

Genome analysis reveals new protein associated with breast cancer progression

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A novel systems-based approach that combines comprehensive gene expression profiling with genome-wide transcription factor analysis and protein-protein interaction has led researchers to an important genetic marker that can help physicians know which breast cancer patients are at highest risk and will require more aggressive treatment, a research team based at the University of Chicago Medical Center reports in the April 15, 2008, issue of the journal *Molecular Systems Biology*.

The researchers found that high expression of a protein known as H2A.Z, which is associated with the expression of genes within the nucleus, can help physicians predict which patients are most at risk for disease spread and death. It could also serve as a new target for therapy.

“Elevated H2A.Z expression is significantly associated with metastasis and shorter survival, and it could quickly help doctors make better predictions and treatment choices for their patients,” said study director Kevin White, PhD, professor of human genetics and director of the Institute for Genomics and Systems Biology at the University of Chicago and Argonne National Laboratory. “It could also provide clues to new therapies.”

“But, perhaps more important,” he added, “we think we have developed an integrated approach to genomic analysis that can be applied to a wide range of cancers.”

Instead of a standard whole-genome analysis, looking for genetic

variations that correlate with disease risk, White and colleagues integrated multiple genetic technologies to measure the effects of estrogens, which play a crucial role in many breast cancers, on multiple cellular pathways, what they refer to as a “transcriptional regulatory cascade.”

The female hormone estrogen acts by binding to the estrogen receptor, which carries the hormone’s signal to a cell’s nucleus, where it activates many other genes. One of those genes is a known cancer-related gene called c-MYC, which in turn regulates its own cascade of gene targets.

White’s team set out to map out the many sequential genetic events that occur in breast cancer cells after estrogen binding, using a series of innovative technologies. They ultimately found that estrogen-stimulated c-MYC enhanced production of H2A.Z, which altered the positioning and activation of various genes in ways that increased the odds that a cancer would spread to the lymph nodes and ultimately to distant sites, often resulting in the patient’s death.

This is not a simple process. In tumor cells from patients with estrogen-dependent breast cancers, the researchers found estrogen affected 1,615 genetic regions. One of those was the promoter for the gene for c-MYC, which, when activated, could bind another set of overlapping 311 genetic regions.

Both estrogen and c-MYC interact with the gene for H2A.Z, leading to increased production of this protein in breast cancer cells. When the researchers looked at tumor tissue samples collected from 500 patients, they found that elevated levels of H2A.Z were highly correlated with the spread of the cancer to lymph nodes and decreased patient survival. Adding H2A.Z expression to other known risk factors provided “significant prognostic information,” the authors note, “beyond what these factors alone provide.”

“Although it has been implicated in genomic stability and gene transcription, H2A.Z has never been reported to be associated with cancer,” said White. “We would not have found this clinically important factor without taking such a large-scale integrated approach.”

“We suspect this integrated systems approach will lead us to a number of previously unsuspected genes that play a role in disease initiation and progression,” he said. “Many of these could become targets for new treatments.”

Source: University of Chicago

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