SCIENCE NEWS of the week

Nontoxic Drugs Halt Cancer Spread in Mice

Cancers ignore the biochemical commands that normally structure and limit cell growth. Most also develop the unnatural ability to metastasize, spawning proliferative cells that rip through barrier tissues to colonize new sites far from the initial tumor. In fact, these invasive secondary growths are usually the reason cancers kill.

While most drug therapies target secondary tumors with cell-killing chemicals, a few researchers are developing innovative, nontoxic alternatives to merely subvert the biochemical changes that allow colonization. Researchers unveiled several promising recruits in this new war on metastasis at a meeting in Baltimore last week.

Basement membranes cover and separate different tissues in and around organs. These smooth, thin walls also tend to bar loose cells in one area from invading another. Two years ago, George Martin and his co-workers at the National Institute of Dental Research in Bethesda, Md., developed an assay that evaluates metastatic potential by measuring how many tumor cells penetrate gels made of an extract of basement membranes.

At about the same time, the group identified the chemical structure of laminin, a basement-membrane protein that stimulates many cells to attach to the membrane and grow there. Moreover, they identified the precise regions on the laminin molecule where malignant cells bind to basement membranes. Last year, the team uncovered the cascade of biochemical events enabling malignant cells to increase production of an enzyme they need to shear through the collagen that reinforces the membranes.

On the basis of these observations, Martin and his colleagues designed a host of potential anti-metastatic compounds, identifying the most promising with their new assay. They injected these along with cancer cells into mice, then quantified the cancer cells' ability to colonize distant tissues.

At last week's symposium, sponsored by the Johns Hopkins University Center for Alternatives to Animal Testing, Martin described the leading candidates to emerge from this battery of tests. One is a five-amino-acid compound engineered to block the site on the laminin molecule where malignant cells bind. Mice injected with 1 milligram of it and 500,000 malignant melanoma (skin cancer) cells developed less than 10 percent of the lung metastases seen in untreated animals.

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Nude mice injected with human ovarian carcinoma cells 45 days earlier. Thin pair at right, receiving lipoxygenase inhibitor daily, did not develop rapidly proliferating tumors that swelled the bodies of the untreated pair at left.

A second group of candidate compounds, known as lipoxygenase inhibitors, blocks the chain of biochemical reactions required for malignant cells to cut through collagen in basement membranes. In a series of just-completed animal tests headed by Rafael Fridman, these compounds dramatically suppressed the spread of human ovarian carcinoma, a highly metastatic cancer.

Preliminary studies suggest each of the candidate compounds is nontoxic and its effects reversible. That means, says Martin, that to keep malignant cells from asserting their invasive nature, treatment would have to continue as long as these cells survived. In men with the metastatic – and therefore lethal – form of prostate cancer, for instance, treatment might have to continue for life.

Martin, who is now at the National Institute on Aging's center in Baltimore, says he suspects physicians would be most likely to use such a treatment to prevent the spread of newly diagnosed cancers until surgery, radiation or chemotherapy wipes them out. Moreover, his data suggest that by preventing potentially metastatic cells from embedding – and hiding out – in basement membranes, the new drugs might increase the cancer-killing efficacy of more traditional anticancer drugs.

Martin's approach "is a super idea and holds great promise," says Donald O. Allen, chairman of pharmacology at the University of South Carolina School of Medicine in Columbia. Martin cautions, however, that much more research will be needed to show which, if any, of the compounds are safe and effective in humans. *– J. Raloff*

Ozone hole hikes Antarctic ultraviolet

Detailed measurements reveal that increased amounts of harmful ultraviolet radiation reach Antarctica as a result of the yearly ozone hole, the National Science Foundation reported last week.

An initial biological study finds the extra radiation has not caused significant immediate harm to phytoplankton – tiny, free-floating plants that form the base of the marine food web. However, researchers caution that ultraviolet light streaming though the hole could change biological communities in the Antarctic over many years. The hole is a reduction in the ozone layer that normally shields Earth's surface from much of the sun's ultraviolet rays.

Taken last year between Sept. 19 and Dec. 21, the measurements show that biologically harmful ultraviolet light reached twice its normal strength at the surface in October – early spring in Antarctica and the period of greatest ozone loss. At this time, levels of 300-nanometer ultraviolet light were typical of summer for that region, report Dan Lubin and John E. Frederick of the University of Chicago.

Their calculations show that even more radiation would have passed through the hole in 1987, when ozone amounts over Antarctica reached record lows. "Biologically effective radiation levels were a factor of four or five above what they would have been," says Frederick. These levels "were quite a bit bigger than anything down there had ever seen before."

Other researchers will use these ultraviolet records to examine how the ozone hole affects phytoplankton and other organisms, says Osmund Holm-Hansen, head of the polar research program at Scripps Institution of Oceanography in La Jolla, Calif. In work last year near Palmer Station, he found that total ultraviolet radiation – both the normal amount and the extra light allowed by the ozone hole – slowed photosynthesis by phytoplankton in the uppermost meter of water by 25 percent. However, damage drops off with depth. When averaged over 50 meters depth, which is the range for phytoplankton, the reduction in photosynthesis is no longer significant, he says.

Deneb Karentz of the University of California, San Francisco, another researcher who has worked at Palmer, says scientists worry the ozone hole will alter the ecology by promoting organisms that are better adapted to ultraviolet radiation. *– R. Monastersky*