

Big Things in Small Packages:

Small RNAs Play a Big Role in Cancer Biology

Exquisitely tuned gene expression is essential to orchestrate both the development and functioning of the myriad cell types in the human body. When that tuning goes awry, one result is cancer. Small microRNAs (miRNAs) have emerged relatively recently as key modulators of gene expression, acting at a stage between transcription of the genes and translation into proteins. Although they are tiny, miRNAs—at a little over 20 nucleotides long—pack a big punch since each regulates a variety of genes, and they are involved in diverse pathological processes, including cell proliferation and death.

Of course, miRNAs are themselves tightly controlled. Faulty regulation of miRNAs, especially downregulation of these minuscule molecules, has been found in every tumor type tested thus far and has also been implicated in cancer progression and metastasis. Recognizing this, Xin Wei Wang, Ph.D., Head of the Liver Carcinogenesis Section in CCR's Laboratory of Human Carcinogenesis, asked whether miRNAs could serve as biomarkers for liver cancer. "Hepatocellular carcinoma, which makes up about 90 percent of liver cancer, is very heterogeneous in terms of biology and clinical outcome," explained Dr. Wang. "Our hope is to identify biomarkers that will distinguish the patients who will benefit from different treatments."

Knowing that hepatocellular carcinoma (HCC) has a two- to six-fold higher incidence in men than in women, Dr. Wang and his collaborators hypothesized that the differences in tumor microenvironments between the genders may be associated with prognosis. Therefore, they examined cancerous and noncancerous liver tissues in men and women to discover the biological and genetic differences that could be attributed to HCC development and progression.

In the October 2009 issue of *The New England Journal of Medicine*, the researchers reported a correlation between one miRNA, miR-26, and survival and response to interferon- α treatment in male and female liver cancer patients. The team analyzed three independent cohorts and found that miR-26 expression levels were higher in nontumor liver tissue from female patients than from male patients,



(Image: Eshran Tyler)

A patient's microRNA profile of low miR-26 (represented by the yellow miRNA) could be used to predict effectiveness of interferon therapy (vials) for hepatocellular carcinoma.

and liver tumor tissue had reduced miR-26 expression when compared to normal liver tissue, indicating that miR-26 is a liver tumor suppressor. The reduced miR-26 expression was strongly associated with particular patterns of overall gene expression, including activation of the NF κ B/IL-6 signaling pathway. Because estrogens inhibit IL-6 expression, Dr. Wang and his colleagues suggest that this pathway may contribute to the sex disparity in development of this tumor type. The researchers also showed that patients with reduced miR-26 expression in their tumors had lower survival rates but were more responsive to interferon- α

treatment than patients with normal miR-26 expression.

Dr. Wang looks to these results as a clinically useful tool that could ultimately turn miRNA profiling into a standard procedure for liver cancer patients. Having a genetic profile that can stratify patients would allow clinicians to decide on an appropriate course of treatment early after diagnosis that is as individualized as each tumor and each patient.

To learn more about Dr. Wang's research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?profileid=5764>.