D and blood pressure, and vitamin D treatment can reduce plasma activity of the blood pressure regulator renin and blood pressure itself. Beginning on page 229, Yan Chun Li and colleagues show that 1,25-dihydroxyvitamin D3 functions as a potent negative endocrine regulator of the renin-angiotensin system. Mice lacking the vitamin D receptor exhibit drastically increased renin and plasma angiotensin levels. As a consequence, the animals display increased water intake and elevated blood pressure. Cell culture experiments further revealed that vitamin D regulation of renin expression is mediated by the vitamin D receptor, occurs at the transcriptional level, and appears to be independent of calcium metabolism.



Estrogen, telomerase, and prostate cancer. One of the earliest molecular alterations in prostate cancer is telomerase reactivation. Having previously shown that estrogen reverses telomerase silencing in breast and ovarian cancer cells, Antonella Farsetti and colleagues report (see pages 219–227) that estradiol treatment results in increased transcription of *hTERT*, the catalytic subunit of telomerase, and increased telomerase activity in prostate cancer explants and cell lines. These findings are consistent with previous suggestions that the age-dependent decline of androgen-to-estrogen ratio might be involved in the development of prostate cancer. Indeed, when Farsetti and colleagues treated cells with testosterone but prevented aromatization to estrogen, they found reduced telomerase activity compared with testosterone treatment alone. While future experiments need to address the respective contributions of androgens and estrogens to prostate cancer development and progression, this study suggests that signaling through estrogen receptors contributes to the pathogenesis of prostate cancer.



Viral aspects of asthma. Michael Holtzman and colleagues described previously that airway epithelial cells are specially programmed for anti-viral immunity, and that the behavior of those cells in asthma resembles a persistent anti-viral response. Paramyxoviral infections are the leading cause of lower respiratory tract illness in infants. Studying the consequences of airway infection with Sendai virus, a mouse paramyxovirus, in a mouse model of bronchiolitis, the researchers now report that a single, transient paramyxoviral infection can cause both acute and chronic manifestations of an asthma-like phenotype (see pages 165–175). Based on further analysis of genetically modified mice, this chronic asthmatic response appears to be under distinct controls from the acute response to viral infection and from the response to allergen challenge. Taken together, the findings raise the possibility that besides resembling a persistent anti-viral response, asthma might even be caused by viral infection, possibly triggered by a paramyxovirus in infancy.



Gas6 promotes progressive kidney disease. Glomerular cell proliferation is a hallmark of many kidney diseases, suggesting molecules that control this proliferation as potential targets for therapeutic intervention. Studying Gas6, a vitamin K–dependent growth factor that signals through its receptor Axl, Hidenori Arai and colleagues showed previously that this signaling pathway is necessary for mesangial cell proliferation in a rat model of acute glomerulonephritis. In a report beginning on page 239, the researchers examined the role of the Gas6/Axl pathway in a mouse model of severe and progressive renal disease. They generated mice lacking Gas6 and showed that those are, to some extent, protected from nephrotoxin-induced nephritis. Administration of recombinant Gas6 in the knock-out animals worsened the disease response to nephrotoxin, whereas recombinant Gas6 by itself had no effect on kidney morphology in wild-type mice. These results suggest that down-regulation of the Gas6/Axl pathway might have beneficial effects in progressive kidney diseases.