Enzyme encourages cancer's deadly spread

The race for a crucial cancer gene has ended in a photo finish. Research teams in Australia and Israel have both found the long-sought gene for heparanase, an enzyme that cancer cells use to spread through the body.

Physicians have long known that for many cancers, the initial tumor doesn't prove fatal. Instead, that first tumor may shed cancerous cells that make their way into the bloodstream and later act as seeds for new tumors in other parts of the body. These displaced, or metastasized, cells generally turn out to be the real killers.

For a cancer cell to move into blood vessels and then out from them, it must chew through cell layers and the dense matrix of proteins and sugars that surrounds those cells. A large family of protein-cutting enzymes, called proteases, helps in this task.

Yet in the extracellular matrix, considerable amounts of heparan sulfate, a complex carbohydrate, also block the cancer cells. About 20 years ago, scientists showed that another enzyme, dubbed heparanase, cleaves this molecule.

Heparanase normally shows up in certain blood and immune cells, probably helping them travel to sites of infection or inflammation. Cancer cells, investigators have suspected, also use the enzyme to move about the body.

While scientists have measured cancer cells' heparanase activity for some time, it was only last year that Christopher R. Parish of the John Curtin School of Medical Research in Canberra, Australia, and his colleagues succeeded in purifying the enzyme. This allowed them to deduce its amino acid sequence and identify the gene encoding the enzyme. A group led by Israel Vlodavsky of the Hadassah-Hebrew University Hospital in Jerusalem found the gene in a similar manner, and both research teams describe it in the July NATURE MEDICINE.

Parish's team also showed that a highly metastatic line of cancer cells has much more activity of the heparanase gene than do tumor cells that don't spread as easily. The Israeli researchers provided even more direct evidence of the enzyme's importance. They added a working heparanase gene to tumor cells that rarely metastasize and injected them into rodents. Compared with the original tumor cells, the engineered cells spread more readily to multiple tissues and more quickly killed the animals.

Heparanase may do more than simply help cancer cells spread. Heparan sulfate normally sequesters cell growth factors, including ones that trigger blood vessel growth. By degrading the carbohydrate and freeing these factors, heparanase may stimulate the growth of cancer cells, in part by encouraging formation of blood vessels that feed a growing tumor.

Not surprisingly, scientists are eager to develop inhibitors of heparanase. Parish's group has worked with an Australian firm, Progen Industries in Brisbane, on a large sugar molecule called PI-88 that blocks the enzyme's actions. In animals, PI-88 shrinks primary tumors and limits the spread of cancer cells. Progen plans to soon commence tests of the drug in people with cancer.

It may prove simpler to block heparanase than to thwart the many proteases used by cancer cells: There seems to be only one heparanase in the body. "If it's true that we're dealing with only one enzyme, then it's an easier target," says Vlodavsky.

Both Progen and Insight, an Israeli firm with which Vlodavsky collaborates, have started to look for drugs that impede heparanase even more effectively than PI-88. "It's potentially a new generation of antitumor agents," says Jeffrey D. Esko of the University of California, San Diego. "That's exciting."

By limiting immune-cell movement, heparanase inhibitors may also tackle inflammatory diseases or autoimmune disorders. Parish's group is investigating whether immune cells that cause a rodent version of multiple sclerosis can do so without heparanase. —*J. Travis*

Sneaky caterpillar makes an ant's perfume

A butterfly caterpillar that pretends to be an ant—getting real ants to feed and protect it—actually makes its own ant scent instead of just picking up nest odors to fool its victims, says an international team of researchers.

The possibility that caterpillars manufacture odors to infiltrate and rob an ant colony has intrigued scientists for years. *Microdon* flies and several beetles seem able to do it. However, evidence of the ploy in butterflies "has been elusive," in the words of Toshiharu Akino of the National Institute of Sericulture and Entomological Science in Tsukuba, Japan, and his colleagues. In the July 22 PROCEEDINGS OF THE ROYAL SOCIETY OF LONDON B, these researchers argue that they have finally demonstrated it.

"Understanding this system is so important to understanding biodiversity," explains coauthor Graham W. Elmes of Furzebrook Research Station in Wareham, England. He estimates that for every ant species there are 10 hangers-on, totaling a diverse 100,000 species worldwide.

Ant colonies are vulnerable to a variety of swindles, Elmes points out. For instance, a food-stealing beetle can just hunker down and wait out ant attacks until it picks up camouflaging odors.

The interactions can get elaborate. Some Australian ants herd caterpillars up spun-silk pathways into the treetops to graze during the night, then guide them back to special chambers at dawn, says David Lohman, a graduate student at Harvard University.

At "the pinnacle of social evolution," according to Elmes, sit insects like the endangered Eurasian species in the new study, the blue butterfly *Maculinea rebeli*. Its larvae first eat seeds, then drop to the ground. Workers of the ant species *Myrmica schencki* lug home the larvae, which are roughly the size of their own. Then, for 11 or more months, ant nursemaids regurgitate all the food the caterpillars need as they grow many times larger than their foster siblings. "They're just like little cuckoos," says Elmes.

An ant feeds the big, fat butterfly caterpillars just as it does the rightful ant brood.

Ant larvae are silent, so Elmes doubts that caterpillar sounds trigger adoption.

The researchers reared caterpillars away from an ant colony, then dipped them in a solvent to extract surface chemicals. Glass pellets treated with this extract, but not plain pellets, attracted the attention of ants from a lab colony. The ants eventually put most of the pellets on the garbage dump, as they do with dead larvae, Elmes notes. In one case, they took a scented pellet into the nest.

Analyzed with mass spectrometry, the extracts of the outer coating of caterpillars resemble extracts from ants, Elmes says. As caterpillars live in the nest for a while, perhaps picking up its scent, the resemblance increases.

Lohman welcomed the study "as the most detailed to date" on butterfly chemical mimicry although the researchers collected only one set of eggs from the endangered species.

Konrad Fiedler of the University of Bayreuth in Germany says, "For the first time, it's shown that these larvae can mimic the chemical language of ants." The work "has ramifications for conservation biology," he adds. Protecting the butterfly species, or even restoring it, demands sound knowledge of its ant nannies. —*S. Milius*