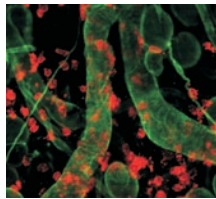




Genetic determination of fasting blood glucose levels

High levels of blood glucose when fasting are diagnostic for diabetes and have been implicated in the pathogenesis of type 2 diabetes. It is therefore hoped that identifying genetic variants that affect fasting glucose levels will provide insight into the pathogenesis of type 2 diabetes. As such, Chen and colleagues analyzed genome-wide association studies for SNPs associated with variation in fasting glucose levels in nondiabetic individuals (pages 2620–2628). One SNP, rs563694, was found to have a statistically significant association with fasting glucose levels in a test cohort of 5,088 nondiabetic individuals from Finland and Sardinia and in a follow-up cohort of 18,436 nondiabetic individuals of mixed European descent. Specifically, the A allele of rs563694 was associated with increased fasting glucose levels, and this increase accounted for approximately 1% of the variation in fasting glucose levels among individuals. Although rs563694 is located between the genes glucose-6-phosphatase catalytic subunit 2 (*G6PC2*) and ATP-binding cassette, subfamily B (MDR/TAP), member 11 (*ABCB11*), the authors speculate that *G6PC2* is most likely to be responsible for the variation in fasting blood-glucose levels; this hypothesis is supported by their analysis of other SNPs and several recently published studies.

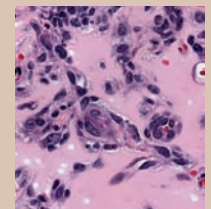
A noninfectious proinflammatory role for neutrophils



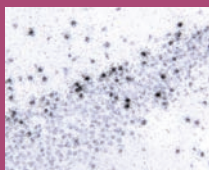
Although neutrophils are best known as one of the first types of cell to respond to invading microorganisms, they also contribute to noninfectious chronic inflammation. One mechanism by which neutrophils mediate host defense is by internalizing microorganisms and degrading them using neutrophil serine proteases (NSPs), but whether NSPs have a role in noninfectious chronic inflammation has not been clearly determined. However, using mice lacking two very similar NSPs, proteinase 3 (PR3) and neutrophil elastase (NE), Kessenbrock and colleagues have now shown that these two NSPs have a crucial role in noninfectious inflammation induced by the subcutaneous formation of antigen-antibody immune complexes (ICs) (pages 2438–2447). When compared with littermate controls, mice lacking NE and PR3 exhibited reduced neutrophil infiltration to subcutaneous sites of IC formation. This was not a generalized defect in neutrophil extravasation to sites of noninfectious inflammation, as neutrophil infiltration in response to application of phorbol esters to the skin was not impaired. Further analysis indicated that NE and PR3 cleaved the antiinflammatory molecule progranulin (PGRN) both in vitro and in vivo and that PGRN administration to wild-type mice inhibited neutrophil infiltration to subcutaneous sites of IC formation. These data led the authors to conclude that NE and PR3 mediate local proinflammatory effects by degrading, and thereby inactivating, PGRN.

Common infant tumor: cellular origin and mouse model

Infantile hemangioma (IH) is a benign vascular tumor that develops in 5%–10% of infants of mixed European descent. Although the life cycle of IH is well defined, with rapid postnatal growth of endothelium followed by slow spontaneous regression of the blood vessels to fatty tissue, the cellular origin of the tumor has remained elusive. In this issue (pages 2592–2599), Khan, Boscolo, and colleagues have identified a stem cell as the cellular origin of IH and developed the first animal model for this common tumor of infancy. Multipotential stem cells were isolated from proliferating human hemangioma tissue based on expression of the stem cell marker CD133. After implantation in immunodeficient mice, clonal populations expanded from single CD133⁺ cells generated human blood vessels that expressed markers of IH. Two months after implantation, the number of blood vessels diminished, and human adipocytes became evident. Confirmation of hemangioma-derived CD133⁺ stem cells as the cellular precursors of IH was provided by the observation that when these cells were marked with GFP and then implanted in immunodeficient mice, the blood vessels that developed contained GFP⁺ cells, as did the adipocytes that appeared later.



CSF metabolites give insight into SIV-induced encephalitis



Soon after an individual becomes infected with HIV, the virus infects cells in the CNS and, during the late stages of disease, can cause dementia and encephalitis. To identify biomarkers of HIV-induced CNS damage and gain insight into the mechanisms underlying this pathology, Wikoff and colleagues used a new global metabolomics approach to analyze how the levels of metabolites in the cerebrospinal fluid (CSF) of rhesus macaques are affected by SIV-induced CNS disease (pages 2661–2669). Using capillary reverse phase chromatography and electrospray ionization with accurate mass determination followed by novel, nonlinear data alignment and online database screening, the authors observed that the level of each of several metabolites was increased in the CSF after the manifestation of SIV-induced encephalitis. These data were then combined with DNA array transcriptomic results, revealing that the increased levels of free fatty acids and lysophospholipids correlated with increased amounts of two phospholipases in the encephalitic brain, one of which (phospholipase A2 group IVC) is known to release some of the fatty acids shown to be affected. The identification of metabolic biomarkers of SIV-induced CNS damage has provided insight into potential mechanisms underlying this pathology, and the authors hope that similar approaches could be used to provide new information about other neurodegenerative and neuropsychiatric disorders.