Mice smoke out key emphysema enzyme

With every breath of life-giving air, elastic fibers in the lungs help those organs expand and contract. For the 2 million people suffering from emphysema, a disease usually induced by smoking, this essential routine doesn't come easily.

From a variety of evidence, emphysema investigators have theorized that the destruction typical of this disease results when large numbers of immune cells migrate to the lungs and release enzymes that degrade elastin, the major protein in the elastic fibers there.

Now, by creating mice that lack one such enzyme and showing that they resist smoke-induced emphysema, scientists have garnered strong support for this explanation of the disease.

"The hypothesis has lasted 30 years, and now we're able, with modern genetic manipulation, to confirm it directly in mammals," says Steven D. Shapiro of Washington University School of Medicine's Barnes-Jewish Hospital in St. Louis.

The results, reported in the Sept. 26 SCIENCE, also add a subtle twist to the old hypothesis. They highlight different immune cells, ones called macrophages, from those on which emphysema researchers had previously focused their studies.

Shapiro's experiments on the genetically engineered mice are "the first to suggest in an animal model that the presence of macrophages is essential to the development of smoke-induced emphysema," says Gordon L. Snider of the Boston Veterans Affairs Medical Center, who has studied the disease for decades.

Shapiro and his colleagues verified that they could induce emphysema in mice by placing the animals in a smoking chamber where the rodents were exposed to the equivalent of two nonfiltered cigarettes a day, 6 days a week, for up to 6 months.

When the scientists examined the lungs of the animals, they found all the characteristic signs of emphysema. "Early on, there's a recruitment of inflammatory cells, predominantly macrophages, and that's followed by a gradual destruction [of lung tissue] and enlargement of the air spaces," says Shapiro.

The researchers then used the smoking chamber to test mice genetically engineered to lack the macrophage enzyme called MME. This enzyme breaks down several proteins, including elastin. The mutant mice did not suffer the lung destruction observed in the unaltered mice.

Another finding surprised Shapiro and his colleagues. They had assumed that the macrophages lacking MME still rushed into the lungs. The scientists found few immune cells in the lungs of the mutant mice, however.

To explain the absence of macrophages, Shapiro suggests that cigarette smoke signals the few immune cells normally patrolling the lungs to release MME. This enzyme, in addition to destroying elastin, somehow attracts more macrophages. Consequently, macrophages without MME do not recruit additional immune cells to the lungs.

Until recently, most research on emphysema centered on elastin-destroying enzymes made by immune cells called neutrophils, even though macrophages make up 90 percent of the immune cells in the lungs, notes Snider.

To investigate the relative contributions of the two classes of immune cells, Shapiro's group is now exposing to cigarette smoke a group of mice engineered to lack an elastin-destroying enzyme made by neutrophils.

Compounds that inhibit enzymes similar to MME and the neutrophil enzymes are under development to treat cancer and may be adapted for the treatment of emphysema, adds Shapiro. He speculates that cigarette makers may one day add such protective compounds to their product. —*J. Travis*

Transgenic plants provoke petition

Genetically modified crops will have a tough row to hoe if some organic farmers and environmentalists have their way.

On Sept. 16, more than 20 groups and individuals filed a petition with the Environmental Protection Agency in a first-of-its kind bid to rescind approvals of a group of plants genetically engineered to produce a particular pesticide. The agency began limited registrations of the plants in early 1995. This year, farmers planted those transgenic crops, including corn, cotton, and seed potatoes, on more than 3 million acres in the United States.

The critics, including Greenpeace International, the Sierra Club, and the International Federation of Organic Agriculture Movements, also want to block future approvals of similar plants. In the petition, they charge EPA with the "wanton destruction" of what they contend is the world's most important biological pesticide. The opponents fear that some insect pests will develop resistance to the pesticide; in addition, cross-pollination between the transgenic plants and their wild relatives could produce wild plants containing genes for the pesticide, possibly leading to resistance in other insects as well.

The plants at the heart of the controversy have been genetically engineered to manufacture one of a group of natural toxins produced by the bacterium *Bacillus thuringiensis* (Bt). Organic farmers commonly treat their crops with the bacterium, which has been registered with EPA as a spray pesticide since 1961, because its toxins have no known detrimental effects on fish, birds, or mammals. Bt toxins also degrade readily in the environment, mainly through exposure to sunlight.

The principal toxins in commercial preparations of Bt are found in protein crystals formed when the bacterium produces spores. The toxins are activated only by digestive enzymes in an insect's gut.

The petitioners contend that the transgenic plants are a threat because they continuously produce massive doses of a modified, already active version of a single Bt toxin, which could lead to the development of resistance in insects within 2 to 10 years. This resistance would make Bt useless, the critics say, forcing farmers to change to harsher chemical pesticides.

Paul Clarke of Greenpeace in New York says the organization considers EPA approvals of transgenic plants to be "an assault upon the genetic diversity of native plants." Field tests of other transgenic crops have resulted in significant migration of the engineered genes into nearby crops or into the transgenics' wild, weedy relatives, he says.

Albert J. Heier, an EPA spokesman, says scientists spent considerable time and effort during the original approval process addressing the potential for development of pesticide resistance. "We used agency experts, as well as outside experts, and we looked at all the data we had," he says.

Heier says registrants of the transgenic Bt plants, typically the companies that developed them, must put together a program that educates growers about how to delay or prevent resistance among pests (SN: 7/8/95, p. 21). Registrants also must monitor insect populations for Bt resistance and submit annual reports to EPA.

Nevertheless, participants in last week's action contend that EPA's efforts have been inadequate. Clarke says that if 90 days pass without a "substantive" response, the petitioners will file suit to force EPA to cancel current registrations of Bt transgenics, as well as hold up future approvals, until the agency completes further study. —*S. Perkins*