

# Cancer cell 'bodyguard' turned into killer

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If you're a cancer cell, you want a protein called Bcl-2 on your side because it decides if you live or die. It's usually a trusted bodyguard, protecting cancer cells from programmed death and allowing them to grow and form tumors. But sometimes it turns into their assassin.

Scientists knew it happened, but they didn't know how to actually cause such a betrayal. Now they do. And it may lead to the development of new cancer-fighting drugs.

Researchers at Oregon State University and the Burnham Institute for Medical Research in La Jolla, Calif., have developed a peptide that converts the Bcl-2 protein from a cancer cell's friend to a foe.

"Now we can force this protein to backstab the cancer cell where it resides," said Siva Kolluri, an assistant professor of cancer biology in the environmental and molecular toxicology department at OSU. He's also the lead author of an article that reported the discovery in the *Cancer Cell* journal in October.

The key to the conversion is peptide NuBCP-9, a string of nine amino acids that bind to Bcl-2 and attack the mitochondria, the powerhouse of cells. Researchers derived it from Nur77, a nuclear receptor that can cause cells to die. To see if it worked outside the petri dish, researchers injected the peptide and its mirror-image molecule into cancer tumors in mice and found that the cancer cells died and the tumors shrank. To their surprise, they also found that a structurally mirrored-image stable peptide worked as well as the original peptide.

The findings could lead to the development of cancer-fighting drugs that target Bcl-2, Kolluri said. He explained that Bcl-2 is an attractive drug target because its levels are elevated in a majority of human cancers and it is responsible for cancer cells' resistance to many chemotherapeutic drugs and radiation.

Michael Melner, a scientific program director at the American Cancer Society in Atlanta, Ga., said the research Kolluri and his team did "will cause a lot of attention in the cancer field."

"These investigators have done a nice job of combining findings of a basic nature as well as the preliminary studies needed to move to a preclinical evaluation. It's unusual for one single paper to make such a large step forward," he said.

Now one of the next steps, Melner said, is for researchers to determine what types of cancer and what stages of the disease this deadly Bcl-2 converter would combat.

Linda Wolff, a leukemia researcher at the National Institutes of Health's Center for Cancer Research in Bethesda, Md., said the researchers' discovery is "rare" in the world of cancer research. She added that it's important for two reasons.

"First, it may lead to a therapy that could potentially be used against many types of cancer," she said. "The reason for that is because it targets Bcl-2, and Bcl-2 is expressed in many types of cancers. So it could be useful in breast cancer and other carcinomas and leukemia, for example.

"The second reason it's important is that although the peptide they studied causes cancer cells to die, its effect on normal cells seems to be quite minimal," Wolff said. "A big problem in cancer research has been getting therapies that don't kill normal cells."

Dr. David Hockenbery, a member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center in Seattle, Wash., said that this new way of altering a protein so it injures a cell rather than merely disables it "is very unusual." He added that this finding would spur researchers to develop drugs or stable peptides that act on Bcl-2 at the Nur77 binding site.

"Quite conceivably, individual cancers may respond better to one type of Bcl-2 inhibitor than another," he said. "In the future, the availability of several targeting approaches against Bcl-2 should be useful in personalized cancer therapies."

Source: Oregon State University

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