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In This Issue

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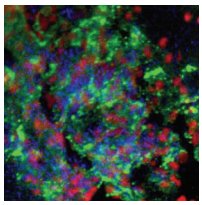
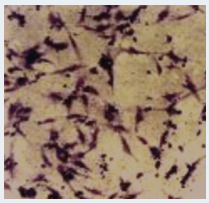


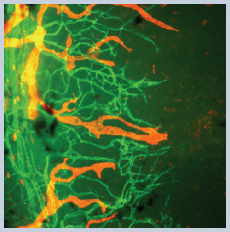
HIV-associated dementia complex, termed HIV encephalitis, occurs in about one-quarter of infected individuals. Unfortunately, the symptoms and signs of dementia are not usually evident until the late stages of encephalitis, after irreversible damage has occurred. Thus, diagnostic tools for the detection of HIV encephalitis prior to the manifestation of neurological signs would greatly aid in developing therapeutic intervention. Clayton A. Wiley and colleagues have tested the use of PET scans to detect and monitor HIV encephalitis progression (pages 981–989). Using a macaque model, they administered radiolabeled ligands for the peripheral benzodiazepine receptor (PBR), which is abundantly expressed on brain macrophages, and used PET imaging to monitor macrophage infiltration in simian immunodeficiency virus–infected (SIV-infected) macaques. They detected increased ligand binding only in the brains of SIV-infected macaques that developed encephalitis. Moreover, histopathological studies enabled them to correlate various stages of SIV encephalitis with levels of radiolabel uptake and binding, indicating that PET scans can be used to observe progression of the disease in addition to facilitating early detection. The development of such diagnostic tools will be of great importance in the care and treatment of HIV-infected patients.

Overcoming obstacles in antiangiogenesis gene therapy



Antiangiogenic gene therapy strategies against cancer are considered preferable to direct tumor-targeting strategies because tumor cells, with their high somatic mutation frequency, often develop resistance to apoptotic stimuli. Gene therapy in the vasculature, however, also has limitations, including lack of expression specificity and loss of transgene expression due to the body's immune response. Dror Harats, Shoshana Greenberger, and colleagues have overcome these two obstacles by using a modified promoter for an endothelial cell (EC) protein to drive expression of the hybrid apoptotic induction gene *Fas-c* (pages 1017–1024). The promoter confers the necessary specificity and also includes modifications to enhance expression in hypoxic and cytokine-rich microenvironments, such as those found in tumor angiogenic vessels. The transgene produces a receptor that, upon activation by TNF-α, initiates the Fas-induced apoptotic pathway. Treatment of two tumor mouse models resulted in tumor growth rate reduction and decreased tumor size. Histology revealed that EC apoptosis was largely responsible for the antitumor effects. Liver analysis further indicated the apoptotic effects were specific to ECs, and the EC-expression restriction of apoptosis enhanced transgene stability by dodging the humoral response. This approach to gene therapy offers the promise of improved antiangiogenic gene-therapy cancer treatments.

VEGF-A versatility



Lymphangiogenesis and hemangiogenesis are both important processes in angiogenesis, which plays a central role in tumor progression, chronic inflammatory disorders, and most blinding ocular diseases. The VEGF family of growth factors is a key contributor to these processes. Previous studies indicated that VEGF-A is primarily responsible for hemangiogenesis, whereas VEGF-C and -D induce lymphangiogenesis. Whether VEGF-A also plays a role in lymphangiogenesis, however, remains unclear. Wayne Streilein and colleagues addressed this concern by testing the effects of VEGF-A inhibition on both hemangiogenesis and lymphangiogenesis using a mouse model of suture-induced inflammatory corneal neovascularization (pages 1040–1050). By administration of a fusion protein that traps VEGF-A and specifically prevents activation of one of its receptors, VEGFR2, they showed that loss of VEGF-A function fully blocked both hemangiogenesis and lymphangiogenesis after suture placement. Furthermore, VEGF-A inhibition resulted in impaired recruitment of inflammatory cells into the cornea, and selective macrophage depletion in sutured corneas disabled corneal angiogenesis. These findings demonstrate critical roles for VEGF-A and for macrophages in the pathological induction of both hemangiogenesis and lymphangiogenesis and identify important targets for antiangiogenic therapies.

The APCs of autoimmune disease

Automimmune diseases are a complex set of disorders that all result from a failure of the immune system to recognize "self" due to the presence of autoreactive T cells. The body has several means of removing autoreactive T cells, including T cell deletion in the thymus and peripheral tolerance for T cells that escape thymic deletion. These mechanisms, however, fail in some individuals, resulting in an autoimmune response that can be crippling. Many of the factors, both environmental and genetic, involved in autoimmune disease development remain a mystery. Vijay Kuchroo, Hanspeter Waldner, and colleagues used autoreactive transgenic T cells in an experimental autoimmune encephalomyelitis (EAE)–resistant mouse strain and now present data showing that the activation state of APCs plays a role in the development of autoimmune diseases (pages 990–997). T cell number and response were the same in both the transgenic EAE-resistant and EAE-sensitive backgrounds; however, the APCs in the EAE-resistant background had a lower activation state and lower T cell stimulating response than those in the EAE-sensitive strain. Furthermore, innate immune receptor activation of the APCs resulted in EAE development even in the resistant background, providing insight into why viral infection is often associated with the onset of certain autoimmune disorders.