Abcc10 may be effective in extending the effectiveness of anticancer drugs

May 16 2011

Today's anticancer drugs often work wonders against malignancies, but sometimes tumors become resistant to the effects of such drugs, and treatment fails. Medical researchers would like to find ways of counteracting such resistance, but first they must understand why and how it happens. New findings by Fox Chase Cancer Center researchers identify one protein, Abcc10 (also known as Mrp7), as being intimately involved in resistance to certain drugs used to treat breast, ovarian, lung, and other cancers. The results suggest that blunting the activity of Abcc10 might help counter resistance and extend the effectiveness of these anticancer drugs.

The findings appear in the May 16, 2011 issue of the journal Cancer Research.

In earlier work, Elizabeth A. Hopper-Borge, Ph.D., an assistant professor at Fox Chase, showed that Abcc10 confers resistance to a number of anticancer agents, particularly taxanes, which include paclitaxel (Taxol) and docetaxel (Taxotere). These drugs—originally derived from the Pacific yew tree—work by disrupting cell division, thus arresting the growth and spread of tumors. The initial finding that Abcc10, a member of a ubiquitous family of proteins called ATP-binding cassette transporters, thwarts taxanes' anti-tumor activity was something of a surprise, says Hopper-Borge, because none of the other family members seem to have that ability.

In the new research, Hopper-Borge and colleagues wanted to further

explore, in both cultured cells and mice, the role of Abcc10. They developed a "knockout" mouse, in which the gene that codes for Abcc10 was missing, or knocked out. These mice appeared normal and healthy in every other respect, suggesting that Abcc10 is not essential for overall health and survival.

The researchers isolated cells from the knockout mice and tested the cells' reactions to taxanes and two other anticancer drugs, vincristine and Ara-C. Compared to cells from normal mice that still possessed the gene for Abcc10, the knockout mouse cells were much more sensitive to the drugs.

Abcc10 and its ilk work by pumping drugs out of cells, so one might expect to see the drugs accumulating in cells that lack Abcc10, and that's exactly what Hopper-Borge's group saw. It had been suggested that other proteins might take over for Abcc10 if that protein were knocked out, but the researchers found no evidence suggesting that had happened.

Next, the research team studied the effects of one particular taxane, paclitaxel, on mice and found that the knockout mice were more sensitive to the drug, as reflected in body weight, white blood cell count, and ability to survive escalating doses of the drug.

"After seeing the effects on white blood cells, we decided to look at the tissue types that produce white blood cells to see if we could actually see differences there," says Hopper-Borge. As expected, knockout mice treated with paclitaxel had smaller spleens and thymus glands and underdeveloped bone marrow, compared to normal mice treated with the same drug.

The results provide the first evidence from living organisms that Abcc10 is a cell's built-in protection against the effects of powerful drugs, and raises the possibility of using Abcc10 inhibitors to break down that

resistance and sensitize tumor cells to anticancer agents. The fact that mice lacking the protein have no obvious health problems is encouraging, suggesting that Abcc10 inhibitors could be used in human patients without causing side effects that might be expected to result from interfering with the pump's normal functions.

Several Abcc10 inhibitors already have been identified, but they also inhibit other cellular transporters, which could have deleterious effects. For that reason, Hopper-Borge thinks the best approach may be developing inhibitors that work only in tumor cells or coming up with compounds that modulate, rather than completely inhibit the protein's activity.

But using such treatments in patients is still far in the future, she emphasizes.

"I'd like to stress that we did this work in a mouse model," Hopper-Borge says. "Our results so far suggest that this protein may be a clinically relevant target, but we need to do more studies to find out for sure."

Provided by Fox Chase Cancer Center