Newly identified proteins critical to FA pathway DNA repair function

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Identification of two new proteins in the Fanconi anemia DNA repair pathway may help explain genetic instability in people with Fanconi anemia and how otherwise healthy people are susceptible to cancer from environmentally triggered DNA damage.

A study in the March 26 *Molecular Cell* adds another layer of complexity to the multifaceted Fanconi anemia (FA) pathway. The research was led by scientists in the division of Experimental Hematology and Cancer Biology at Cincinnati Children's Hospital Medical Center.

Mounting scientific evidence suggests the FA repair pathway is necessary to limit genomic instability caused by abnormal structural changes during DNA replication and cell division. In some people the pathway is genetically unstable, putting them at risk for the Fanconi anemia blood disorder, physical defects and possibly cancer.

"Although only a small number of people have Fanconi anemia, this study helps us explain the very intricate steps that occur during DNA repair processes and how defects in DNA repair processes can lead to cancer in the general population," said Amom Ruhikanta Meetei, Ph.D., senior investigator on the study.

The researchers show how the two novel proteins - which they named MHF1 and MHF2 - work together to bind to specific DNA structures and are "indispensable for the functional integrity of the FA pathway." The proteins were identified working through a specific core component

protein of the FA pathway called FANCM, one of eight currently known to make up the FA core complex.

FA cells are extremely sensitive to exposure from agents that can cause DNA interstrand crosslinks (ICLs), abnormal structures that block DNA replication. When disruptions from environmental factors or inherent genetic instability create the possibility for ICLs, the study shows that MHF1 and MHF2 help FANCM prevent or repair these crosslinks, which if unresolved can lead to cell defects and disease

The researchers also report that loss of MHF1 alone disrupts normal function of the entire FA pathway. In fact, when the researchers suppressed MHF1, it destabilized FANCM and caused increased chromosome aberrations after exposure to capothecin, an agent that causes ICLs.

As they move forward with their research, the investigators next want to analyze cells from people who have Fanconi anemia to see if they detect mutations in MHF1 or MHF2 that could help explain genetic instability in these patients, said Thiyam Ramsing Singh, Ph.D., first author on the study and a member of Dr. Meetei's laboratory.

The precise molecular functions of the FA pathway and how they influence the development of cancers are still being uncovered. The identification of FANCM as part of the FA core complex and its DNA repair function was an important step forward, and was first reported in 2005 by Dr. Meetei and his research colleagues.

Provided by Cincinnati Children's Hospital Medical Center

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