Research News

New kid on the block

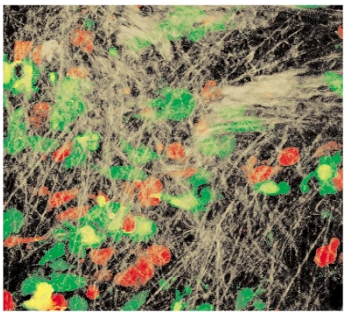
Two clinical studies in the 2 January 2003 issue of the *NEJM* report that natalizumab, a recombinant monoclonal antibody against α4 integrin, is effective in treating autoimmune diseases. In the first study, David Miller *et al.* reported that patients with multiple sclerosis who received monthly injections of natalizumab had a reduced number of inflammatory central nervous system lesions and fewer clinical relapses than controls. Natalizumab blocks the interaction between α4β1 integrin, which is expressed by lymphocytes, and its receptor VCAM-1, which is expressed by the central nervous system endothelium in patients with multiple sclerosis. Blocking this interaction would keep pathogenic T cells from entering the central nervous system. In a second study, Subrata Ghosh *et al.* showed that just two injections of natalizumab increased remission rates in patients with Crohn's disease. In this case, the antibody is likely to prevent the interaction of α4β7 integrin, expressed on T cells, with MAdCAM-1, which is expressed in venules of the gut and gut-associated lymphoid tissues. In these patients, the drug had only partial anti-inflammatory effects, indicating that intestinal inflammation involves other pathways of leukocyte recruitment.

Leptin link

The hormone leptin not only regulates food intake and metabolism, but also activates the T-cell-mediated immune response. Researchers now show that leptin is involved in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS). MS is characterized by a T-cell-mediated autoimmune response against the brain and spinal cord, as well as weight loss. In the 15 January 2003 issue of the *Journal of Clinical Investigation*, Veronica Sanna *et al.* report that just before developing the clinical symptoms of EAE, mice experience an increase in serum leptin levels. This increase correlates with a reduction in food intake and weight loss. The leptin surge is also accompanied by an increased number of T cells and macrophages in the lymph nodes, as well as acute demyelinating lesions in the brain and spinal cord. Acute starvation, which prevents the production of leptin, delayed the onset and reduced the severity of disease. Thus, leptin might be the missing link between energy metabolism and the immune response.

Let's move

Tumors can invade the body through the proteolytic breakdown of the extracellular matrix (ECM). Now, researchers have discovered another method used by cancer cells to overcome tissue barriers: a primitive 'amoeboid' style of crawling. Metastatic cancer cells are highly motile and produce proteolytic enzymes such as matrix metalloproteinases to degrade the ECM. Treatment with protease inhibitors impairs invasive tumor cell behavior but doesn't stop it completely. This might explain why matrix metalloproteinase inhibitors have not proven successful in cancer clinical trials. Katarina Wolf *et al.* studied this phenomenon by observing the movement of proteolytic tumor cells through a three-dimensional fibrillar collagen matrix. In the January 20 issue of the *Journal of Cell Biology*, they report that cancer cells pretreated with protease inhibitors take on a round, amoeboid shape (treated cells here in red, untreated in green). This shape allows them to move by 'gliding' rather than forming more rigid integrin-ECM interactions. The cells were able to squeeze through matrix gaps, and filter through the ECM rather than breaking it down; this style of movement might increase their ability to invade new tissues. The authors will next try to discover the mechanism that controls this "mesenchymal-amoeboid transition."



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Translation, please

Tumorigenesis is commonly associated with defects such as oncogene activation and apoptosis inhibition. Now, Davide Ruggero *et al.* report in the 10 January 2003 issue of *Science* that deregulated ribosome function might also lead to cancer. The authors began studying rRNA modification defects in a mouse model of dyskeratosis congenita, a rare X-linked recessive disease caused by point mutations in the *DKC1* gene. *DKC1* encodes dyskerin, an enzyme that modifies ribosomal RNA. Dyskerin also physically associates with the RNA component of telomerase, hTR, to regulate telomere length. *Dkc1* mutant mice (*Dkc1*^{m}) developed bone marrow failure and cancer in the first and second generations, similar to human dyskeratosis congenita patients. But quantitative fluorescence *in situ* hybridization analysis showed that there were no detectable changes in telomere length in cells of these mice, so lack of telomerase activity could not be the cause of tumor formation. The authors then took another look at the cells of the first- and second-generation *Dkc1*^{m} mice and detected reductions in rRNA processing. They conclude that defects in ribosome function can lead to cancer, perhaps by interfering with translation of factors that regulate cell proliferation.

The flu of the mother

Mice infected with human influenza virus during mid-gestation give birth to offspring with behavioral and drug responses that resemble mental illnesses, report Shi *et al.* in the 1 January 2003 *Journal of Neuroscience*. The mice were hyperanxious, asocial, averse to exploration, and exhibited impaired responses to startling auditory stimuli, inhibition—all features characteristic of autism and schizophrenia. Moreover, these mice responded differently than did wild-type controls to psychoactive drugs, with increased startle response rather than the expected decrease for wild-type animals. The neonatal offspring of infected mothers had no detectable virus in their brains; instead, it seems that the maternal immune response accounted for the behavioral changes. This was confirmed by experiments artificially evoking an immune response without a virus, which led to a maternal response and pups with symptoms mimicking those seen in offspring from the influenza-infected mice. These results jibe with several epidemiological studies hinting at a link between increased risk of mental illnesses and maternal infection. This risk increases during the critical second trimester of pregnancy, a time that coincides with early fetal brain development.

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