New discovery may advance colorectal cancer diagnosis and treatment

July 22 2014

A Vanderbilt University-led research team has identified protein "signatures" of genetic mutations that drive colorectal cancer, the nation's second leading cause of cancer deaths after lung cancer.

The technological tour de force, described in the current issue of the journal *Nature* as the first integrated "proteogenomic" characterization of human cancer, "will enable new advances" in diagnosing and treating the disease, the scientists concluded.

"It's a first-of-its-kind paper. I think it's a very important advance in the field," said senior author Daniel Liebler, Ph.D., Ingram Professor of Cancer Research and director of the Jim Ayers Institute for Precancer Detection and Diagnosis at the Vanderbilt-Ingram Cancer Center.

The research team, representing Vanderbilt and six other institutions, is part of the Clinical Proteomic Tumor Analysis Consortium (CPTAC), sponsored by the National Cancer Institute of the National Institutes of Health (NIH).

Proteomics is the study of proteins. While many genetic mutations associated with cancer have been identified, it has been more difficult to analyze the structure and function of proteins that actually do cancer's "work." Until now.

The researchers used advanced mass spectrometry techniques to gather proteomic data on 95 human colorectal tumor samples characterized

previously by The Cancer Genome Atlas, a federally funded project to identify genetic abnormalities in cancer.

Data analysis was led by first author Bing Zhang, Ph.D., associate professor of Biomedical Informatics. "Integrating the proteomics data with the vast amount of pre-existing genomic data is a daunting task," Zhang said, "however, it is also the key to turn the data into novel insights."

It is a basic biological principle that DNA – the genetic code – is "transcribed" into messenger RNA, then "translated" into proteins. Yet the researchers found that abnormalities in the genes or even the RNA of the samples did not necessarily "translate" into abnormal proteins.

Similarly, some sections of chromosomes that were "amplified" in the tumor samples did not result in amplified or increased protein levels.

Those that did, however, produced "striking effects," suggesting that proteomics might help identify and prioritize the most "impactful" genetic abnormalities that could be targets for new diagnostic tests or drug treatments, Liebler said.

The researchers also identified five subtypes of colon cancer based on their protein content, one of which was associated with poor outcomes. Proteomics thus may help identify patients who would benefit most from chemotherapy after surgery.

"Our discovery of proteomic subtypes opens the door to protein-based diagnostics that could potentially identify the bad cancers that need the aggressive therapy," Liebler said. "That's what we're really hot on going forward."

Liebler said that the support of the Ayers Institute, established in 2005

with a $10 million gift from Jim Ayers, chairman of FirstBank in Lexington, Tenn., and his wife Janet Ayers, was critical for building the infrastructure for conducting the research.

"Without the Ayers Institute, we wouldn't have been in a position to even apply for the CPTAC program, to be a part of this at all," Liebler said.

"This is exciting news that appears to have tremendous implications for cancer diagnosis and treatment," said Janet Ayers. "Jim and I extend our congratulations to Dr. Liebler and the team working with the Jim Ayers Institute for Precancer Detection and Diagnosis at the Vanderbilt-Ingram Cancer Center.

"These are the kinds of discoveries we hoped for when the institute was launched just a few years ago," she said. "To start seeing results like this so quickly is extremely rewarding."

Provided by Vanderbilt University Medical Center