MedicalXpress

Team identifies new function of genes linked to Fanconi anemia and certain types of cancer

May 3 2016

Researchers from UT Southwestern Medical Center have identified an important new function of genes in the Fanconi anemia pathway—a finding that could have implications for development of new therapies to treat this disorder and some cancers.

Fanconi anemia (FA) is an incurable blood disorder affecting about 1 in every 130,000 people caused by mutations in any of 19 FA genes. Mutations in FA genes can lead to birth defects, cognitive impairment, bone marrow failure-related blood disorders, cancers that include pediatric leukemia, premature aging, and other abnormalities.

FA pathway genetic mutations also can be found in cancers of patients without the disorder, said study first author Dr. Rhea Sumpter, an Instructor in Internal Medicine at the Center for Autophagy Research at UT Southwestern. These include mutations in the FANCS (also called BRCA1) and FANCD1 (also called BRCA2) genes, which greatly increase the risk of developing familial breast and ovarian cancers, regardless of whether the person has FA.

In the study, published online recently in *Cell*, UT Southwestern investigators and colleagues from Indiana University School of Medicine and three European institutions found that FA genes are required for selective autophagy, a natural cellular housekeeping process. In particular, the human FANCC gene plays a key role in two types of

selective autophagy: the removal of viruses inside the cell (virophagy) and the removal of damaged cellular components called mitochondria (mitophagy). The study in mice showed that many FA pathway proteins are required for mitophagy.

The scientists also found that the rodent version of the gene called Fancc was necessary for antiviral host defense and mitochondrial stability—and to suppress excessive activation of innate immune system receptors known as inflammasomes by removing damaged mitochondria.

"There's increasing evidence that the failure of cells to appropriately clear damaged mitochondria leads to abnormal activation of the inflammasome—a process that is emerging as an important contributor to many different diseases," said senior author Dr. Beth Levine, Director of the Center for Autophagy Research and a Howard Hughes Medical Institute (HHMI) Investigator at UT Southwestern.

"The finding that FA genes function in clearing mitochondria and decreasing inflammasome activation provides a potential new inflammasome-targeted avenue of therapy for patients with diseases related to mutations in the FA genes," added Dr. Levine, also Professor of Internal Medicine and of Microbiology, and holder of the Charles Cameron Sprague Distinguished Chair in Biomedical Science.

FA pathway genes previously had been known to play a role in DNA repair. This new link to autophagy opens up unexplored horizons for understanding the function of these genes in human health and disease.

"Our findings suggest a novel mechanism by which mutations in FA genes may lead to the clinical manifestations in patients with FA anemia and to cancers in patients with mutations in FA genes," Dr. Sumpter said. "We've shown that this new function of the FA genes in the selective autophagy pathways does not depend on their role in DNA

repair."

In addition, the autophagy function may partly explain why patients with Fanconi anemia are highly susceptible to infection and cancer, Dr. Levine said.

While further research is needed to understand how these findings may be used to treat disease, the investigators have identified a novel avenue for developing potential therapies for FA and cancer patients.

"I believe the clearest therapeutic possibilities to come from our study results are the development of new FA agents that target the inflammasome and production of interleukin 1 beta (IL-1β), a pro-inflammatory cytokine," Dr. Sumpter said. "Clinically, IL-1β signaling has been targeted with FDA-approved drugs very successfully in several auto-inflammatory diseases that involve excessive inflammasome activation. Our results suggest that FA patients may also benefit from these therapies."

Provided by UT Southwestern Medical Center