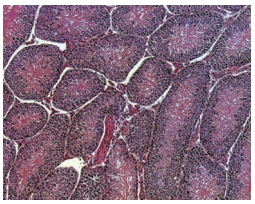
## The first oncogenic chemokine receptor

Kaposi sarcoma (KS) is the most common malignancy in patients with HIV/AIDS. Recent work on the chemokine receptor vGPCR has suggested a critical role for this molecule in KS pathogenesis. vGPCR is a constitutively active receptor that causes angiogenic lesions and tumors when expressed in transgenic mice. Grisotto and colleagues now show that vGPCR induces proliferation of the endothelial cells in which it is expressed, suggesting that autocrine effects are responsible for the intense angioproliferation that characterizes the transgenic models and the human disease (pages 1264–1273). Chemokine receptors such as vGPCR may cause angiogenesis by triggering proliferation of endothelial cell precursors present in the periphery. The cells in which vGPCR is expressed are intimately associated with the vascular wall and can transfer disease as measured by angioproliferation and subsequent tumor development to *Rag*-deficient mice. With time, these cells appear to differentiate and lose transgene expression, which explains the low number of vGPCR-expressing cells in tumors. Unregulated expression of this receptor during the latent phase of infection may be a key event, leading to proliferation and transformation of the targeted cell. These results establish that vGPCR triggers angioproliferation directly and define this molecule as the first known oncogenic chemokine receptor.

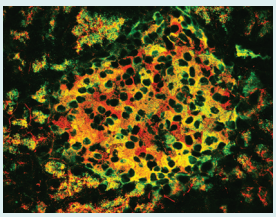
## Bradykinin flows through the fountain of youth



How do angiotensin-converting enzyme inhibitors provide benefits in diabetic nephropathy and in other age-associated disorders, such as Alzheimer disease, congestive heart failure, and myocardial infarction? Kakoki and colleagues provide some answers by showing that the bradykinin B2 receptor can suppress hyperglycemia-induced oxidative stress and mitochondrial damage (pages 1302–1309). In 12-month-old mice, many indicators of senescence (alopecia, skin atrophy, kyphosis, osteoporosis, testicular atrophy, lipofuscin accumulation in renal proximal tubule and testicular Leydig cells, and apoptosis in the testis and intestine), virtually absent in wild-type mice, were clearly apparent in diabetic mice and were markedly enhanced when the diabetic mice also lacked the bradykinin B2 receptor. Bradykinin's ability to suppress hyperglycemia-induced reactive oxygen species in cultured endothelial cells was dependent on NO. The most likely causal mechanism of the age-related phenotypes is hyperglycemia-induced oxidative stress, enhanced by lack of B2 receptors, which led to increased mitochondrial turnover and mitochondrial DNA mutations. These findings led the authors to suggest that premature senescence underlies many of the complications of diabetes and that bradykinin plays an important role in preventing their development by reducing oxidative stress.

## A cure for type 1 diabetes?

Patients with autoimmune diabetes (T1D) face a lifetime of insulin injections. In an effort to cure recent-onset autoimmune diabetes, Bresson and colleagues used a combination therapy in 2 animal models of T1D (pages 1371–1381). The therapy is based on a combinatorial regimen of oral and intranasal immunization with islet antigens and low-dose anti-CD3 $F(ab')_2$. The authors were able to exploit the fact that anti-CD3 treatment can induce a milieu for Treg induction and can rapidly dampen autoaggressive responses in order to expand in vivo proinsulin-specific Treg numbers. The Tregs then suppressed heterologous autoreactive immune responses. The authors observed a strong synergy between anti-CD3 and nasal immunization with proinsulin peptide, resulting in improved outcomes compared with those of monotherapies (anti-CD3 or peptide alone). Suboptimal anti-CD3 doses together with the bystander suppressive activity of antigen-specific Tregs should prevent systemic side effects (such as EBV reactivation, as observed in a recent anti-CD3 trial in humans). The interventions were only effective early in the prediabetic phase, but any potential cure for diabetes is an exciting find.



## Hunting for a treatment for Huntington disease

There is currently no treatment to delay or prevent the appearance and progression of the fatal inherited neurodegenerative disorder Huntington disease (HD). Several studies have identified the transglutaminase inhibitor cystamine as a potential therapy for HD. Borrell-Pagès and colleagues now show that cystamine's neuroprotective effect involves not only transglutaminase but also the chaperone protein HSJ1b (pages 1410–1424). HSJ1b completely inhibited mutant polyglutamine-huntingtin–induced death of striatal neurons in culture and rescued neuronal dysfunction in a *Caenorhabditis elegans* model of HD. Unlike typical chaperones, HSJ1b had no effect on aggregation of polyglutamine-huntingtin but rather enhanced the secretion of Golgi-derived clathrin-coated vesicles containing the prosurvival brain-derived neurotrophic factor (BDNF). Cystamine injections into rodents led to an increase in cerebral BDNF levels in vivo. Cysteamine, the FDA-approved precursor of cystamine, had a similar effect on the levels of BDNF in brains of wild-type mice and in 2 HD mouse models. This is the first study that demonstrates that cysteamine is neuroprotective in HD mice through the regulation of cerebral BDNF levels. As cysteamine also increased plasma BDNF levels in a primate model of HD, it may be useful as a marker of clinical efficacy in HD trials.