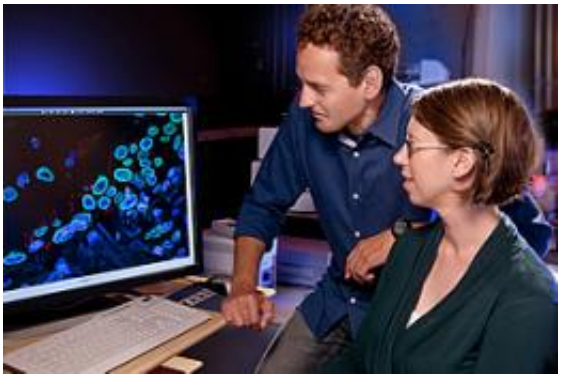
Researchers identify potential biomarker for cancer diagnosis

July 9 2013



From left to right: Martin Hetzer, Professor, Molecular and Cell Biology Laboratory and Emily M. Hatch, Research Associate. Credit: Courtesy of the Salk Institute for Biological Studies

Scientists studying cancer development have known about micronuclei for some time. These erratic, small extra nuclei, which contain fragments, or whole chromosomes that were not incorporated into daughter cells after cell division, are associated with specific forms of cancer and are predictive of poorer prognosis.

In a new study, published on July 3, 2013 in *Cell*, a team of scientists at the Salk Institute for Biological Studies finds that disrupted micronuclei, which can trigger massive DNA damage on chromosomes, might play an even more active role in carcinogenesis than previously thought. They also found that disrupted micronuclei can be an objective biomarker for

the genetic instability common to many solid tumors, including non-small cell lung cancer (NSCLC).

"Our study shows that more than 60 percent of micronuclei undergo catastrophic dysfunction in solid tumors such as NSCLC," says Martin Hetzer, a professor in Salk's Molecular and Cell Biology Laboratory and holder of the Jesse and Caryl Phillips Foundation Chair. "We identified disrupted micronuclei in two major subtypes of human non-small cell lung cancer, which suggests that they could be a valuable tool for cancer diagnosis."

As a result of a glitch in cell division, whole chromosomes can sometimes end up outside the nucleus. During normal division, a cell duplicates its chromosomes and sends them to two newly formed daughter cells. One set of chromosomes goes to each daughter cell, but, for a variety of reasons, the chromosomes sometimes are not divided evenly, with one cell receiving an extra set and the other cell coming up short. These lagging chromosomes, which acquire their own nuclear membrane and are called micronuclei, often don't make it to the nucleus, ending up elsewhere within the cell and becoming wrapped in their own nuclear envelope. Micronuclei appear at a higher frequency in cancer cells.

In their study, Hetzer and his team found that during a certain phase of cancer cell division previously undetected defects in the nuclear lamina, filaments that provide support and stability to the cell's nucleus, cause the nuclear envelope surrounding micronuclei to catastrophically collapse, leading to the loss of basic nuclear functions such as replication, transcription, and DNA damage recognition and repair. More than 60 percent of micronuclei undergo this irreversible loss of function following nuclear envelope collapse, precipitating cancer-causing aneuploidy, the accumulation of an abnormal number of intact chromosomes within cancer cells.

"In the micronuclei," says Emily Hatch, a research associate in the Hetzer laboratory, "we saw holes developing in the lamina. We think the membrane has no support at the site of these holes, so it weakens and ruptures. We don't fully understand why this happens in micronuclei."

Previous studies have found that the DNA damage and arrest of gene transcription caused by nuclear envelope collapse can promote aneuploidy. This damaged DNA can then enter the next generation of daughter cells and undergo chromothripsis, a rearrangement of genomic information in one chromosome, which leads to massive DNA damage and the formation of tumors.

In the current study, Hatch identified biomarkers to identify disrupted micronuclei, which may greatly increase pathologists' ability to recognize these structures in tumor sections. Currently, few objective markers exist to detect genomic instability in solid tumors, she says, although several cancers rely on the identification of aneuploidy.

"Our ability to identify disrupted micronuclei in solid tumors suggests a new way to evaluate aneuploidy in these tissues," adds Hetzer, who says that it is not clear if all or how many cancers are affected by disrupted micronuclei. In addition to NSCLC, scientists believe that micronuclei disruption may play a role in bone cancer, melanoma and other forms of lung cancer.

Because they are strongly correlated with mitotic errors, micronuclei are regarded as an accurate indicator of genomic stability and aneuploidy, two hallmarks which characterize non-small cell lung cancer. Hetzer's team found disrupted micronuclei in pulmonary adenocarcinomas, the most common form of primary lung cancer and roughly 50 percent of all NSCLCs, and squamous cell carcinomas, which make up about 30 percent of NSCLCs.

Provided by Salk Institute