Bee toxin takes the sting out of cancer

One challenge in cancer treatment is to balance toxicity with specificity: potential therapies must be toxic enough to damage rapidly dividing cancer cells yet specific enough to not harm other tissues. Cytolytic peptides are small proteins that are drawn to cell membranes and destroy them by creating structural defects that cause the cells to break apart. The peptides have antibiotic, anti-inflammatory and anticancer properties, and their mechanism of action is such that cells cannot easily develop resistance to them. These characteristics make them potentially valuable in cancer treatment if they can be effectively targeted to tumors. Melittin is a particularly toxic but nonspecific cytolytic peptide that naturally occurs in the venom of the honeybee (*Apis mellifera*). In a new study, researchers packaged melittin in nano-spheres to deliver it directly to tumor cells without harming other tissues.

Paul Schlesinger and colleagues at Washington University School of Medicine (St. Louis, MO) had previously developed the nano-spheres, which contain a core composed of perfluorocarbon, an inert

Heinrich Volschenk

component of artificial blood. They are large enough to carry active compounds but small enough to circulate through the bloodstream and attach to cell membranes. The nano-spheres protect melittin from enzymatic degradation and prevent it from harming normal cells. The spheres tend to collect in solid tumors because tumors have greater permeability and retention than do normal cells, and the spheres can also be loaded with molecules that direct them to tumors.

The new study used mice carrying human breast cancer tumors or melanomas. After injecting the mice with nano-spheres carrying melittin, Schlesinger's group noted that tumor growth slowed and some tumors even began to shrink (*J. Clin. Invest.* published online 10 August 2009; doi:10.1172/JCI38842). Growth of breast cancer tumors slowed by ~25%, and melanoma tumors shrank by ~88%.

Having determined that the nano-spheres could reliably deliver melittin to established tumors, the researchers wondered if they would be effective against early-stage neoplasms or even precancerous cells. For these experiments, Schlesinger and colleagues used mice with a precancerous stage of squamous carcinoma. After loading nano-spheres with both melittin and a tumor-targeting molecule and injecting them into mice, the researchers noted an 80% reduction in the proliferation of precancerous cells.

None of the mice in the study showed any signs of toxicity; they had normal blood cell counts and no indications of organ damage. The researchers concluded that their nano-spheres are an effective means of delivering cytolytic peptides that could be developed for cancer treatment.

Monica Harrington

CUNNING PARASITE MANIPULATES IMMUNE SYSTEM

Each year, approximately two million people worldwide become infected with leishmaniasis, a disfiguring tropical parasitic infection that can be fatal. People with the infection often are socially excluded because of their disfigurement. No preventative vaccines are currently available, and though treatments do exist, many endemic areas have limited access to these medicines.

Female phlebotomine sand flies act as disease vectors and carry *Leishmania* spp., the flesh-eating parasites that cause the infection. When inside the fly, the parasites synthesize a gel-like substance that blocks the front end of the fly's midgut. When an infected fly bites a person, it regurgitates this plug, thereby injecting its saliva and the parasite-containing gel into the person's skin.

Though scientists know that this gel plug aids in transferring *Leishmania* into a mammalian host's skin, they understand little about how the plug contributes to the early stages of such infections. Now, researchers led by Matthew Rogers of the Imperial College of Science, Technology and Medicine (London) have reported that the plug is necessary for the early establishment of *Leishmania* infection in mouse skin cells (*PLoS Pathog.* **5**, e1000555; 2009). The plug not only helps sand flies deliver *Leishmania*, but it also tricks the mouse immune system into feeding, rather than killing, the parasites.

When studying *Leishmania* infection in mice, the team found that the flies with larger gel plugs transmitted more parasites to mice than did the flies with smaller gel plugs. The scientists also tested whether, for variable doses of *Leishmania* transmission, the presence of the plug impacted the size of infection in the mice. They found that when both high and low doses of *Leishmania* were transferred, if the plug was present, the mice had much larger infections than when the plug was not present.

