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Replication at DNA damage sites highlights Fanconi anemia and breast cancer proteins

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While Fanconi anemia (FA) is a rare and dangerous disease, new laboratory research at The University of Texas M. D. Anderson Cancer Center shows it may lead researchers toward clues in more common diseases, including highly hereditary types of breast cancer.

In a study published in the Sept. 11 issue of the journal *Molecular Cell*, scientists report that recruitment of proteins to DNA damage sites is controlled by replication in both FA and BRCA cancer proteins.

Lei Li, Ph.D, professor in Experimental Radiation Oncology at M. D. Anderson, and corresponding author of the study, has spent much of his 15-year career studying how the body repairs DNA damage. He says DNA crosslinks are the most severe type of DNA damage; they're actually turned against cancer in certain drugs, including cisplatin.

Answers have been elusive

People with FA, a hereditary disease, are extremely sensitive to DNA crosslinks and at a very high risk for cancer. How the Fanconi pathway protects cells from DNA crosslinks and whether FA proteins act directly on crosslinks has remained unclear despite extensive research.

"Our lab has been working for almost 10 years on why FA cells are so sensitive to crosslinking," Li said. "We've known it must have something to do with how they deal with DNA crosslinks, but this is the first time

we've been able to pinpoint a reason for some of them."

FA involves 13 genes; a mutation in any one of them can cause the disease. Three of the FA genes recently were found to be identical to breast cancer susceptibility genes BRCA2, BACH1 and PALB2.

"This led us to begin to examine breast cancer genes, since we thought they might have something to do with the repair of DNA crosslinkers," Li said.

Researchers developed a novel genetic technique, eChIP, a chromatin-IP-based strategy, to examine FA proteins with DNA crosslinks.

"The model scientists have been following for many years is that all 13 genes must work together to deal with DNA crosslinks, that there must be some kind of cascade or chain reaction," Li said. "We developed a new genetic technique to look specifically at what proteins are present at the crosslinks."

New method yields answers

Using this new tool, researchers found that all the FA genes are present in the site of a crosslink. This is the first time FA proteins have been linked directly with DNA crosslinking damage at the molecular level.

"The surprise is that the breast cancer proteins, although they are present at crosslinks, must have DNA replication at the crosslinks," Li said. "If there is a DNA lesion on the genome but no DNA replication, the canonical FA proteins are used to deal with the damage. The breast cancer-related FA proteins are taking care of the DNA lesion that stops DNA replication."

Li said this leads to a new paradigm that there must be two separate

subgroups or subpathways within the 13 FA genes.

"The major implication of this study is that now we have a new working model," Li said. "This provides a new direction for future research of breast cancer proteins and DNA damage response in general.

"Our next step is to continue to look at how FA proteins and the subgroup of breast cancer-related proteins help protect cells from DNA crosslink damage. And, in a more general sense, how these cellular mechanisms eventually may help us minimize mutations that ultimately lead to cancer."

Source: University of Texas M. D. Anderson Cancer Center (news : web)

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