Androgen receptor may explain male dominance in liver cancer

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A University of Rochester study helps to explain why men get liver cancer more often than women and opens the door for a new treatment pathway, by showing a direct link between the androgen receptor, which is more active in men, and the hepatitis B virus as it relates to the deadly cancer.

The study is published May 19, 2010, in *Science Translational Medicine*, a new journal from the American Association for the Advancement of Science, AAAS.

Primary liver cancer is the fifth most common cancer in men. It often arises after infection from the hepatitis B virus (HBV), which is widespread across the globe and growing in the United States. Other studies of liver cancer have focused on risk factors such as age, family history, and use of alcohol and cigarettes, but those epidemiology studies have not explained the mechanisms driving hepatocellular carcinoma and why men are more susceptible.

Now, corresponding author Chawnshang Chang, Ph.D., the George Hoyt Whipple Distinguished Professor of Pathology at the University of Rochester Medical Center, and colleagues, showed that the androgen receptor (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering DNA replication of the virus. Chang's laboratory created a mouse model for HBV-induced liver cancer and reported that knocking out AR suppressed the HBV-induced cancer.

According to an accompanying editorial in the journal, the identification of the AR pathway is a potential new treatment target that could translate to the clinic.

"Our study is the first in vivo evidence to demonstrate a direct connection between HBV-induced liver cancer and the AR," Chang said. "This is important because so far most work has focused on eliminating total serum androgen levels, a type of therapy that has shown little success."

"This important paper offers insight into something we have long observed but not entirely understood, namely that men with HBV are much more likely to develop cancer than women with the same infection," said Aram Hezel, M.D., a gastrointestinal oncologist at the James P. Wilmot Cancer Center at University of Rochester Medical Center. "This is great use of the tools of genetics and mouse modeling to explain a clinical finding and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma."

"This study also raises the possibility of prevention among men with HBV infection through inhibition of the androgen receptor," Hezel added. "The potential impact on clinical care is great."

For decades Chang has focused on the particular role of the AR in human health. In 1988 he successfully cloned AR, which led to breakthroughs in several AR-related diseases such as prostate and bladder cancer, and Kennedy's neuron disease, a rare and progressive motor disorder similar to Lou Gehrig's disease, and that affects only men.

The AR is central to the action of testosterone and has a profound effect on many organs. In previous experiments, Chang has shown that mice

without AR have dramatically lower rates of bladder cancer, a cancer that strikes men three times more often than women.

Male dominance in liver cancer suggested that the AR would be a key factor, as well. (About 74 percent of liver cancer cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage liver cancer. Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed liver tumors in mice.

Chang developed ASC-J9 earlier this decade and first reported on its clinical potential in March 2007 in the journal Nature Medicine. The drug is a synthetic compound loosely based on the compounds found in curcumin, the polyphenol that gives the spice tumeric its yellow color. It has been used for centuries as a folk medicine in Asia and India. In this case, however, scientists significantly altered the natural substance to be more powerful, and are carefully screening it for safety and effectiveness.

AndroScience Corp., a biotech company founded by Chang and others in 2000, is evaluating ASC-J9 in several clinical settings, although not yet in the treatment of liver cancer, Chang said. The URMC owns a stake in AndroScience, and has licensed several of Chang's research findings.

In the current study, researchers found that AR cooperates with the hepatitis B virus to trigger the expression of several oncogenes, resulting in normal liver cells transforming into cancer cells. Furthermore, they showed that liver tumors without the AR had fewer proliferating cancer

cells, which helps to explain the gender disparity in the disease.

Some of the findings are in agreement with earlier studies by Chang's lab on the role of AR in prostate cancer. Just as in prostate cancer, the liver tumor microenvironment is rich in various cell types, each of which has a distinct role in promoting the cancer.

"It will be interesting to see if targeting AR at different stages or in different liver cancer cell types may also lead to differential effects during the progression of cancer," the paper concluded.

The hepatitis B and C viruses account for approximately 80 percent of primary liver cancer cases worldwide. Newborn vaccines and screenings for HBV and HCV, particularly in Asian and African countries, have reduced the incidence of liver cancer in later years. Still, an estimated 560,000 new cases are diagnosed annually. In high-risk areas such as China, Japan and sub-Saharan Africa the male-to-female ratio of liver cancer can be as high as 8 to 1. The current best treatment is surgery; median survival is generally six months.

Provided by University of Rochester Medical Center