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Study identifies the process in which heat shock protein 90 contributes to metastases in ovarian cancer

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By incapacitating the activities of a protein that guides other proteins to fold into a stable shapes, Fox Chase Cancer Center researchers shut off the spigot for two proteases that help ovarian cancer cells chew their way out of the tissue they grow in and dig in at new locations.

Building on earlier work that showed that inhibition of heat shock proteins—the protein origami helpers—limited metastases in ovarian cancer in mice, Shane W. O'Brien, MS, Scientific Assistant at Fox Chase and colleagues explored how the heat shock proteins are involved in metastasis. O'Brien will present these findings on Tuesday, April 8 at the AACR Annual Meeting 2014.

Metastatic disease is particularly important in ovarian cancer, the No. 5 cancer killer in women, because it is usually diagnosed only after it has metastasized beyond the ovaries and begun growing throughout the abdomen.

"Ovarian cancer disseminates widely throughout the abdominal cavity and adheres to the colon and other vital organs. That's what really causes mortality," says Denise C. Connolly, PhD, Associate Professor at Fox Chase and senior researcher for the project. "Being able to identify therapeutic targets that actively inhibit the process of metastasis should be beneficial to these patients."

In one set of experiments, the researchers blocked heat shock protein 90 (HSP90) in one of two ways, either using a small molecule drug called ganetespib or with small-interfering RNAs (siRNAs), which are designed to target the production of specific proteins by binding to and degrading the messenger RNA that makes them. Both methods inhibited the ability of ovarian cancer cells to gnaw through a material similar to the extracellular matrix on which cancer cells live. With HSP90 blocked, the researchers examined what was happening to proteases. Proteases break down proteins and peptides, and, among other things, help cancer cells to escape their environment. Previous research had shown that matrix metalloproteinases (MMP) and cathepsin proteases are involved in the metastatic process, but this research identified the specific proteases affected by the inhibition of HSP90—MMP-2 and cathepsin L.

In mouse studies, researchers injected human ovarian cancer cells into a sac that surrounds the mouse ovary. Treating the mice with ganetespib inhibited the growth of the primary tumor and metastases. Researchers found that activities of MMPs and cathepsins fell rapidly with the use of ganetespib, even before the impact of drug on tumor size was apparent.

The researchers used protease-cleavable fluorescent probes to quantify the level of protease inhibition. The probes are designed with a peptide backbone that can only be cleaved by an active protease of interest. When the protease binds to the peptide backbone and degrades it, the probes fluoresce in the near infrared and can be read via fluorescent molecular tomography and image analysis software. By visualizing the mouse in three dimensions, the researchers were able to pinpoint the precise location of the fluorescence.

"That allowed us to watch what happens in real time when you block HSP90," O'Brien said. "We found inhibition of HSP90 could inhibit activation of these fluorescent probes." In conjunction, magnetic

resonance imaging helped determine tumor volume, and necropsies revealed a significant reduction in metastases.

"Inhibiting HSP90 can inhibit the spread of ovarian cancer," O'Brien said. "Being able to disrupt that holds promise in the search for a treatment for the primary cause of death in ovarian cancer patients."

Provided by Fox Chase Cancer Center