News
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****Gene amplification implicated in drug-resistant cancer

DALLAS--Chemotherapy almost works against many types of cancer...almost. While chemotherapeutic drugs are effective in curing some cancers, in others the cancer cells cleverly elude the toxic grasp of drugs that should kill them.

Initial doses of a cancer-killing agent are often relatively efficient. Solid tumor growth is slowed as some tumor cells are picked off by the toxic drug. Cancers of the blood, the leukemias, may also regress. Leukemias are often more vulnerable to to chemotherapy than solid tumors since blood cancer cells can be bathed in a poisonous drug.

But cancer cells are capable of mutating out of drug sensitivity with surprising speed. They may remain drug-resistant long after the drug has been taken away.

Cancer researcher Dr. Fred Baskin of the Department of Neurology at The University of Texas Health Science Center at Dallas is investigating how genetic alterations in cancer cells block the effects of drugs. According to Baskin, the answer to the chemotherapy problem is not in looking for another drug to kill cancer--millions of drugs have been screened for their cancer-killing effectiveness. The answer, he says, is to take the 100 drugs that almost work and make them work. He has recently identified an enzyme protein which could provide valuable clues to the resistance of cancer cells to many different drugs.

"It is commonly agreed that cancer cells are made resistant by the drugs, judging from the speed at which the cells become resistant and the frequency with which this happens," says Baskin, whose research is being funded by a grant from the National Cancer Institute. Mutant cancer cells, armed with a drug-resistant property, can grow and replicate in the face of the original drug, or worse, many unrelated drugs. The powerful drug adriamycin, for example, produces cross-resistance to a wide array of drugs. Once the use of this or other drugs is stopped, cancer cells may or may not mutate back to their original state.

(over)

When chemotherapy does work before resistance emerges, the drugs are as toxic to normal cells as to cancer cells. Oncologists work with a so-called "therapeutic index" for cancer drugs--that is, to find a drug that is as toxic as possible to the cancer cell without killing the patient.

Baskin suggests "a little more art and a little less brute force."

The basis of his work encompasses a process taking place within cancer cells. Called "gene amplification," this process appears to be the cancer cell's most common protective mechanism in blocking the effect of toxic drugs. Gene amplification involves an over-production of a particular gene and its neighbors in a chromosome. Where drug-sensitive cancer cells generally have only one gene for a particular purpose, a drug-resistant cancer cell would have hundreds or perhaps thousands of copies of that gene. These gene copies instruct the cancer cell to make proportionately more of their resistance-related protein, commonly a protein which blocks transport of the drugs into the cell.

Chromosomes containing amplified genes are sometimes greatly expanded beyond their normal lengths. Staining techniques reveal elongated regions on these chromosomes called "HSRs" (Homogeneous Staining Regions). HSRs are associated with quite stable resistance. Another detectable form of gene amplification are the "DMs" (Double Minute chromosomes), tiny paired flecks of gene material surrounding normal-looking chromosomes. DMs may arise from the breakdown of long HSRs.

Resistance to methotrexate, the most commonly used chemotherapeutic drug, has been the best studied example of drug-induced gene amplification, says Baskin. Methotrexate kills cancer cells by inhibiting the action of an enzyme, dihydrofolate reductase. This enzyme is essential for the rapid growth of cells. Methotrexate will kill many rapidly growing cells, normal or cancerous, and the more rapidly growing the cell, the more toxic the drug.

But if one wants to give methotrexate for a month, after approximately the first week the cancer cells are now resistant, that is, they no longer respond to the drug. Remarkably, the resistant cancer cells commonly produce a greatly elevated amount of methotrexate's target enzyme, dihydrofolate reductase. Normal cells in the patient's body also have a gene making dihydrofolate reductase. But since normal cells don't appear to amplify genes, the normal cells don't make more of the enzyme to protect themselves against the massive doses of methotrexate now needed to kill the cancer cells. And in methotrexate-resistant cancer cells, where there may be 100s of copies of the gene making dihydrofolate reductase, it would take 100s of times more methotrexate to kill the cancer and the patient couldn't survive this dose. "In the best studies, methotrexate is curing 50 percent of some kinds of childhood leukemia patients, for example," says Baskin. "This also means that 50 percent are meeting with drug resistance before they reach a cure."

Most chemotherapeutic drugs don't have specific enzyme targets like methotrexate. The greatest majority act either generally against many other proteins or against nucleic acids. These drugs, too, induce drug resistance and some unknown gene is amplified when resistance occurs.

How can we prevent gene amplification or its effects?

Baskin and his co-workers have recently identified an enzyme that is present in high quantities in many cancer cells resistant to a diverse group of commonly used drugs, e.g., vincristine, adriamycin and Baker's antifolate. This enzyme, alkaline phosphatase, is a product of gene amplification in many cases of drug-resistant cancer, says Baskin. He is now looking at ways of inhibiting alkaline phosphatase in the hope of making cancer cells less drug-resistant.

"Alkaline phosphatase could be what we're looking for or it could just be the product of an innocent neighboring gene. The real culprit gene could be producing another protein not yet identified, but first alkaline phosphatase will be thoroughly investigated.

"An entire new approach to making chemotherapy work is being opened up by findings on gene amplification. Gene amplification may play a part in the emergence of cancers, as well as in the growth of a wide variety of types of normal tissue."

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