Combining two peptide inhibitors might block tumor growth

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A new study suggests that combining two experimental anticancer peptide agents might simultaneously block formation of new tumor blood vessels while also inhibiting the growth of tumor cells.

This early test of the two agents in a breast cancer model suggests that the double hit can stifle tumor progression, avoid drug resistance and cause few side effects, say researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) who developed the agents and evaluated their effectiveness in laboratory and animal tests.

The scientists designed one of the agents to prevent human epithelial growth factor from interacting with HER-2, a molecule that marks a particularly aggressive form of breast cancer. The other inhibitor blocks the action of vascular endothelial growth factor (VEGF), which stimulates the growth of new blood vessels that tumors need to grow beyond a certain size.

The findings are described in two papers published online in the *Journal of Biological Chemistry*. One presents the development of a novel VEGF inhibitor; the other describes the HER-2 inhibitor and the preclinical testing of the two agents together.

"When we combined our peptide HER-2 inhibitor with the VEGF peptide that inhibits angiogenesis, we observed significant additive

benefits in reducing tumor burdens in preclinical studies," says principal investigator Pravin Kaumaya, professor of obstetrics and gynecology, of molecular and cellular biochemistry, and of microbiology, and director of the division of vaccine development at the OSUCCC – James.

The strategy of targeting both HER-2 and VEGF pathways should also discourage the development of drug resistance, Kaumaya says, because it simultaneously inhibits two pathways that are essential for tumor survival. "Combined peptide inhibitors might be appropriate in several types of cancer to overcome acquired resistance and provide clinical benefit," he adds.

Peptide inhibitors consist of short chains of amino acids (the VEGF inhibitor is 22 amino acids long) that conform in shape to the active site of the target receptor. In addition, Kaumaya engineered the VEGF peptide to be resistant to protease, an enzyme, thereby increasing its efficacy. The shape of the peptide HER-2 inhibitor engineered by Kaumaya and his colleagues, for example, is highly specific for the HER-2 receptor. It physically binds to the receptor, which prevents another substance, called epithelial growth factor, from contacting the receptor and stimulating the cancer cells to grow.

Other categories of targeted drugs in clinical use are humanized monoclonal antibodies and small-molecule TKI inhibitors. Both groups are associated with severe side effects and are very expensive, Kaumaya says. "We believe peptide inhibitors offer non-toxic, less-expensive alternatives to humanized monoclonal antibodies and small-molecule inhibitors for the treatment of solid tumors, with the potential for improved efficacy and better clinical outcomes," he says.

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