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Study identifies miR122 target sites in liver cancer and links a gene to patient survival

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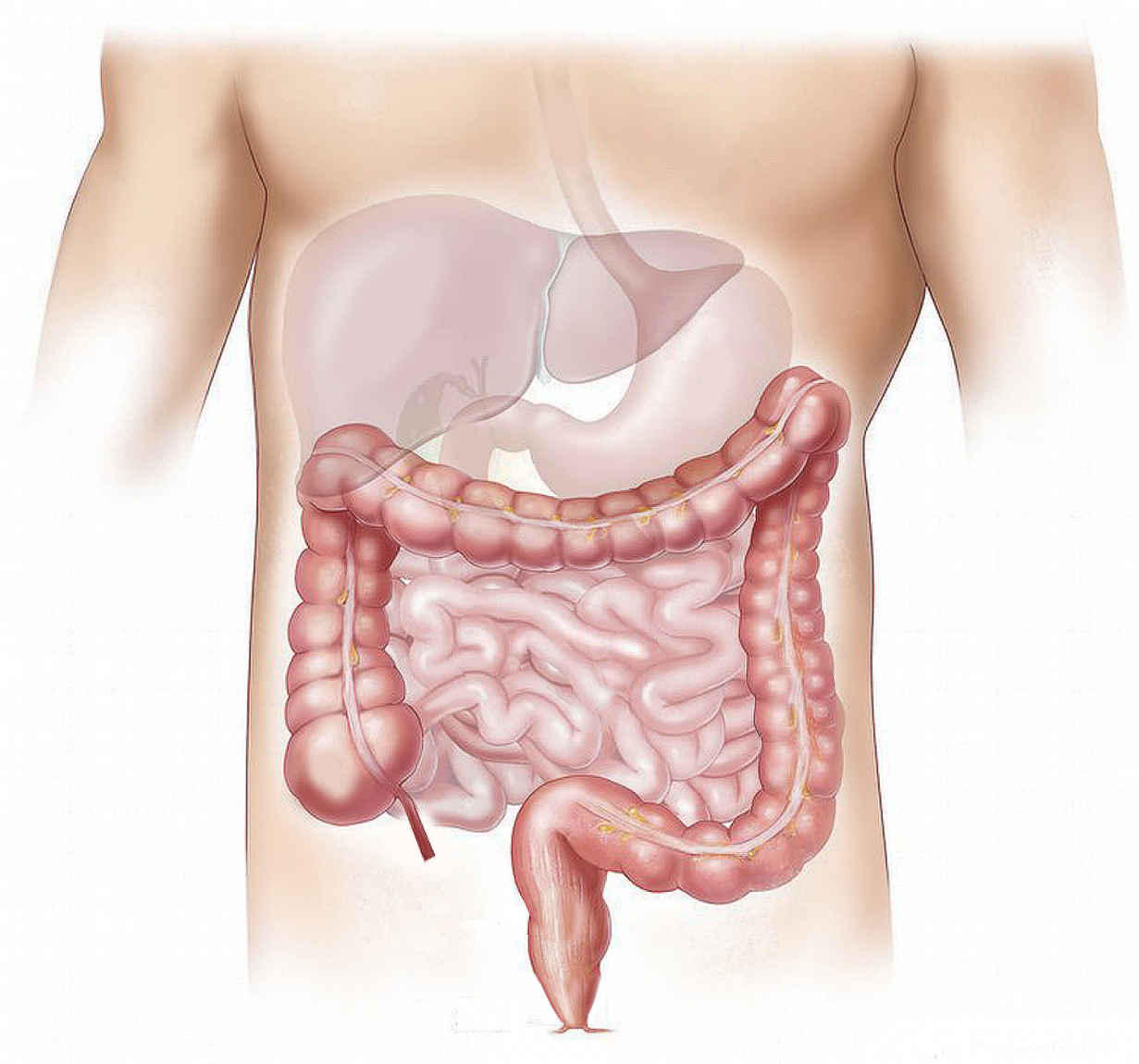

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A new study of a molecule that regulates liver-cell metabolism and suppresses liver-cancer development shows that the molecule interacts with thousands of genes in liver cells, and that when levels of the molecule go down, which often happens during liver-cancer development, the activity of certain cancer-promoting genes goes up.

The findings could one day help doctors better predict survival in liver cancer patients and help determine whether the molecule – called microRNA-122
(miR-122) – should be developed as an anticancer drug.

The study, reported in the journal *Molecular Cell*, was led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at Rockefeller University's Howard Hughes Medical Institute.

The researchers sought to biochemically (rather than computationally) define all miR-122 target sites in the liver and hepatocellular carcinoma (HCC), the most common form of liver cancer, and to learn which target genes were critical for liver cancer development or progression.
miR-122 is found almost exclusively in liver cells, where its role includes regulating cholesterol and lipid metabolism.

The researchers identified more than 11,000 miR-122 binding sites in a mouse model. They further found that:

- miR-122 targets nearly 4,800 genes in humans;
- Of these targets, 965 are shared with mice;
- Of the shared targets, a majority are more highly expressed in HCC tumor tissue from patients;

- Loss of miR-122 in HCC results in the over-expression of certain cancer-related genes.

Increased levels of three conserved target genes, BCL9, SLC52A2 and STX6 in tumor tissues could predict poor survival of human HCC patients.

"Our goal is to understand how miR-122 regulates liver metabolism and suppresses cancer development, and to identify common targets in humans and mice that may be involved in HCC development," says co-principal investigator and OSUCCC – James researcher Kalpana Ghoshal, PhD, associate professor of pathology. "That knowledge is critical for determining whether this molecule should be developed as a possible therapeutic agent for liver cancer."

The findings significantly extend the number of miR-122 binding sites identified by earlier studies because the methods used by the investigators identified sites that other techniques miss, Ghoshal adds. (Note: one gene can have multiple microRNA target sites.)

For this study, Ghoshal and her colleagues used a mouse model that lacked miR-122, along with normal mice; liver cancer tissues and normal liver tissues from nine HCC patients; and data from 373 HCC patients in The Cancer Genome Atlas Liver Hepatocellular Carcinoma dataset.

Other key findings include:

- While miR-122 is highly conserved (it's present in liver cells from fish to humans), a large proportion of miR-122 targets were species specific;
- The findings revealed binding sites that earlier studies missed; the consequences of miR-122 binding to the additional sites need to be determined;

- Human HCC has a core set of conserved miR-122 binding sites.

More information: Joseph M. Luna et al. Argonaute CLIP Defines a Deregulated miR-122-Bound Transcriptome that Correlates with Patient Survival in Human Liver Cancer, *Molecular Cell* (2017). DOI: 10.1016/j.molcel.2017.06.025

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