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In This Issue

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A model for relapsing polychondritis. Relapsing polychondritis is a multisystem autoimmune disease involving cartilage destruction but no known causative antigen. The human lymphocyte antigen HLA-DQ8 has been associated with various autoimmune diseases in humans and may be important in polychondritis. Veena Taneja and colleagues have generated transgenic mice expressing DQ8 in a NOD background lacking endogenous class II molecules (pages 1843–1850). When immunized with type II (CII) or type IX (CIX) collagen, the mice developed clinical and histological symptoms similar to those seen in humans with relapsing polychondritis. Immunization was associated with an active T cell response and production of antibodies to CII and CIX. Transgene-negative littermates did not develop any serological or clinical manifestations following immunization with CII. These mice provide a unique model of relapsing polychondritis with a high disease incidence and involvement of multiple organs that will be useful for studying autoantigens and regulatory cells involved in disease pathogenesis. See figure Chemokine ligand helps fight off fungi. Invasive pulmonary aspergillosis, a severe pneumonia with high mortality, almost exclusively afflicts immunocompromised patients despite intervention with antifungal agents. Chemotactic molecules, including chemokine ligands, are essential in recruiting leukocytes to the site of infection. In order to better understand the role of innate host defense in aspergillosis, Borna Mehrad and colleagues examined a neutropenic mouse model of aspergillosis and observed […]

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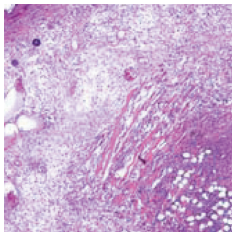

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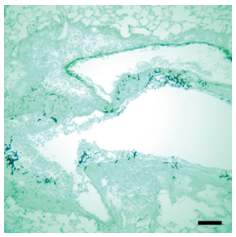
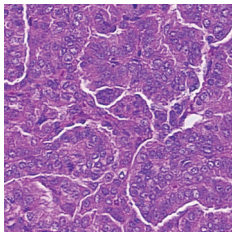
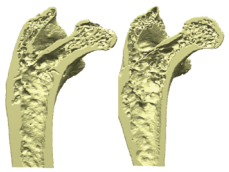


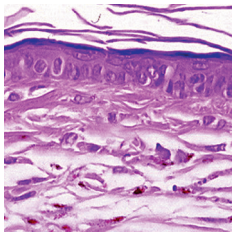
Chemokine ligand helps fight off fungi. Invasive pulmonary aspergillosis, a severe pneumonia with high mortality, almost exclusively afflicts immunocompromised patients despite intervention with antifungal agents. Chemotactic molecules, including chemokine ligands, are essential in recruiting leukocytes to the site of infection. In order to better understand the role of innate host defense in aspergillosis, Borna Mehrad and colleagues examined a neutropenic mouse model of aspergillosis and observed a rapid and marked induction of the chemokine ligand MCP-1/CCL2 in the lung (pages 1862–1870). Neutralization of MCP-1/CCL2 increased pathogen burden and mortality and reduced the recruitment of NK cells to the lungs but did not affect the number of other leukocyte effector cells present. The data indicate that MCP-1/CCL2–mediated recruitment of NK cells to the lungs is a critical and previously unrecognized early host defense mechanism in invasive aspergillosis.



Autophagy active in tumor suppression. Autophagy is a regulated lysosomal pathway whereby long-lived cellular proteins and cytoplasmic organelles are degraded. The *beclin 1* autophagy gene is monoallelically deleted in 40-75% of cases of human sporadic breast, ovarian, and prostate cancer. However, little is known about the role of autophagy in cancer biology. Beth Levine and colleagues studied a targeted mutant mouse model with a heterozygous disruption of *beclin 1* and observed an increase in cellular proliferation and the frequency of spontaneous malignancies and a reduction in autophagy in vivo (pages 1809–1820). The report demonstrates that *beclin 1* is a haplo-insufficient tumor-suppressor gene and suggests that autophagy is a novel and important mechanism in the regulation of cell growth and tumor suppression.



TRPV5: the Ca^{2+} gatekeeper. Ca^{2+} ions play a fundamental role in many cellular processes, and their concentration is kept under strict control to allow proper physiological functions. The Ca^{2+} concentration in blood is tightly controlled despite variations in dietary intake and body demand. René Bindels and colleagues show that TRPV5, a newly identified member of the transient receptor potential family, constitutes the molecular gatekeeper facilitating Ca^{2+} reabsorption in the kidney (pages 1906–1914). Despite enhanced vitamin D levels, mice lacking TRPV5 displayed diminished active Ca^{2+} reabsorption, which caused severe hypercalciuria. In the $TRPV5^{-/-}$ mice, Ca^{2+} reabsorption malfunctioned within the early part of the distal convolution with compensatory hyperabsorption of dietary Ca^{2+}. Furthermore, knockout mice exhibited significant disturbances in bone structure, including reduced trabecular and cortical bone thickness. These data demonstrate the key function of TRPV5 in active Ca^{2+} reabsorption and its essential role in Ca^{2+} homeostasis.



Are your alloantigens histocompatible? Most bone marrow transplants are between MHC-matched/minor histocompatibility antigen (miHA)–mismatched individuals. miHAs with expression restricted to the recipient hematopoietic compartment could be prospective targets for graft-versus-leukemia therapy, but it is unclear whether this would trigger graft-versus-host disease (GVHD). Using established bone marrow irradiation chimeras across multiple miHA-disparate mice, Robert Korngold and colleagues studied the occurrence of lethal GVHD mediated by donor $CD4^+$ T cells in recipient mice expressing only hematopoietically derived alloantigens (pages 1880–1886). Acute GVHD failed to develop in this situation, although these mice did later develop significant chronic GVHD-like epidermal lesions. Importantly, acute lethal GVHD only occurred when nonhematopoietic cells expressed the alloantigens. These data suggest that GVHD across miHA barriers depends upon the expression of nonhematopoietically rather than hematopoietically derived alloantigens for maximal acute target tissue infiltration and injury.