Molecular scissors help cancer cells break out and spread

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A University of Michigan research team has identified how cancer cells employ a sort of molecular scissors to cut their way out of tumors and begin spreading throughout the body.

This spread of cancer cells, called metastasis, marks a turning point in the progression of the disease, after which treatment and recovery become more difficult.

"We asked how cancer cells cut their way through tissues," said Stephen Weiss, Life Sciences Institute research professor and division chief, molecular medicine and genetics in the U-M Medical School. "They use what we call proteases, a type of molecular scissors. However, there are so many different types of these scissors encoded by the human genome, we wanted to focus our attention on finding the subset used by cancers."

In all forms of cancer, a hallmark of malignancy is the tumor's ability to penetrate the basement membrane, a specialized connective tissue that lines the internal and external surfaces of the body including blood vessels, nerves, muscle and fat. Of the more than 500 enzymes that could be used by cells as molecular scissors, the Weiss team found that three proteases, termed MT1-MMP, MT2-MMP and MT3-MMP, are the most likely candidates that regulate cancer cell invasion.

The tumor cells appear to use these three enzymes to cut their way through the basement membrane, thus allowing cancer cells access to blood vessels which act as conduits for the spread of malignant cells to

distant sites in the body.

"These closely related proteases allow cancer cells to start eating through basement membranes and the surrounding tissues," Weiss said. "This is the first critical step in the malignant process and allows the rapid spread of cancer cells through the body."

By identifying this set of proteases, the studies by Weiss and his colleagues have provided the first known proof that a small set of genes and proteins may underlie the cancer cell metastatic process. While their work is still at an early stage, the researchers are attempting to develop new inhibitors of these proteases so that they could test their importance in animal models of human cancer.

"A cancer cell metalloprotease triad regulates the basement membrane transmigration program," by Kevin Hotary, Xiao-Yan Li, Edward Allen, Susan L. Stevens and Stephen J. Weiss, appears as an advanced online publication in the journal *Genes & Development* and in print on Oct. 1, 2006.

Source: University of Michigan