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Amplifying Cancer's Signal

Editorial Staff
Division of Research, Wayne State University

Amplifying cancer's signal

In the United States and most other developed countries, lung cancer is the leading cause of cancer-related death. Notoriously hard to detect in its early stages, the overall five-year survival rate for the disease is only 14 percent.

Maik Hüttemann, Ph.D., assistant professor of molecular medicine and genetics in Wayne State University's School of Medicine, along with research associate Jeffrey Doan, Ph.D., is working to improve those odds by developing a screening technique for a gene that may be indicative of lung cancer. He is developing a platform technology which utilizes probe ligation and rolling circle amplification to screen for any target gene in many different types of diseases.

To begin, though, the research has centered on cytochrome c oxidase (or COX), the "pacemaker of aerobic metabolism." The level of *COX4-2,* a lung-specific COX gene, directly correlates with the amount of oxygen in lung tissue. "And oxygen levels," Hüttemann said, "can indicate whether tissue is healthy or cancerous."

"In 70 percent of all human diseases, we find a change in the oxygen environment," Hüttemann said. "*COX4-2* levels may be one of the early indicators of that shift in lung cancer tissue."

In healthy cells, the primary type of metabolism is aerobic oxidative phosphorylation in the mitochondria. This type of metabolism produces adenosine triphosphate (ATP), biological energy that fuels most of the body's processes. In cancer cells, however, the predominant type of metabolism is glycolysis, an anaerobic process. Rather than energy, products of glycolysis and associated pathways are required for the proliferating cell. "The switch from aerobic to glycolytic metabolism reflects the cancer cell's need for building blocks for DNA, lipid, and protein biosynthesis," Hüttemann said.

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— Dr. Hüttemann

In an ongoing study, Hüttemann and colleagues found that *COX4-2* is dramatically downregulated in lung cancer. This was measured against the somatic form of the gene, *COX4-1*, which is expressed at similar levels in cancer and non-cancer tissue. The finding holds for various types of lung cancer and lung cancer cell lines – approximately 80 were tested – including a cell culture model simulating carcinogenesis in vivo. "In that model, *COX4-2* is downregulated from the earliest stages," he said. "And, this makes sense because we have shown that *COX4-2* makes cells more aerobic, which is the opposite of what the cancer wants. Therefore, our results suggest that the *COX4-2* gene is a mechanism-based marker for lung cancer."

Hüttemann's current work aims to expand on these findings by investigating expression levels of *COX4-2* with greater accuracy. He is developing probe ligation and rolling circle amplification techniques to detect levels of both COX4-1 and *COX4-2*. "Differences between the levels of these two genes may indicate the presence of cancer."

The techniques entail Hüttemann's lab synthesizing DNA segments, or "probes," that recognize and attach to the target gene. Using DNA polymerase and a circular DNA template, DNA generation amplifies the target of the gene-specific probes 1000-fold.

"Using the DNA extensions, the signals of the two genes are 'amplified,' enabling our lab to locate and quantify the levels of *COX4-1* and *COX4-2* with much greater accuracy than we ever could before," Hüttemann said.

Hüttemann's group is currently working to further develop the techniques into a robust working assay in the lab. Once this is achieved, the next step will be to test it using clinical specimens from lung cancer patients.

Improved ability to measure the levels of the COX genes may result in a test for the early screening of lung cancer. "Only 15 percent of lung cancer tumors are detected in time to do something about it," Hüttemann said. "Our hope with this assay is to develop a robust screening method. In particular, individuals at high risk for developing

lung cancer, including smokers would benefit from such a test."

Although lung cancer is Hüttemann's primary interest, he also aims to develop the assay as a platform technology to screen for any gene.

"Although this step is further into the future, if we can successfully develop the technology to detect a gene of interest and amplify its signal, our ability to screen for specific genes may increase dramatically," Hüttemann said. "This, in turn, may help in the early detection of not only different kinds of cancers, but perhaps other diseases such as neurodegenerative disorders, diabetes and innumerable other health problems with a genetic footprint."

About Dr. Maik Hüttemann:

Dr. Hüttemann received a B.S. and an M.S. in chemistry, and a Ph.D. in biochemistry and molecular biology from the University of Marburg in Germany. He joined Wayne State University in 2000.

To learn more, visit:

http://genetics.wayne.edu/faculty/huttemann/index.php

Maik Hüttemann and his research team are developing a platform technology to screen for target genes in lung cancer and other diseases.