

Research yields potential target for epithelial ovarian cancer treatment

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Epithelial ovarian cancer is often referred to as a silent killer: Advancedstage disease has a low survival rate, and in a vast majority of patients, the disease has already spread to other organs at the time of diagnosis because the symptoms are difficult to identify. Fox Chase Cancer Center researchers who are investigating the biological mechanisms behind metastatic epithelial ovarian cancer recently found that an enzyme called focal adhesive kinase (FAK) can play a critical—and previously unstudied—role in the growth and spread of the disease. The research will be presented on Monday, April 7 at the AACR Annual Meeting 2014.

FAK, which is also known as PTK2, helps cells adhere to each other and to other substances It also mediates multiple normal processes that are often disrupted or corrupted in <u>cancer cells</u>, including cell growth, proliferation, survival, angiogenesis and migration. Previous research suggests FAK may play an important role in many types of cancer, including breast, cervical, brain and others, and the drug has been investigated as a diagnostic marker or even a therapeutic target in invasive or <u>advanced breast cancer</u>.

Research done by Fang Xiao, MD, PhD, Research Associate at Fox Chase, and Denise Connolly, PhD, Associate Professor at Fox Chase, led them to identify the importance of FAK in ovarian cancer, but the enzyme wasn't part of their investigation at the beginning.

They initially set out to study a transcription factor called STAT3,



known to be important in the proliferation and survival of cells. Previous studies suggest STAT3 also plays a role in the migration and invasion of tumor cells, and it has been observed in both primary tumors and human ovarian cancer cell lines. But STAT3 itself is not a promising candidate for targeted therapy, Connolly says, because, as a transcription factor, it lacks catalytic activity that could be blocked directly.

"At the beginning of our experiment we manipulated cells to see how STAT3 played a role in ovarian cancer," says Xiao.

Suspecting they could find a related molecule to inhibit the protein's actions in cancer cell lines, Xiao and Connolly conducted laboratory experiments to better understand the underlying biology. They began by trying to target STAT3 by inhibiting Src, a well-known non-receptor tyrosine kinase that plays a role in tumor cell migration and invasion. It also activates STAT3. The researchers found that when they blocked the activity of either STAT3 or Src, the migration of <u>ovarian cancer cells</u> diminished. When they blocked Src alone, they expected to see STAT3 activation drop off, too, but that's not what happened.

"Surprisingly, it increased STAT3 activity," says Xiao. That response suggested the STAT3 protein had some other way to become activated.

The researchers then studied proteins that interacted with STAT3 within focal adhesions, the molecular complexes where cells attached to the extra-cellular matrix. These experiments, which used drug interactions and a RNAi-mediated approach, demonstrated that STAT3's activation both at <u>focal adhesions</u> and in the nucleus depended on FAK.

"We showed that FAK inhibition resulted in dramatic reduction or inhibition of STAT3," which suggests targeting the enzyme could be a way to also inhibit the action of STAT3 in epithelial ovarian cancer.



"What's unique about Xiao's study is that focal adhesion kinase so far hasn't been shown to activate STAT3 in solid tumors," says Connolly, whose research focuses on understanding the biological underpinnings of epithelial ovarian cancer. "My laboratory in general is interested in any pathway that could contribute to <u>ovarian cancer</u> and progression, particularly pathways that could be exploited as therapeutic targets."

Evidence from lab experiments suggests the kinase is a potential target for therapy.

Provided by Fox Chase Cancer Center

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