Researchers connect haywire protein to breast cancer, leukemia

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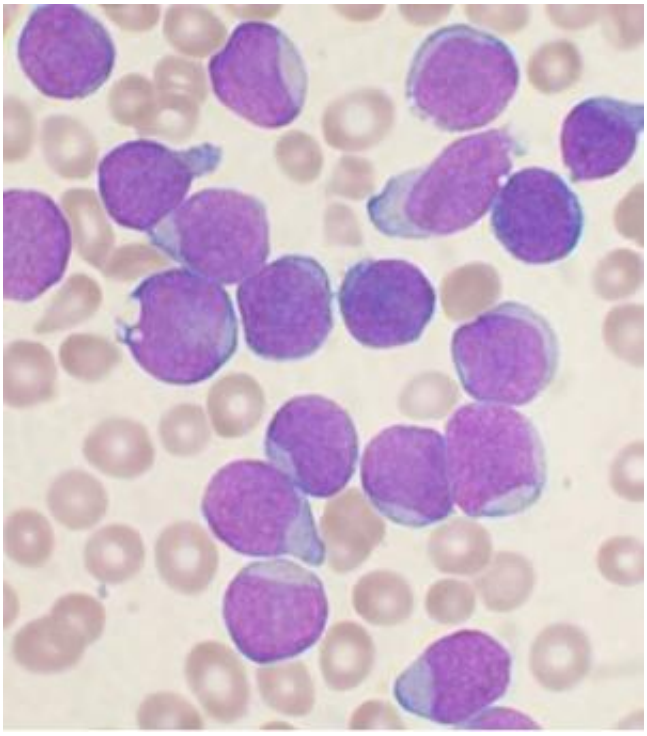

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A new study led by scientists at The Scripps Research Institute (TSRI) sheds light on the cause of some cancers, including breast cancer and leukemia.

In the new study, the researchers found that too much of a key protein,

called cyclin E, slows down DNA replication and introduces potentially harmful cancer-linked mutations when cells divide.

"Overexpression of cyclin E is one route to cancer," said TSRI Professor Steven Reed, senior author of the new study.

The findings were published May 7, 2015 in the journal *Current Biology*.

A Good Protein Gone Bad

A cell must copy its DNA before dividing into two identical daughter cells. Each round of cell division comes with the risk of DNA replication errors—the chance that some areas might be duplicated, deleted or out of order.

In normal cells, cyclin E binds to and activates an enzyme, Cdk2, which begins the DNA replication process. Cells need just the right amount of cyclin E to divide properly. Unfortunately, some genetic mutations can cause too much cyclin E to be produced in cells.

Reed and his colleagues at TSRI originally discovered cyclin E, and previous studies led by Reed's lab showed that abnormally high levels of cyclin E are associated with chromosome instability, increasing the chances that a chromosome will acquire more mutations as it divides. Researchers have found that cyclin E is frequently overexpressed in cancer cells and that overexpression is linked to a decreased survival rate for breast cancer patients.

Until this new study, scientists did not know exactly how cyclin E introduces chromosome instability and errors into DNA.

DNA 'Tug-of-War'

The researchers investigated the role of cyclin E by comparing normal human mammary cells with human mammary cells forced to overexpress cyclin E at the same levels seen in some breast cancer cells.

In an experiment spearheaded by TSRI Research Associate Leonardo Teixeira, now at the Brazilian National Cancer Institute, the researchers found DNA replication took significantly longer in the cyclin E-deregulated cells. In fact, the cells seemed to enter the next stage of cell division before the DNA was even done replicating. Intriguingly, they found that a small number (16) of very specific regions on the chromosomes frequently had failed to complete replication.

The researchers then screened the cyclin E-deregulated cells for errors later in the cell division process, when the original cell begins to pull apart into separate daughter cells. Visualizing chromosomes marked with a fluorescent protein, they found that the chromosomes of the daughter cells of the cyclin E-deregulated cells stuck together in the spots where replication had not finished.

"You could see a tug-of-war going on," said Reed. "That would cause either the chromosome to tear or both chromosomes to go to one side." The researchers spotted abnormal DNA "bridges" tying daughter cells together—they even saw cells where chunks of chromosomes ripped away and floated nearby. After these abnormal divisions took place, a third of the cyclin E-deregulated cells showed DNA deletions at the specific regions identified previously as having a tendency to not finish replication prior to cell division.

The Link to Cancer

Next, the researchers investigated how the genetic instability from DNA deletions in cyclin E-deregulated cells could contribute to cancer.

Interestingly, many of the sites with DNA deletions were areas in which DNA was already known to be fragile or difficult to replicate.

Using a database of tumor DNA sequences, they found that six of the 16 DNA regions they had identified in their cell-based studies showed damage in breast tumors that could be directly linked to cyclin E overexpression. One area commonly damaged in cyclin E-deregulated cells even matched up with an area commonly rearranged in a type of leukemia called mixed lineage leukemia, where cyclin E had already been shown to be a contributing factor.

One of the unanswered questions posed by this work is how cells are allowed to divide before all the chromosomes are completely replicated. It had been believed that "checkpoints" exist to prevent such accidents from happening. Reed believes that these unreplicated regions are small enough to bypass the cellular "checkpoints" and keep cells dividing under such circumstances and accumulating potentially harmful mutations.

Reed said the next step for his team is to sequence the entire genomes of cells that undergo damage from cyclin E overexpression to understand exactly how the deletions contribute to cancer.

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