

## UF RESEARCHERS IDENTIFY KEY TARGET FOR CANCER THERAPIES

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GAINESVILLE, Fla. — New therapies must target a key protein interaction to destroy aggressive cancer cells' protective force field, University of Florida scientists reported this week at the American Association for Cancer Research's annual meeting in San Diego.

The barrier deflects damage from radiation or chemotherapy, making some cancer cells difficult to destroy, but researchers from UF and the University of North Carolina at Chapel Hill may have discovered why. Their study revealed that mutations in the tumor-suppressing p53 protein lead to overabundance of a second protein called focal adhesion kinase, or FAK, which makes the cells less vulnerable to attack.

"These findings are significant to future cancer research and the development of new therapies," said Vita Golubovskaya, Ph.D., an assistant professor in the UF department of surgery, who presented the findings. "The high correlation between these two markers is critical for predicting patient prognosis."

The next step will involve developing cancer therapies that target this interaction, Golubovskaya added.

Both p53 and FAK are found in low levels in normal, healthy cells. The p53 protein ensures that cells strike a wholesome balance between growth and death. In its normal state, p53 suppresses the FAK protein and weakens the molecular force field around cancer cells. But mutations in the p53 protein can interfere with this regulatory function.

Mutations in the p53 gene are commonly found in patients with cancer, and those with more aggressive forms of the disease boast particularly high levels of p53 and FAK. Most cancer therapies are largely ineffective against the resulting FAK force field, which has been identified in melanoma and most solid tumors of the breast, lung, brain, thyroid and colon.

Scientists are still unsure what causes mutations in p53 and why FAK binds to the damaged protein. But the study revealed that the interaction interferes with the signaling process that normally induces cell death, allowing cancer cells to grow unchecked.

The population-based study centered on 600 patients with breast cancer. UNC researchers, led by Kathleen Conway-Dorsey, Ph.D., an assistant professor of cancer epidemiology, analyzed p53 mutations in tumor tissue samples from the patients. UF researchers then identified the FAK protein in the breast cancer samples and performed a statistical analysis, finding that the p53 mutation is associated with overabundance of FAK.

(MORE)

“Basically, tumors of breast cancer patients with p53 had a higher probability of high expression of FAK,” said Golubovskaya. “We have shown before that FAK overexpression will highly correlate with more aggressive breast cancers.”

The findings provide important information from human tumor samples about how the tumor suppressor p53 acts to negatively regulate FAK expression, said David D. Schlaepfer, Ph.D., a professor of reproductive medicine at the Moores Cancer Center at the University of California, San Diego.

“The results connecting p53 mutations and increased FAK expression further our understanding of the factors that modulate FAK expression during tumor progression,” he said.

Results from the current study could help predict patient prognoses, researchers say. Many patients with mutant p53 and an overabundance of FAK don’t fare well, but new therapies could change that by targeting the protein interaction. The next step will involve identifying the types of p53 mutations that contribute to an overabundance in FAK.

Surgery remains the treatment of choice for patients with cancer, Golubovskaya said. Scientists and surgeons often focus their efforts on determining why cancer developed. Overabundance of the FAK protein can be detected during very early stages of breast cancer, even in pre-malignant tissues. UF cancer researchers are currently developing FAK inhibitors that will pave the way for future therapies.

“We now need to answer questions about why the interaction happens and what regulates it,” Golubovskaya said. “If FAK is overexpressed, how can we stop it early to slow cancer growth and metastasis? Answering these questions together with surgeons and scientists can help to fight this deadly disease.”

The research was supported by Golubovskaya’s grant from Komen for the Cure and a National Institutes of Health grant held by surgical oncologist William Cance, M.D., chairman of the UF College of Medicine’s department of surgery.

Cance and colleagues were the first to pull FAK out of human tumors to show that 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. In 2004, the team found the regulatory region of this protein and in 2005, found the interaction of FAK and p53 proteins. The significance of this finding was reviewed by Golubovskaya and Cance in the journal *International Review of Cytology* last year.

“These findings put together another piece of the complex cancer puzzle and open the way for highly specific molecular cancer therapy that can target the p53-FAK interaction,” said Cance, who also is an associate director at the UF Shands Cancer Center.