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Anti-sense might make sense for treating liver cancer

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A new study shows that it is possible to selectively target and block a particular microRNA that is important in liver cancer. The findings might offer a new therapy for this malignancy, which kills an estimated 549,000 people worldwide annually.

The animal study, 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 Mayo Clinic, focused on microRNA-221 (miR-221), a molecule that is consistently present at abnormally high levels in liver cancer.

To control the problem molecule, the researchers designed a second molecule as a kind of mirror image of the first. That mirror molecule is called an antisense oligonucleotide, and it selectively bound to and blocked the action of miR-221 in human liver cancer transplanted into mice. The treatment significantly prolonged the animals' lives and promoted the activity of important tumor-suppressor genes.

"This study is significant because hepatocellular carcinoma, or liver cancer, generally has a poor prognosis, so we badly need new treatment strategies," says principal investigator Thomas Schmittgen, associate professor and chair of pharmaceutics at Ohio State's College of Pharmacy and a member of the OSUCCC – James Experimental Therapeutics program.

The findings are published in the journal *Cancer Research*.

For the study, Schmittgen and his colleagues injected liver cancer cells labeled with the luminescent lighting-bug protein luciferase into the livers of mice. The researchers used bioluminescence imaging to monitor tumor growth.

When the tumors reached the appropriate size, they gave one group of animals the molecule designed to block miR-221; the other group received a control molecule.

Key findings include the following:

- After treatment with the antisense oligonucleotide, half the treated animals were alive at 10 weeks versus none of the controls.
- The antisense oligonucleotide significantly reduced levels of miR-221 in both tumor and normal liver samples.
- Treatment with the antisense oligonucleotide caused a three-fold increase in the activity of three important tumor-suppressor genes that are blocked by miR-221 in liver cancer. (The tumor suppressors were p27, p57 and PTEN.)

"Overall, this study provides proof-of-principle for further development of microRNA-targeted therapies for hepatocellular carcinomas," Schmittgen says.

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