Small RNA plays big role suppressing cancer

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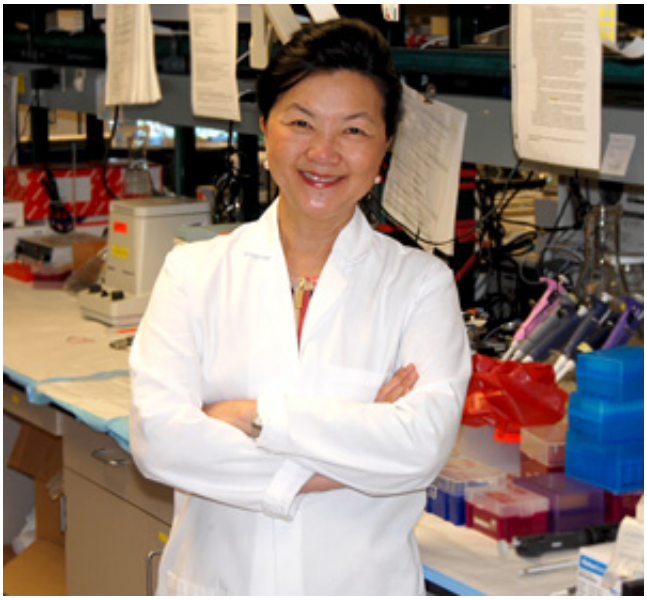

Yu-Jui Yvonne Wan

The micro RNA miR-22 has long been known for its ability to suppress cancer. However, questions remain about how it achieves this feat. For example, which molecules are regulating miR-22, and which are miR22 targets?

Researchers at UC Davis have unraveled some of these relationships, identifying several interactions that directly impact liver and colon cancer. The work provides new insights into how miR-22 operates and could potentially lead to new cancer therapies. The study was published in *The Journal of Biological Chemistry*.

"There are quite a few molecules present in the gastrointestinal (GI) tract that regulate miR-22," said Yu-Jui Yvonne Wan, vice chair for research in the Department of Pathology and Laboratory Medicine and senior author on the paper. "If so many chemicals in the GI tract can regulate miR-22, it must be physiologically significant. We needed to better understand the molecules that regulate miR-22 in cancer, as well as the pathways miR-22 controls."

Micro RNAs, like miR-22, play a major role in gene expression by selectively silencing particular genes. To understand the role of miR-22 in liver and colon cancer, Wan and her colleagues studied mice that lacked the bile acid receptor, farnesoid x receptor (FXR), which balances bile acid and cholesterol. Without FXR, mice spontaneously develop liver cancer. They also examined the expression of miR-22 in human liver cancer and colon cancer specimens.

The researchers found that the journey begins with bile acids, such as hydrophilic chenodeoxycholic acid, which activates FXR. In turn, FXR increases miR-22, which reduces the expression level of Cyclin A2, a protein that influences cell division and protects liver and colon cells from excessive proliferation.

The team confirmed these results using different models and found there is an inverse relationship between miR-22 and Cyclin A2 expression levels in liver and colon cancer cells.

The research also showed that miR-22 can be activated by vitamin D3, which can reduce the toxicity of hydrophobic bile acids. These pieces of information highlight the potential impact of diet and vitamins on GI cancer formation.

"People who are obese, or eating a high-fat Western diet, tend to have dysregulated bile acid synthesis," said Wan. "When that happens, FXR

can be inactivated, potentially decreasing the level of miR-22, increasing the expression of Cyclin A2 and disrupting the cell cycle. So this pathway may play a role in Western diet-associated carcinogenesis."

In addition, miR-22 has a complicated relationship with a number of cancers, including breast and lung, and may offer promise as a cancer therapeutic target. In addition to targeting Cyclin A2, miR-22 also inhibits the expression level of histone deacetylases (HDACs), proteins that control gene expression by modification of histone structure. A number of HDAC inhibitors are FDA- approved anti-cancer drugs, and miR-22 can potentially be used to treat cancer.

"I'm not so sure miR-22 is all good," said Wan. "We don't know what it will target in normal cells. Our next step is to identify more miR-22 effects."

More information: *Journal of Biological Chemistry*, www.jbc.org/content/290/10/650 … ed-83f9-1d4db31aa09b

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