Researchers identify new cell targets for preventing growth of breast and other tumors

April 23 2008

Researchers at the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill have discovered new targets for cancer treatment aimed at blocking a key step in tumor progression.

This step – the creation of new blood vessels – enables tumors to grow out of control and ultimately spread cancer to other parts of the body.

Targeting blood vessel formation, or angiogenesis, promises to be less toxic than the standard chemotherapy approach that kills cancer cells and normal cells alike. The new tactic has been shown by others to be successful in the treatment of breast cancer and colon cancer with the drug bevacizumab (commercially known as Avastin), which inhibits an important player in angiogenesis, a protein called vascular endothelial growth factor (VEGF).

“There is a large amount of data that shows if you block angiogenesis, you can block tumor growth,” said Dr. Nancy Klauber-DeMore, associate professor of surgery in the UNC School of Medicine and senior author on the study. “But VEGF is not responsible for all of angiogenesis. We wanted to identify more targets for this therapeutic approach.

“The most exciting aspect of this study is that we now have a very large list of potential targets that we will continue to work on for at least the next decade,” Klauber-DeMore said.

A report of the study appeared online this month in the *American Journal of Pathology*. It will be published in the May 2008 print edition of the journal.

Angiogenesis only occurs normally in a few instances, such as wound healing, female reproduction and fetal development. But it also plays an important role in the growth and spread of cancer. New blood vessels provide essential nourishment to cancer cells, allowing them to grow, travel to other parts of the body and form new cancers.

Because tumors cannot grow or spread without the formation of new blood vessels, Klauber-DeMore sought new targets that are produced in excess ('overexpressed') on tumor blood vessels. The hope is that by identifying proteins on these vessels, new drugs may be developed that block these proteins and put a stop to tumor blood vessel growth.

In a technique that took three years to perfect, the UNC researchers microdissected individual vascular cells from frozen sections of five cancerous and five normal breast tissue samples. They scanned the activity of thousands of genes in the isolated cells and then compared the gene activity between the tumor and normal vascular samples. They found 1,176 genes that differed in activity or "expression" between the two cell populations. Of these, 55 genes were overexpressed more than four-fold in blood vessels from breast cancer.

Because proteins that either lie on the cell surface or are secreted from the cell are the easiest targets for drug development, the researchers searched a database to pinpoint the likely cellular location of the proteins encoded by the candidate genes. They found that seven of the genes encoded membrane or secreted proteins. Four of these – namely FAP, SFRP2, JAK3 and SMPD3 – had not just increased gene expression, but also increased protein expression in breast tumor vessels, and thus could be good targets for the development of novel cancer therapies.

The researchers need to do further research to accurately define whether these proteins induce angiogenesis, Klauber-DeMore said. They can then design new compounds and test existing ones to see if they inhibit tumor growth.

“We’ve only looked at seven out of a list of 55 potential targets,” Klauber-DeMore said. “This work points us in the direction we need to go to develop the next generation of angiogenesis inhibitors.”

Klauber-DeMore said that other researchers, led by George Coukos at Fox Chase Cancer Center, are trying the same approach with ovarian cancer, suggesting that this strategy may be applicable to many different tumor types.

Source: University of North Carolina at Chapel Hill