Experiment forestalls mouse colon tumors

People with a deadly type of inherited colon cancer may someday benefit from a method that prevents cancer-prone colon tumors in mice. Peter W. Laird, Laurie Jackson-Grusby of the Whitehead Institute for Biomedical Research in Cambridge, Mass., and their colleagues say the finding might eventually lead to the development of a drug that would stave off this cancer in humans.

Familial adenomatous polyposis (FAP) is caused by a mutant gene. People born with the defective gene soon develop hundreds or thousands of small, initially benign tumors (polyps) that carpet the large intestine. If left untreated, such people almost always develop colon cancer before age 40.

Laird and his coworkers started their inquiry with mice specially bred to exhibit a precancerous colon condition. These so-called Min mice carry a defect in the same gene that causes FAP in humans. And like their human counterparts, such mice have intestines littered with polyps.

Researchers had previously proposed that colon tumors thrive with reduced DNA methylation, a natural chemical process that may alter the activity of certain genes, including cancer-causing genes. So the team developed mice with a genetic defect that caused a decline in DNA methyltransferase, an enzyme that adds methyl groups to DNA.

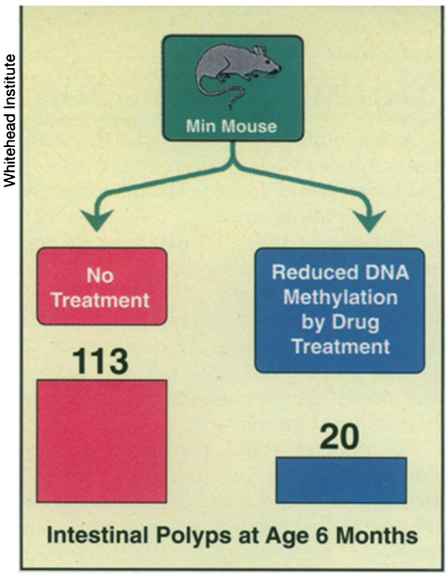
The researchers then bred those mice with the Min mice. The team expected the test mice to sprout more colon polyps than traditional Min mice.

"What we found was exactly the opposite of the prediction," says coauthor Rudolf Jaenisch, also at Whitehead. "When we decrease methylation, we protect these mice against tumors."

At 6 months of age, Min mice that had received no treatment averaged 113 polyps. Min mice with genetically reduced DNA methyltransferase showed, on average, 46 such tumors, a 60 percent reduction.

The researchers wondered what would happen if they slashed the amount of this enzyme even further with a drug called 5-aza-2'-deoxycytidine. When they gave test mice injections of the drug, the average number of polyps per mouse fell to just two, a 98 percent decline.

Whitehead Institute



Using drug treatment alone, the Boston researchers blocked much of the polyp formation expected in young Min mice.

In a separate experiment, researchers wanted to look at the effects of the drug alone, without any genetic tinkering to reduce DNA methyltransferase. When the team gave young Min mice just the drug treatment, they reduced polyp formation to about 20 per mouse, an 80 percent reduction.

The researchers describe their findings in the April 21 CELL.

Nobody really knows how to explain the surprise findings. One theory holds that because of the decline in enzyme concentration, methyl groups become less likely to attach to inappropriate regions of DNA — namely, those containing a tumor suppressor gene. Abnormal methylation may inadvertently shut off the tumor suppressor gene and thus spur a tumor's growth. Further work must reveal precisely what role DNA methylation plays in colon cancer, Laird adds.

In the meantime, the research raises a question about whether treatment to reduce DNA methylation would help prevent colon polyps in humans.

"I think there really is a chance if the enzyme is blocked or blunted that this could delay tumor progression," comments tumor biologist Stephen B. Baylin of Johns Hopkins University School of Medicine in Baltimore.

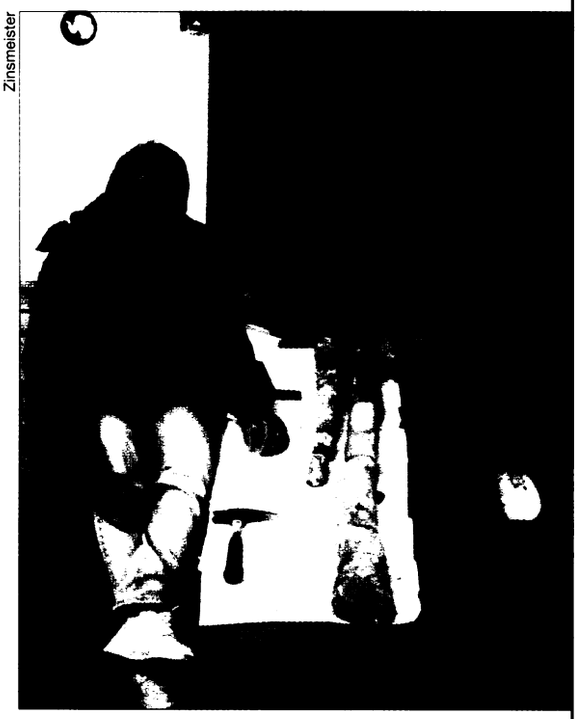
Yet Baylin as well as Laird and his colleagues warn that the drug used in this experiment could prove too toxic to give to healthy young people at risk of developing colon polyps. The new research findings "open up the possibility of searching for a drug that doesn't have these toxic effects," Jaenisch says.

— K. Fackelmann

A Forrest Gump of the dinosaur era

Nature does not always favor the fleetest or most sophisticated. Paleontologists have unearthed the remains of a huge, strangely shaped mollusk from the Cretaceous period that succeeded in spite of its ungainly body.

Zinsmeister



While digging on Seymour Island off the coast of Antarctica, Anton Oleinik (left) and William Zinsmeister from Purdue University in West Lafayette, Ind., discovered a 6-foot-long fossil belonging to a 65-million-year old ammonite called Diplomoceras maximum, *shown between the two researchers. Scientists had found only fragments of the animal in the past and therefore did not realize it had a long, awkward shell shaped like a giant paper clip (see sketch below).*

Relatives of the chambered nautilus, ammonites filled the seas during the Mesozoic era, the age of the dinosaurs. Because 95 percent of ammonites had beautifully coiled bodies, paleontologists have traditionally considered the uncoiled forms as evolutionary dead ends that could not compete well, says Zinsmeister.

Oleinik

But the Diplomoceras *proliferated near Seymour Island, and the new find shows that some grew quite large. "They seemed to have competed as well as their swift and agile cousins. That's why I refer to the fossil as the Forrest Gump of the ammonites," says Zinsmeister.*

— R. Monastersky