News
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****Researchers identify mechanism that may hold key to safer, more effective cancer treatments

Researchers at The University of Texas Southwestern Medical Center at Dallas have discovered a new mechanism used by some cells to regulate absorption of a vitamin necessary for cell reproduction. Their discovery may lead to the development of safer cancer treatments and new ways to find tumors while they are still very small.

Richard Anderson, Ph.D., and Barton Kamen, M.D., Ph.D., together with Stephen Lacey, M.D., and Karen Rothberg, Ph.D., have identified on the surfaces of certain cells a receptor protein that binds with folates, the generic term referring to an entire class of water-soluble vitamins.

The receptor starts the process of transporting folates into the cell by binding the vitamin tightly. Receptors carrying folate molecules gather inside a tiny pocket, called a vesicle, in the cell's surface membrane. In a process postulated to resemble the opening and closing of an air lock in a space ship, the folate enters the cell when the vesicle closes on the outside and opens on the inside.

Scientists first purified folic acid in 1941. By 1945 they had determined its chemical structure. Researchers then discovered that folates are very potent anti-anemia compounds and cells cannot reproduce without them.

In determining how the folate receptor works, the UT Southwestern research team also found that when cells accumulate a certain amount of folate, they become saturated and will not accept any more. Additionally, saturated cells will not accumulate significant amounts of folate analogues or "anti-folates" used in cancer treatments.

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Since the mid-1940s, clinical investigators have identified and used anti-folates, such as methotrexate, to treat many types of cancer and psoriasis. More recently, methotrexate has been used to treat diseases such as arthritis and asthma. Because anti-folates resemble folates in their molecular structure, they trick the folate receptors into binding with them. Once the anti-folate is absorbed into the cell, it stops cell division and eventually kills the cell.

Because cells will not accumulate any more folate or anti-folate once they reach their saturation point, UT Southwestern researchers theorize that maintaining lower concentrations of methotrexate in the blood for longer periods could be a more effective form of treatment than the large single doses currently used to treat certain types of cancer. The low-dose treatment also produces fewer toxic side effects and is more economical for the patient, said Kamen, the pediatric oncologist in the research group. Kamen added that cancer researcher Sidney Farber determined more than 40 years ago that low-dose daily treatment was effective in the treatment of children with leukemia.

Working with clinical colleagues, Kamen found that lowering the dosage more than 300-fold decreased the methotrexate concentration in the cancer cells only by one-half. Now, more than 140 children with acute leukemia are being treated in Dallas with lower-dose, oral methotrexate. After 25 months of therapy, the treatment results are excellent so far Kamen said.

A parallel national study of nearly 2,000 patients should begin in the spring of 1990 and will compare the effectiveness of the repetitive, oral low-dose methotrexate to continuous intravenous infusions of methotrexate in combination with other standard drugs in the treatment of acute leukemia of children. This study is based on another preliminary investigation by Dr. Kamen's colleagues in Milwaukee, Baltimore and Houston in which prolonged IV infusions of methotrexate and 6-mercaptopurine produced a survival rate better than 90 percent after four years for children with the common type of

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leukemia. "We think the reason for the high survival rate might be that periodically administered low doses encourage cells to maintain an optimum concentration of the drug," Kamen said.

"Before our research, the usual adage in anti-folate therapy was 'more is better.' Now we've discovered that once the methotrexate level in the plasma reaches a certain point, you can't make the cells take up any more drug no matter how hard you try. We've confirmed that the dosage schedule is just as important as the amount of drug given."

For the spring trial, both treatment programs will rely on prolonged exposure to methotrexate, but the oral therapy will involve a lower dose. The doctors hope to determine how low a dose they can use effectively. Another exciting potential application of the UT Southwestern team's research is the use of the folate receptor as a target or marker to identify cancerous tumors while they are small. "Because certain types of cancer cells overexpress folate receptors, we may be able to use radioisotopes to identify tumor cells at a much earlier stage of development than current diagnostic techniques allow," Kamen said.

Dr. Anderson, Kamen and their colleagues also are pursuing their discovery of the novel mechanism the cell uses to acquire folates. "At the very least, this mechanism also explains how cells are able to absorb and concentrate low molecular-weight molecules like vitamins when they are in low concentration in the body," said Anderson, the cell biologist in the research group.

Further research may help close the considerable gap in the scientific understanding of how vitamins enter cells. "This work is very exciting because it reveals yet another mechanism by which cells take up nutritionally important molecules," Anderson said.

This is the second major advance by UT Southwestern researchers in efforts to discover how physiologically important molecules enter cells. Michael S. Brown, M.D., and Joseph L. Goldstein, M.D., were

awarded the Nobel Prize for Physiology or Medicine in 1985 for their discovery of cholesterol receptors. Anderson was also a member of that research team.

In their new research, Anderson and his colleagues demonstrated that cells use a different process to absorb folate than they use to take up cholesterol. The findings of the UT Southwestern researchers were published recently in the Journal of Cell Biology, the Journal of Clinical Investigation and the Journal of Biological Chemistry.

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Note: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.