Study finds novel molecular therapeutic target for colon cancer

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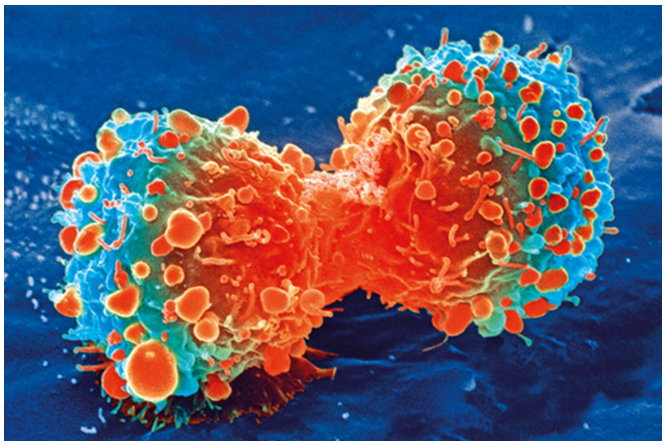

Cancer cell during cell division. Credit: National Institutes of Health

Researchers have found a way to help make chemotherapy more effective in treating colon cancer. They identified a new pathway (RICTOR/mTORC2) as a biological target for the disease. Targeted inhibition of RICTOR or the mTORC2 pathway could be used as a distinctive therapeutic opportunity with chemotherapy for treating colon cancer.

"Identification of biological targets to enhance sensitivity to chemotherapy is becoming a priority for effectively treating cancers to reduce toxicities caused by chemotherapy or to overcome resistance," explained corresponding author Sam Thiagalingam, Ph.D., associate professor of biomedical genetics, medicine and pathology & laboratory medicine and pharmacology & experimental therapeutics at Boston University School of Medicine (BUSM).

Previous studies by Thiagalingam and his colleagues found that SMAD4 gene mutations correlate to an advanced stage of colon cancer and SMAD4 acts as a metastasis suppressor by interacting to block the functionality of transcription factors that promote metastatic cancer progression. Furthermore, clinical data and studies performed using cell culture systems by Thiagalingam and others found that loss of or low SMAD4 expression is associated with poor response to 5-fluorouracil, the backbone of almost all chemotherapy combinations used in the treatment of metastatic colon cancer.

The researchers hypothesized that SMAD4 could elicit the metastatic suppressor function not only by blocking functionality of transcription factors but also by disabling metastasis promoting signaling pathways. "We found for the first time that SMAD4 interacts with RICTOR to suppress mTORC2 functionality and therefore the loss of SMAD4 function results in oncogenic activation of the mTORC2 pathway, leading to enhancement in metastatic colon cancer progression and resistance to chemotherapeutic agents," said Thiagalingam.

According to the researchers, this study suggests that effectiveness of cancer therapies involving chemotherapeutic agents such as irinotecan for colon, pancreatic or other cancers eliciting defect in SMAD4 functionality would be highly effective when combined with targeted inhibition of RICTOR/mTORC2 pathway.

In addition to colon cancer, poor prognosis has been associated with mutations, deletions and low levels of SMAD4 in gliomas and pancreatic, prostate and lung cancers.

These findings appear online in the journal *Molecular Cancer Research*, a journal of the American Association for Cancer Research.

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