Team finds new route for ovarian cancer spread

July 14 2014

Circulating tumor cells spread ovarian cancer through the bloodstream, homing in on a sheath of abdominal fatty tissue where it can grow and metastasize to other organs, scientists at The University of Texas MD Anderson Cancer Center report in *Cancer Cell*.

"This completely new way of thinking about ovarian cancer metastasis provides new potential avenues to predict and prevent recurrence or metastasis," said senior author Anil Sood, M.D., professor of Gynecologic Oncology and Reproductive Medicine and Cancer Biology.

The researchers found the circulating tumor cells (CTCs) rely on HER3, a less-famous sibling of the HER2 receptor protein prominent in some breast cancers, to find their way to the omentum, a sheet of tissue that covers and supports abdominal organs.

HER3's heavy presence on these cells makes it a biomarker candidate and suggests possible therapeutic options to thwart ovarian cancer progression, the researchers noted. "The CTCs are not just a correlation, they seem to have a functionally important role in metastasis," Sood said.

High expression of HER3 in ovarian cancer tumors is associated with shorter survival, the team found.

Ovarian cancer has been thought mainly to spread via direct surface contact with neighboring organs in the abdominal cavity. "However, it also metastasizes to more distant organs such as the liver and spleen,

which seems to indicate arrival through the bloodstream," Sood said.

Ovarian tumor cells are found abundantly in the blood vessels of the omentum and CTCs are present in ovarian cancer patients. However the importance of CTCs was not well understood.

Two mice, one blood supply

The researchers used a parabiosis mouse model, in which two mice are joined at the skin from hip to shoulder. They share blood supply but not lymphatic vessels. "This was the most convincing way to prove that CTCs play a role in metastasis," said first author Sunila Pradeep, Ph.D., instructor of Gynecologic Oncology and Reproductive Medicine.

When the host mouse of each pair was injected with ovarian cancer cells , a primary tumor developed and metastases were found in the omenta of all of the host mice. In the guest mice, metastatic cells and tumors appeared first in the omentum before spreading to other organs.

The team compared gene expression in tumors between the original ovarian cancer cell line and its metastatic version found in the omentum.

Expression of HER3, also known as ERBB3, was highly elevated and activated. The binding protein, or ligand, most likely to cause that activation is NRG1, which was found abundantly on the metastatic cells.

More than 95 percent of CTCs collected from mice with the metastatic version of ovarian cancer were HER3-positive. The more HER3-positive cells the mice had, the greater the tumor burden.

HER3 expression reduces human survival

In tumor samples from 11 ovarian cancer patients, 90 percent of cells were HER3-positive. Tumor cells found in the omental blood vessels of five patients analyzed also had strong HER3 expression.

In a cohort of 217 advanced-stage patients, lower HER3 expression correlated with improved overall survival of 4.9 years compared to 3.15 years for high-HER3 tumors.

Analyzed by itself, HER3 expression was significantly associated with advanced-stage disease at diagnosis. When other variables such as the patient's age, disease stage and tumor grade were controlled for, HER3 expression remained an independent factor for patient survival. They also found:

- HER3 expression to be significantly higher in human stage 3 and 4 tumors compared to stage 1 and 2 tumors.
- Blocking HER3 with siRNA significantly lowered expression of the protein, decreased tumor growth and reduced metastasis in mice.
- Plugging HER3 with the antibody MM-121 reduced the size and number of tumors and frequency of metastasis in treated mice to a tiny fraction of that found in control mice.
- Results were repeated with additional high-grade serous ovarian cancer and colon cancer models.

NRG1 in omentum draws in circulating tumor cells

Experiments showed knocking down HER3 in cancer cell lines in the lab did not have the same effect as it did in the mice. This led the researchers to suspect something present in the omentum microenvironment caused the cancer's dependency on HER3.

The binding ligand NRG1 is more abundant in the omentum than in

other tissues. The team found:

- Colonies of cancer cells treated with NRG1 were triple the size of untreated tumor cell colonies.
- Analysis of 11 human tumors found NRG1 evident both in the tumors and the microenvironment.
- Blocking NRG1 with siRNA in mice with ovarian cancer significantly reduced metastasis.

"The NRG1 ligand expressed in the omentum attracts HER3-positive CTCs," Sood said.

The next steps for the team are to further flesh out the details and understand opportunities to intervene in this cancer-spreading process. The findings provide a rational route to develop new drugs, Sood noted.

Potential uses include using HER3-positive cells as a biomarker for recurrence for patients or for occurrence in women at high-risk for developing ovarian cancer. Maintenance anti-HER3 therapy after treatment could prevent metastasis to the omentum.

Clinical trials are under way for pertuzumab, an antibody that blocks HER2, to explore whether it might thwart both proteins in ovarian and breast cancer. HER2 and HER3 are members of the epidermal growth factor receptor family of receptor tyrosine kinase proteins.

Provided by University of Texas M. D. Anderson Cancer Center