Discovery may result in new test to determine predisposition to cancer

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Researchers at UCLA's Jonsson Comprehensive Cancer Center have developed an assay that may be used to help identify new genes that can predict a predisposition to cancer.

The study, published in the April issue of Radiation Research, was done in yeast and mammalian cells.

Cancer cells show persistent genetic instability and the researchers, led by Robert Schiestl, have discovered a mechanism that switches on that genetic instability. If they can uncover and understand the molecular pathways at work in promoting genetic instability, they may be able to develop ways to switch that mechanism off, restoring stability.

"We all have several hundred cells in our body that go crazy every day, and they're taken out by our immune system," said Schiestl, a professor of pathology, radiation oncology and environmental health sciences and a Jonsson Cancer Center scientist. "What's important is that those cells don't grow and spread and invade other regions of our body. Cancer cells are able to grow, spread and invade because the continued genetic instability can disturb the cellular program and create a growth advantage. Unfortunately, the immune system is not very effective at taking cancer cells out."

The assay determines the efficiency of the repair mechanism when DNA suffers a double-strand break, when both strands in the double helix are severed. These breaks cause genetic instability and are particularly

dangerous because they can lead to genome rearrangements or deletions of certain genes that, when gone, result in cancer.

"Every cell has double strand breaks all the time," said Schiestl, senior author of the study. "It is how the cell tries to fix these breaks that is key, the capacity and the efficiency of the repair so no further harm occurs."

A cell that can't efficiently repair itself could result in cancer.

In the study, researchers irradiated cells to create double strand breaks. They wanted to determine if a double strand break occurs in one area of the DNA is the instability limited to that area or also evident elsewhere. The standard thinking was that the genetic instability would be localized to the area of the break. However, Schiestl and his team showed that a break in one area has an "in trans" effect, meaning the instability could surface anywhere.

"What we have shown now in this paper is that DNA damage at one position in the genome, causes a certain mechanism of genetic instability all over the genome," Schiestl said.

Specifically, the team irradiated cells and then transformed them with a DNA fragment that detects the efficiency and the accuracy of double strand break repair. The key in this experiment was that the DNA fragment was not irradiated. In this way, the researchers could demonstrate that the radiation triggered a specific mechanism of double strand break repair in the DNA fragment that did not receive any radiation. The effect was still noticeable after almost all the DNA damage the radiation caused in the cells was repaired, showing that the mechanism that is induced by the radiation is independent of the actual damage caused by the radiation.

Schiestl had previously shown that a single DNA double strand break

also induces genetic instability all over the genome at sites that are not damaged, again a proof that double strand breaks induce genetic instability in trans.

Interestingly, many cancer cells show an elevated induction of the specific DNA double strand break repair mechanism found induced in trans in this study, as if the cancer cells had this mechanism somehow induced and were not able to switch it off.

"Now we have to identify the mechanism of the pathway, identify the genes involved in inducing that pathway and that might give us targets that we can inhibit with drugs to try to reduce genetic instability," Schiestl said. "That could lead to a cancer treatment. Any time you can stop the growth of a cancer, you've won. It doesn't damage other tissues or spread to other organs. We might be able to stop the instability before it results in cancer."

Source: University of California - Los Angeles