MedicalXpress

Combination peptide therapies might offer more effective, less toxic cancer treatment

August 16 2012

Two studies suggest that two peptide agents used either together or individually with a low-dose of a standard chemotherapy drug might offer more effective cancer therapy than current standard single-drug treatments.

The studies used animal models of breast cancer to show that the peptide combinations dramatically delay tumor onset and progression by both inhibiting tumor growth and blocking the formation of new tumor blood vessels, say the researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) who conducted the study. In addition, the treatments caused few side effects.

The findings are described in two papers published online in the journal *OncoImmunology*. The first paper describes how vaccination with a HER2 peptide followed by treatment with a VEGF peptide inhibitor prevents tumor formation in a transplantable mammary tumor model. The second paper documents how either HER2 peptide or VEGF peptide treatment combined with low-dose paclitaxel effectively kills tumor cells in both the transplantable tumor model and a transgenic mammary tumor model.

"For treating cancer, combination therapies are much more effective than individual therapies, and peptides in combination, whether by vaccination or as therapy, appear to be safer, nontoxic, and taking us closer to a cure," says principle investigator Dr. Pravin Kaumaya,

director of the division of vaccine development at the OSUCCC – James.

Kaumaya, who is a professor of obstetrics and gynecology, of molecular and cellular biochemistry, and of microbiology at Ohio State, led the research that developed the peptide agents. Peptides are short chains of amino acids, and the HER2 peptide and VEGF peptide are short amino-acid chains that mimic full-length HER2 and VEGF molecules.

The HER2 receptor molecule is important for controlling tumor growth in many cancers; the VEGF receptor molecule controls the formation of new blood vessels needed to feed tumors. Both molecules are overexpressed in many cancers.

In the new studies, the researchers investigated whether the peptide vaccine and the peptide inhibitor worked more effectively in combination, and also whether they could synergize with a standard chemotherapy agent, paclitaxel.

The HER2 peptide vaccine is injected into the body where it causes the immune system to generate antibodies to the HER2 receptor. These antibodies then bind to the overexpressed HER2 receptors on cancer cells, preventing them from stimulating tumor-cell proliferation. The VEGF therapeutic peptide binds directly to the VEGF receptor molecule, preventing it from directing the formation of new blood vessels.

In the first paper, the team shows that vaccinating mice with the HER2 peptide before aggressive mammary cancer cells are transplanted into the mice can delay the onset of the tumors. When this vaccination treatment was combined with weekly treatments of the VEGF peptide, tumor growth was significantly delayed. In animals given the VEGF peptide, which is engineered not to break down in the body, 40 percent

of the animals did not develop tumors at all by the end of the experiment.

In theory, Kaumaya explains, such a peptide vaccine could prevent HER2-driven breast cancer from developing in a daughter who inherited the genetic risk for this cancer from her mother. "We could vaccinate a person who doesn't have the cancer and create a memory for HER2 overexpression in her immune system," he says. "Then, when a tumor starts growing and over-expressing HER2, it would crank up her immune system to produce antibodies to shut the cancer down." This study's results suggest that adding VEGF peptide therapy might halt tumor progression altogether.

The second paper lays groundwork for testing peptide therapies in clinical trials. These experiments tested whether the HER2 peptide vaccine or the VEGF peptide therapy would boost the effectiveness of paclitaxel, a standard chemotherapy drug, when the drug is used at low dose to reduce its toxicity.

"We know from other people's work that treating patients with a low-dose chemotherapy agent like paclitaxel primes the system to be more responsive to other targeted treatments," Kaumaya says. Indeed, the team showed that both peptide treatments used individually with paclitaxel delayed tumor growth and development and produced better response rates than either agent without the drug in both transplanted and transgenic mouse breast cancer models.

Importantly, the combined therapies showed no toxic side effects. In contrast, paclitaxel and the current standard anti-HER2 therapy, trastuzumab, both had toxic effects on the heart.

"Our goal is to find a cure by interfering with various cancer-cell pathways using medicines that are not toxic," Kaumaya says.

Provided by Ohio State University Medical Center