Rogers and his colleagues determined that in the early course of infection in mice, the gel plug recruited macrophages to the site of infection and increased the macrophages' expression of the amino acid arginase, much more so than did saline solution or fly saliva. The gel plug 'tricked' the macrophages into producing arginase, which fed the parasites.

The team hopes to use these findings to look for ways to prevent leishmaniasis infection in humans. "Our previous work in mice has suggested that injecting a synthetic version of the gel into people might provide them with some protection against infection, and we would like to explore that further," said Rogers in a press release.

Kirsten Dorans

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Better cloning for zebrafish

Zebrafish are popular models for studies of genetics, development and diseases such as cancer and cardiovascular disorders. To increase their utility in biomedical research, scientists have worked to develop methods of gene manipulation in zebrafish. Previous attempts have had limited success, but Jose Cibelli and colleagues (Michigan State University, East Lansing) have now refined a technique based on somatic cell nuclear transfer.

In the basic technique, DNA is removed from a zebrafish egg and replaced with DNA from a donor. The modified egg is then induced to divide in hopes that it will produce an adult that is genetically identical to the donor.

Cibelli's group introduced several important refinements that allowed the researchers to successfully produce adult fish that expressed the donor DNA and passed it on to their offspring (*Nat. Methods* published online 30 August 2009; doi:10.1038/nmeth1369). First, they used mature eggs and maintained them in an inactive state in Chinook salmon ovarian fluid. Second, they used a laser to ablate the recipient DNA, leaving the cytoplasm intact, and delivered the donor DNA through the micropyle, the same route of entry used by fish sperm. The researchers believe that this procedure could make zebrafish a more useful model for developmental and disease studies.

Prion prediction fulfilled

For the first time, scientists have experimentally shown that a disease-associated prion protein mutation can generate a unique infectious agent that can transmit this disease to a normal animal (*Neuron* **63**, 438–450; 2009). These results support a central aspect of the prion hypothesis—that prion protein mutations can spontaneously generate infectivity.

Prion diseases are a diverse group of infective neurodegenerative diseases that affect animals and humans (e.g., Creutzfeldt-Jakob disease), progressively destroy brain tissue and ultimately kill those infected. Prions, which are thought to cause these diseases, primarily consist of misfolded prion proteins that are coded by the infected animal or person.

In this study, Susan Lindquist of the Whitehead Institute for Biomedical Research (Cambridge, MA) and her team replaced the endogenous prion protein gene in healthy mice with a gene that carries the mouse equivalent of a human mutation associated with fatal familial insomnia (FFI), an inherited prion disease.

Mice with the FFI mutation showed abnormalities that were very similar to those of people with FFI. And when the researchers injected brain tissue from the FFI mice into normal mice that expressed physiological amounts of prion proteins, the normal mice showed the unique FFI pathology. The researchers hope these mice will help to uncover the mechanism of action of FFI.

Preventing unnecessary animal testing

On 10 August, in an effort to prevent unnecessary animal testing, the European Chemicals Agency (ECHA) made its first public call for data on the reproductive toxicity of a new chemical substance that has been registered, as required by Europe's REACH legislation.

REACH (Registration, Evaluation and Authorisation of Chemicals) requires that by 2018, companies register and submit toxicity data on all chemicals sold in quantities greater than one ton in the European Union. If there is not enough toxicity data available on a particular substance, then the manufacturer or importer of the substance must submit a testing proposal to ECHA, the agency responsible for administering the REACH system.

REACH also requires that vertebrate animal testing of the toxicity of new substances be carried out only as a last resort when ECHA officials cannot sufficiently assess the potential harmful effects of a substance on humans. The company that registered this particular compound had proposed two animal experiments on the reproductive toxicity of this substance. When determining whether proposed tests must be carried out, ECHA will take any reproductive toxicity data submitted about this chemical into account. The agency plans to make many more such public calls on new substances in the coming years.