Two strikes lead to leukemia

New genetic mapping studies explain why a certain mouse strain is predisposed to developing fatal leukemia. Turcotte et al., reporting on page 881, identify a point mutation in the transcription factor IRF-8 (interferon regulatory factor 8) that abolishes its function and sets the stage for a second, leukemia-triggering mutation.

The recombinant mouse strain BXH-2 is known to develop first a myeloproliferative disease characterized by enlarged spleens with excess granulocytes, and later a spontaneous, fatal myeloid leukemia. The myeloproliferative disease is associated with a mutation at the Myls locus on chromosome 8, and the leukemia with insertion of an endogenous murine leukemia virus (MuLV) into host tumor suppressor genes.

The offending virus arises from a recombination event between two innocuous MuLV proviruses; they are carried in the genome of BXH mice but, before recombination, cannot produce replicating virus progeny. Eager to understand how the viral integration event was connected to the Myls locus, Turcotte and colleagues scoured the locus for genetic clues. Their search revealed an inactivating point mutation in IRF-8, a transcription factor that regulates interferon-responsive genes. The mutation was found only in strains that are susceptible to getting leukemia.

The IRF-8 mutation explained the myeloproliferative disease in the BXH-2 mice, as IRF-8–deficient mice were previously shown to have a similar phenotype. IRF-8–deficient mice also develop leukemia, but it is not as rapid or as severe as in BXH-2 mice, perhaps because these strains lack the MuLV proviruses. The authors think that the absence of IRF-8 is only the first hit in leukemia development. The excess cell division and faulty immune response caused by the loss of IRF-8, they suggest, must promote recombination that generates a replication-competent MuLV retrovirus that can then insert into the host genome.

This may be a good model for human chronic myeloid leukemia (CML), which progresses from a chronic phase involving granulocytes to a rapidly fatal crisis stage. The authors are now looking for the homologue of IRF-8 in human CML tumors. JEM

Defenseless against the common cold

Epithelial cell dysfunction may explain why people with asthma fare worse than most when infected with common cold viruses. Wark and colleagues show on page 937 that bronchial epithelial cells from asthma sufferers fail to invoke critical antiviral defenses but still provoke inflammation when infected with rhinoviruses—an ideal combination for asthma induction.

Respiratory virus infections often trigger asthma attacks, and these infections are more severe in asthma sufferers than in healthy individuals. Past studies have demonstrated increased virus replication in asthmatic versus healthy subjects and suggested that alterations in cytokine production that favor asthma-promoting T helper (Th)-2 responses might be to blame.

Wark and colleagues now uncover a defect that may provide the initial trigger for virus-induced asthma. They found that bronchial epithelial cells—the primary targets of viral infection—from asthma sufferers supported more virus replication than did cells from healthy controls. The reason for this was twofold: epithelial cells from asthmatic subjects failed to produce the potent anti-viral cytokine interferon-β (IFN-β) and also failed to initiate apoptosis, mechanisms employed by healthy cells to limit virus replication and eliminate infected cells. These defects may be linked, as IFN-β was recently shown to induce apoptosis in virus-infected cells.

How does this enhanced viral replication lead to asthma? The authors show that epithelial cells from asthma suffers, although unable to produce IFN-β, could still secrete pro-inflammatory cytokines, which can recruit asthma-inducing eosinophils and Th2 cells to the lungs. Future experiments are planned to identify the mutation that causes the IFN-β defect. Although several genetic markers have been linked to asthma in the past, so far none are related to IFNs. JEM
Clean living staves off autoimmunity

Autoreactive T cells are harmless until they are prodded into action by exposure to common microbes, according to Yoshitomi and colleagues on page 949. These results may help explain the contribution of environmental factors to human autoimmune diseases like rheumatoid arthritis and diabetes.

While studying an arthritis-prone strain of mouse, Yoshitomi et al. noted that these mice did not develop disease when housed in a microbe-free environment, despite the presence of T cells that could induce arthritis when transferred to nude mice. Only when mice were moved to nonsterile conditions (where they acquired fungal infections) or were injected with β-glucans from fungal cell walls did the telltale symptoms of arthritis appear. Treatment of the mice with antifungal drugs or antibodies that blocked binding of β-glucans to cells reversed this effect, suggesting a direct link between exposure to fungi and development of disease.

The same fungal products that triggered arthritis stimulated dendritic cells (DCs), the cells responsible for activating T cells, to upregulate costimulatory molecules and secrete cytokines. The authors suspect that β-glucans, detectable in the circulation during infection, reach the local lymph nodes where they prompt DCs to activate autoreactive T cells. Once activated, the T cells invade the joints. The group now plans to investigate possible defects in regulatory T cells in this model, as these cells normally keep autoreactive T cells in check. JEM

Too old to help

Old mice have reduced CD4⁺ T cell function but, according to new data from Haynes and colleagues (page 845), the elderly environment is not to blame. Newly generated T cells functioned normally in elderly mice, suggesting that strategies to boost T cell production might be an effective way to improve vaccine efficacy in the elderly.

Previous work by this group has shown that age-related defects in antibody production result from declining CD4⁺ T cell help, not from faulty B cells. By depleting the existing pool of CD4⁺ T cells and forcing the thymus to churn out a fresh supply, the authors show that newly generated CD4⁺ T cells are equally responsive to antigen whether they are produced in a young or an old mouse. This suggests that their functional demise depended on the age of the individual T cell, not on the age of the mouse.

Although there were no detectable phenotypic differences between old and young T cells, the authors postulate that unknown defects accumulate in T cells as they divide and age in the periphery. In young mice, the new T cells produced by the thymus compensate for the reduced function of their elderly predecessors. But thymic output decreases with age, and eventually old T cells outnumber young ones, causing overall T cell function to decline. Production of B cells, by contrast, does not decrease as drastically with age, which may explain why B cells are more resistant to the effects of aging.

Although the nature of the defects that accumulate in aging T cells are not known, recent studies showing an age-related decrease in immune synapse formation between T cells and antigen presenting cells point to potential alterations in plasma membrane components. Haynes suggests that changes in the lipid composition of the plasma membrane—possibly resulting from routine oxidative stress—may make the membranes less fluid and slow down the movement of key signaling molecules into the immune synapse. JEM

Fungal infections trigger arthritis in susceptible SKG mice (arrowheads indicate fungal spores in the lung.)