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Accelerated discovery a triple threat to triple negative breast cancer

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Houston Methodist Hospital researchers have advanced a potential treatment for metaplastic breast cancer—the most aggressive subtype of triple negative breast cancer, into patients in just under four years.

In a study published in the *Journal of the National Cancer Institute* (early online Dec. 31), a multi-institutional team led by Jenny C. Chang, M.D., director of the Houston Methodist Cancer Center, identified a gene driving the formation of metaplastic breast cancer.

"We not only uncovered the biological pathway stimulating cancer growth, but we found a compound that blocked it, increasing the survival of mice carrying human metaplastic breast tumors," said Chang, the study's senior author.

Metaplastic breast cancers account for less than 1 percent of all breast cancers, according to the Susan G. Komen Foundation. This subtype is the most aggressive triple negative breast cancer and remains therapeutically challenging to treat. Highly unresponsive to chemotherapy, these aggressive tumors leave patients with a three-year survival rate of 40 percent, worse than the 70 percent given triple negative breast cancer patients. Identifying the genetic mutation gave Chang and her team a jumpstart on targeting this cancer.

The research team found the same gene mutated in 39 of the 40 tumor samples from metaplastic breast patients. The mutation was in the gene RPL39, which like HER2 (a gene overexpressed in 1 out of 5 breast

cancers), is considered an oncogene. This means that cells carrying the erroneous form of this gene divide uncontrollably and result in rapid tumor growth. Identifying RPL39 was the first step in determining how to treat this cancer.

RPL39 regulates the expression of an enzyme called inducible nitric oxide synthase (iNOS). The Houston Methodist researchers found that patients with high expression of RPL39 and iNOS had lower overall survival. Intuitively, the team investigated effects of an iNOS inhibitor on the treatment of metaplastic breast cancer and found the L-NMMA compound shrunk tumors in mice bearing human metaplastic breast tumors.

"The results showed elimination of the cancer in nearly all of the mice when combined with standard chemotherapy," said Chang, also professor of medicine at Weill Cornell Medicine. "Our goal is to turn metaplastic breast cancer from a debilitating disease into a chronic illness."

Houston Methodist Hospital is currently enrolling patients diagnosed with metaplastic breast cancer in a phase I clinical trial for L-NMMA.

More information: Bhuvanesh Dave et al. Role of RPL39 in Metaplastic Breast Cancer, *Journal of the National Cancer Institute* (2016). DOI: 10.1093/jnci/djw292

Provided by Houston Methodist