Short Strand of RNA May Help Predict Survival and Response to Treatment for Patients with Liver Cancer

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(PhysOrg.com) -- A small RNA molecule, known as a microRNA, may help physicians identify liver cancer patients who, in spite of their poor prognosis, could respond well to treatment with a biological agent called interferon. The finding, by scientists at the National Cancer Institute (NCI), part of the National Institutes of Health, and their partners at Fudan University, Shanghai, and the University of Hong Kong in China and at Ohio State University, Columbus, appeared in the Oct. 8, 2009, issue of *The New England Journal of Medicine*.

"Interferon is an experimental therapeutic agent that has been used for many years to treat cancer patients, but with modest benefit," said study first author Junfang Ji, Ph.D., of the Liver Carcinogenesis Section at NCI's Center for Cancer Research.

"Our findings are exciting because we are rediscovering a drug that may have great potential for patients with a particular genomic profile. Being able to treat patients with an existing drug based on a tumor's genomic profile should improve its efficacy and reduce the cost of treatment," added study senior author Xin Wei Wang, Ph.D., chief of the Liver Carcinogenesis Section.

Hepatocellular carcinoma, or HCC, is a common type of liver cancer. Surgery is currently the most effective therapy for this disease, but only about 10 percent to 20 percent of patients are eligible for this option, and even among eligible patients the relapse rate is high. Post-operative (adjuvant) treatment with interferon often follows surgery in an attempt to prevent relapse in some patients, but this approach often fails as well.

How HCC develops is unclear. What is known is that it occurs more often in men than in women, and men tend to develop a more aggressive form of the disease. Differences in tumor biology and/or in the tumor microenvironment — the noncancerous tissue surrounding a tumor — may play a role.

Changes in microRNA levels have been noted in various human cancers, so a research team led by Wang looked at variation in the expression of microRNAs involved in HCC. These small RNA molecules play an important role in controlling gene activity by regulating a process known as translation. In translation, another type of RNA molecule, called a messenger RNA (mRNA), copies the genetic code stored within a gene and carries it to cellular structures called ribosomes and, once there, serves as a template to build the cell's proteins. There are many different types of microRNA, and a single microRNA species can affect the expression of many different proteins.

The team measured levels of microRNAs associated with both cancerous and normal tissue in men and women. The researchers analyzed microRNA expression profiles from 241 surgery patients. By first comparing the microRNA profiles of normal liver tissue, and then comparing microRNAs in men and women, the researchers identified several microRNAs that were expressed more abundantly in normal female liver tissue. One of these, miR-26, was highly abundant and showed the greatest difference between the sexes, so it was chosen for further analysis.

Overall, whether male or female, patients who had low levels of miR-26 did not live as long as patients who had higher expression levels of this microRNA. There was about a four-year difference in survival between the patient groups. The researchers validated their findings in three independent groups of HCC patients, and again, those with lower tumor miR-26 levels had poorer survival.

In a separate analysis, the team investigated whether miR-26 status influenced sensitivity to interferon therapy. They examined the levels of miR-26 in tumor samples collected from 135 patients who participated in a trial that evaluated interferon therapy in addition to other standard therapies following surgery. Among the 72 patients who had received interferon therapy as part of their cancer treatment, the researchers found that those with low tumor levels of miR-26 (indicative of a poor prognosis) benefited from receiving adjuvant interferon therapy. These patients survived at least 7.7 years longer than patients with low tumor levels of mi-R-26 that did not receive interferon therapy. In contrast, patients whose tumors had normal levels of miR-26 did not benefit from interferon. The researchers also validated their findings in a separate group of 79 patients.

These findings indicate that miR-26 status in tumors may be useful information both to determine prognosis for patients with HCC and to inform the selection of patients who might benefit from treatment with interferon to prevent disease relapse.

"HCC is an aggressive form of liver cancer and, among the small fraction of patients who are eligible for surgery, the rate of recurrence is high," said Wang. "Our study serves as a proof-of-concept for the use of microRNA expression levels to identify liver cancer patients who may benefit from interferon in addition to surgery."

All patients included in the study underwent surgery between 1999 and 2003 at the Liver Cancer Institute of Fudan University and at the University of Hong Kong Medical Center Centre. Most of the patients were hepatitis B virus-positive Chinese HCC patients. The researchers noted that more work will be needed to evaluate the association of miR-26 status with outcomes in non-Asian HCC patients. They will also need to examine HCC patients who have other underlying liver diseases, such as those infected with hepatitis C virus and/or have cirrhosis related to alcohol abuse. The research team is planning a prospective trial to further investigate the benefit of interferon therapy in HCC patients who have tumors with low levels of miR-26.

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