Combined therapy may improve clinical responses for endometrial, colorectal and gastric tumors

27 February 2020

Shiaw-Yih Lin, Ph.D., professor of Systems Biology. Credit: MD Anderson Cancer Center

A study at The University of Texas MD Anderson Cancer Center discovered a novel therapeutic vulnerability for patients who have tumors caused by a genetic misfire in the DNA mismatch repair (MMR) pathway, a system for repairing genetic aberrations. Study findings were published in the Feb. 27 online issue of *Cancer Cell*.

When tumors lose MMR function, they acquire numerous mutations throughout their DNA which can promote cancer formation. This deficiency is often found in certain cancers, such as endometrial, colorectal and gastric cancer. It can be diagnosed through the presence of genetic irregularities known as microsatellite instability (MSI).

"MMR deficient and MSI cancers display resistance to chemotherapy and only a subset responds to immunotherapy, leaving a large number of patients with few treatment options," said Shiaw-Yih Lin, Ph.D., professor of Systems Biology. "Our study identified proteome instability as a novel therapeutic vulnerability in MSI tumors."

Using cell lines, patient samples, mouse models and computational techniques, Lin's team showed that the abundant mutant proteins in MSI cancers become misshapen and structurally unstable. As tumor cells shift resources to help correctly shape the mutated proteins, they begin to fail to correctly shape normal proteins, ultimately resulting in all of the proteins within the tumor becoming more unstable. The abundance of misshapen proteins requires tumor cells to use a protein degradation pathway not typically used by normal cells. This pathway can be blocked by MLN4924, resulting in toxicity specifically in MSI cancer cells.

In addition to killing the cells, the authors found that treatment with MLN4924 induced an immunogenic form of cell death.

"As the tumor cells were dying following MLN4924 treatment, we observed them secreting molecules to recruit immune cells and expressing a protein instructing immune cells to kill other cells that look like them," said Daniel McGrail, Ph.D., postdoctoral fellow and the study's first author. "By further activating immune cells through dual treatment with anti-PD1, a treatment modality already approved in MSI tumors, we were able to induce durable, curative responses."

The team saw no toxicities from this therapeutic approach, and are hopeful about the translational prospects as both treatment agents are already in the clinic.

Provided by University of Texas M. D. Anderson Cancer Center