

Molecular force field helps cancer cells defend against attack

Much as the famed starship Enterprise would deploy a deflector shield to evade enemy attack, tumor cells are capable of switching on a molecular force field of their own to fend off treatments aimed at killing them. Now University of Florida researchers have found a chink in their armor.

The cells churn out an enzyme that bonds with a protein, creating a protective barrier that deflects damage from radiation or chemotherapy and promotes tumor cell survival. But in laboratory experiments, UF scientists were able to block the union, and the malignant cells died. The findings are opening new avenues of research that could lead to improved cancer therapies, the researchers report this week in the journal *Cancer Research*.

"We have found a gene called focal adhesion kinase which is produced at very high levels in human tumors, and our work has shown this makes the tumors more likely to survive as they spread throughout the body and grow," said William G. Cance, M.D., a researcher at the University of Florida Shands Cancer Center and chairman of the department of surgery at UF's College of Medicine. "It also makes them more resistant to our attempts to kill them. And we're trying to understand exactly why this gene, which is a small enzyme molecule, is very intimately associated with tumor cell survival."

Focal adhesion kinase, or FAK, is commanding increasing attention and has spawned a flurry of research designed to develop new drug therapies, said Cance, who is known internationally for his genetic investigations of tumor survival. These medicines would prevent FAK from linking with the protein known as vascular endothelial growth factor receptor 3, or VEGFR-3. The protein is tied to the growth of channels in the lymph system that serve as cellular superhighways for cancer spread and is found in breast, colon and thyroid tumors.

Cance and colleagues were the first to pull FAK out of human tumors and to show that human cancers make the molecule in large quantities. In 1996, the team was the first to show that if a tumor is prevented from producing the enzyme it dies. The scientists also have identified some protein receptors FAK binds to; VEGFR-3 is the latest they've discovered and represents a "hot area for developing therapeutics," Cance said.

"We've shown that if you disrupt this interaction - if you block the binding of these two proteins - the tumor cells are more prone to being killed," he said.

UF researchers identified FAK's interaction with VEGFR-3 in cell cultures of human breast cancer. Breast cancers that pump out high volumes of FAK and VEGFR-3 are more aggressive tumors, Cance said. The scientists were able to block FAK from binding with VEGFR-3 by introducing a different protein that stopped cancer cells from dividing and caused them to die but spared normal breast cells.

"FAK is a critical molecule, and in the future different ways of targeting either the enzyme itself or targeting the binding between these various proteins will have a major impact on cancer, I believe," Cance said. "We think it's one of the Achilles' heels for tumor cells and you can disrupt it in a number of different ways. For example, we might be able to design drugs that mimic this area of binding and disrupt it in patients."

Because normal cells generate much lower levels of FAK than tumor cells do, treatments could be developed to target FAK and VEGFR-3 at dosages markedly less toxic to healthy tissues yet lethal to cancer.

"We have a therapeutic window," said Cance, the study's senior investigator. "In normal cells we've shown you can knock it out and cells can still resist the loss of expression of focal adhesion kinase, whereas the tumor cells use it as one of their major proteins for survival."

UF surgical resident Christopher Garces, M.D., and UF research assistant professors Elena Kurenova, Ph.D., and Vita Golubovskaya, Ph.D., also were involved in the work, funded by the National Cancer Institute.

"We take our patients, we look at their tumors and we try to find clues to why their tumors grow, why their tumors spread, and we look at the various genes and proteins that make their tumors what they are," Cance said. "So from the patient's standpoint, the more that we can characterize their tumor and understand why it behaves like it does, the greater chance we'll then be able to go back to the patient with therapeutics, and that laboratory bench to bedside is what our research is all about."

H. Shelton Earp III, M.D., director of the Lineberger Comprehensive Cancer Center at the University of North Carolina-Chapel Hill, said, "The Cance lab finding follows on their groundbreaking work showing that human tumors survive in part by overexpressing FAK. This current discovery provides an important clue as to how to exploit this overexpression for the therapy of human cancers."

Steven Frisch, a professor of biochemistry and molecular pharmacology at West Virginia University, said the research raises "the compelling possibility of targeting FAK for a novel cancer therapy."

"FAK plays a major role in the survival of tumor cells in their normal attached state, and, when over-expressed or hyperactivated, it opens a molecular gate that allows tumor cells to detach and metastasize," Frisch said. "The Cance lab's new observations on the VEGFR3-FAK interaction are both of interest for understanding the functions of these two pivotal molecules in cell behavior, as well as sharpening the focus of FAK-based drug discovery efforts to control cancer."

Source: University of Florida

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