Research News

Once bitten...

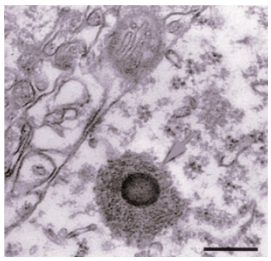
Pathogens transmitted by insect bites cause a variety of diseases, but a recent study suggests that insect bites can also protect against disease. Cutaneous leishmaniasis, spread by the bite of *Leishmania major*-infected sand flies, causes painful skin sores and affects about 1.5 million people, primarily in developing countries. Kamhawl *et al.* developed a mouse model of *Leishmania* infection transmitted by the fly *Phelobotomus papatasi*, and report in the 17 November issue of *Science* that prior exposure to bites of uninfected sand flies confers protection against the disease. The authors found that uninfected sand-fly saliva modifies the tissue environment, producing a long-lasting delayed-type hypersensitivity response. This response induced immunity against *Leishmania* at the inoculation site and resulted in a reduction in the severity of dermal lesions. These findings imply that the exposure of people to the bites of uninfected sand flies influences the incidence and severity of leishmaniasis, and that salivary antigens may be effective vaccine components.

Prion-binding protease

The fibrinolytic protein plasminogen has been identified as the first naturally-occurring protein that selectively binds scrapie prion (PrP^{Sc}), the infectious agent associated with transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease (CJD). Detecting PrP^{Sc} in humans and animals has been a challenge because there is no simple assay to distinguish between it and PrP^{C}, the normal non-infectious cellular form. In the 23 November issue of *Nature*, Fischer *et al.* reveal that plasminogen, a protease that is converted to the fibrin-degrading enzyme plasmin, binds to PrP^{Sc} but not to PrP^{C}. The authors suggest that the interaction between PrP^{Sc} and plasminogen may impair this proteolytic pathway, which is also involved in synaptic remodelling. In addition to diagnostic promise, this discovery may also yield insight into the pathogenesis of prion diseases. Plasmin and PrP^{C} co-localize cultured hippocampal neurons, and plasminogen was found to physically interact with the infectious form of human PrP in brain homogenates of CJD patients. Intriguingly, a lysine residue at the polymorphic codon 219 of PrPC confers protection against disease, and the authors suggest that plasminogen interaction may mediate this protection.

Pesticides that kill more than bugs.

Emory University researchers have provided an excuse to escape your gardening chores, demonstrating that chronic exposure to rotenone, a pesticide commonly used in vegetable gardens, can cause Parkinson disease (PD) symptoms. PD is a common movement disorder resulting from the selective degeneration of dopaminergic neurons in the substantia nigra, a brain region involved in movement control. Although there is a genetic basis for a small number of cases, the majority of cases are 'sporadic' and attributed to environmental factors. In the December issue of *Nature Neuroscience*, Betarbet *et al.* report that rotenone treatment of rats led to the specific degeneration of nigrostraital dopaminergic neurons. These neurons developed cytoplasmic inclusions (picture) similar to the Lewy bodies associated with PD. Another toxin, MPTP, causes PD in humans, and MPTP-treated animals are commonly used as a research model. The authors show that MPTP and rotenone both cause selective degeneration of dopamine-producing neurons by inhibiting the same mitochondrial enzyme, so rotenone may provide a new animal model for testing PD therapies. Although the study does not prove that rotenone causes PD in humans, epidemiological studies have suggested that pesticide exposure is associated with an increased risk of developing the disease.



Stem cells seek and destroy

Neural stem cells (NSCs) can track down and surround intracranial glioma cells, and may eventually be used to deliver therapeutic genes to previously inaccessible malignant brain tumors, scientists report in the 7 November issue of *PNAS*. Aboody *et al.* observed that genetically engineered human or murine NSCs, implanted in areas of rodent brain distal from the tumor site or injected intravenously, target and distribute themselves throughout the glioma tumor bed. Furthermore, the NSCs were able to migrate in juxtaposition to aggressively advancing glioma cells, and were even able to migrate across brain hemispheres toward the tumor. Once localized to the tumor, Aboody *et al.* report that NSCs expressing cytosine deaminase convert a systemically-administered nontoxic prodrug, 5-flourocytosine, to the chemotherapeutic agent 5-flourouracil. This led to an 80% reduction in tumor mass without affecting surrounding normal tissue. The authors suggest that the stem cells are drawn to the tumor by its inflammatory environment. Current therapeutic approaches for brain malignancies are limited to reducing the bulk of the tumor, and are frequently ineffective due to the ability of tumor cells to migrate to other areas of the brain. The engraftable migratory NSCs may allow extended delivery of lethal genes to larger numbers of tumor cells and broader regions of the CNS.

Predicting chemotherapy outcomes though epigenetics

Epigenetic analysis may be a new approach to determining whether cancer patients will respond to certain chemotherapeutics. In the 9 November issue of *The New England Journal of Medicine*, Esteller *et al.* report that promoter methylation of the MGMT gene, which encodes a DNA repair enzyme, enhances the therapeutic effects of alkylating agents and is associated with tumor regression and patient survival. Cell lines in which the MGMT promoter is methylated cannot repair DNA damage caused by alkylating agents such as carmustine, and undergo programmed cell death. Esteller *et al.* analyzed tumor responsiveness to alkylating agents and clinical outcomes in 47 malignant glioma patients, along with MGMT promoter regions using a methylation-specific PCR assay. They observed that the MGMT promoter was methylated in 19 of the 47 tumors (40%). 63% of patients whose tumor DNA contained methylated MGMT promoters had a partial or complete response to carmustine treatment, compared with only 4% (1/28 patients) with unmethylated promoter DNA. The authors suggest that this methylation assay can be used to predict whether cancer patients will be resistant to alkylating drugs, and that it may be possible to increase tumor sensitivity to chemotherapeutics by using agents that inhibit MGMT.

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