Researchers identify critical marker of response to gemcitabine in pancreatic cancer

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A protein related to aggressive cancers can actually improve the efficacy of gemcitabine at treating pancreatic cancer, according to a Priority Report in *Cancer Research*, published by researchers at Thomas Jefferson University.

The protein, called Hu antigen R (HuR), is a stress response protein found in the cytoplasm of pancreatic tumor cells. In certain experimental settings, pancreatic cancer cells that overexpressed HuR were up to 30-fold more sensitive to gemcitabine (Gemzar), according to Jonathan Brody, Ph.D., assistant professor of Surgery at Jefferson Medical College of Thomas Jefferson University.

In a clinical correlate study that included 32 resected pancreatic cancer patients who received gemcitabine, patients who had low cytoplasmic HuR levels had a 7-fold increased mortality risk compared to patients with high levels. This was after adjustment for other variables including age, sex, radiation therapy and other chemotherapy use.

"This marker appears to tell us upfront whether a patient will respond to treatment with gemcitabine, which is the routine treatment for pancreatic cancer," said Dr. Brody, who is the senior author of the study. "Of course, larger and comprehensive prospective studies need to be performed, but we now have a real clue about how to make this treatment better. Finding a mechanism that regulates gemcitabine's metabolism in pancreatic cancer cells is the real novel and exciting aspect of these findings."

Dr. Brody and colleagues found that in pancreatic cancer, HuR helps to regulate an enzyme called deoxycytidine kinase (dCK), which is responsible for metabolizing and activating gemcitabine. As with most chemotherapy drugs, gemcitabine causes cell stress and activates the HuR stress proteins. In turn, the high levels of HuR stimulate the production of more dCK, thus making gemcitabine more efficient, according to Dr. Brody.

"Normally, patients higher HuR cytoplasmic levels have a worse prognosis, since HuR expression is associated with advanced malignancies," Dr. Brody said. "However, in our study, they did better than patients with low HuR levels when they were treated with gemcitabine. We think it's because they already have high HuR levels at the time of treatment, which may be a response to the tumor cell environment."

According to Dr. Brody, research is underway to find a way to activate HuR in patients with a low expression. Other goals include expanding these findings to a larger pancreatic cancer population, and to other tumors that may be treated with gemcitabine, including breast, ovarian and certain lung cancers. They also want to determine if other chemotherapeutic agents engage this intriguing and manipulative pathway.

Source: Thomas Jefferson University (news : web)