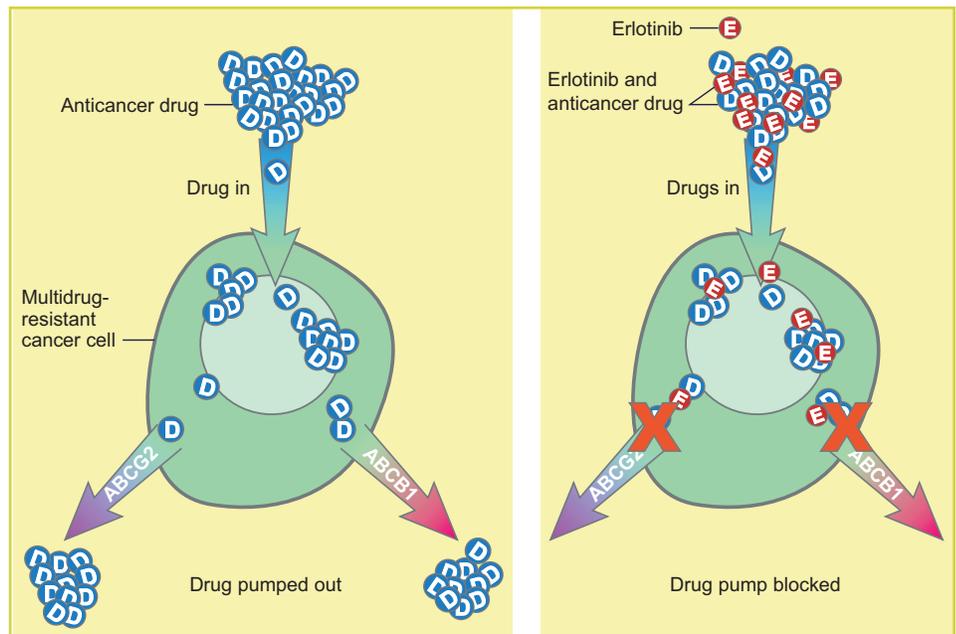


Novel Compounds Line up to Combat Drug Resistance in Cancer Cells

As the war on cancer has intensified and new molecular attacks on cancer cells have been developed, cancer cells have devised innovative ways of defending themselves. Many drugs have been designed or discovered and used to kill cancer cells; in response, these cells are staging new mechanisms to resist the effects of a variety of drugs, a phenomenon called multidrug resistance (MDR). One way cancer cells accomplish this is by catching the intruding drug and throwing it out of the cell before it can act. The arsenal that the cancer cell uses to accomplish this task is a collection of specialized proteins on its membrane called ATP-binding cassette (ABC) transporters.

ABC transporters are a superfamily of proteins that span cell membranes and transfer a wide variety of substances across the membranes in an ATP-dependent fashion. Each transporter translocates specific compounds, and some transporters move more than one compound. In the human genome, 48 different ABC transporters have been identified and divided into seven subfamilies (A–G). Of those seven, three (B, C, and G) come to the rescue of cancer cells by pumping anticancer drugs out of the cell, leaving the drugs no opportunity to act on their targets, including DNA or protein synthesis and assembly of microtubules.



When drug therapy diffuses into cancer cells, ATP-binding cassette transporters B1 and G2 pump the therapy back out. Erlotinib added to the therapy blocks this action.

However, recent experiments have shown that a new drug, gefitinib, can modulate the function of two ABC transporters—ABCB1 and ABCG2—and reverse the MDR mediated by them. ABCB1 and ABCG2 transport a variety of anticancer drugs, including paclitaxel, mitoxantrone, doxorubicin, and methotrexate. As cancer cells may learn quickly how to tackle drugs affecting ABC transporters, more compounds are needed to counter the defense staged by these cells.

As reported in the November 15, 2007, issue of *Cancer Research*, CCR

researchers Susan Bates, M.D., of the Medical Oncology Branch, and Suresh Ambudkar, Ph.D., of the Laboratory of Cell Biology, and their collaborators identified another compound, erlotinib, that increases accumulation of the anticancer drugs paclitaxel, mitoxantrone, doxorubicin, and methotrexate in cells that otherwise would have pushed out the drugs using the ABCB1 and ABCG2 transporters. Erlotinib belongs to the same class of drugs as gefitinib; both were initially developed based on their ability to inhibit epidermal growth factor receptor, a transmembrane tyrosine kinase that is overexpressed in cancer cells

and promotes tumor growth. The authors found that erlotinib stimulated the ATPase activity of ABCB1 and ABCG2 and inhibited their ability to pump chemicals out of the cell by directly competing for the drug-substrate binding site(s) on these transporters. This resulted in increased intracellular accumulation of the anticancer drugs, giving them more time to act and significantly reversing ABCB1- and ABCG2-mediated MDR in these cells.

These findings may be useful for cancer therapy involving anticancer drugs known to be pumped out of cells by ABCB1 and ABCG2. Combination therapy with erlotinib may allow these drugs to more effectively attack and kill cancer cells. This work also paves the way for finding more compounds needed to counter MDR in cancer cells, such as compounds that act differently in modulating ABCB1 and ABCG2 transporters and compounds that can modulate as yet unfettered ABC-C family members.

Reference

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