New subtype of breast cancer responds to targeted drug

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A newly identified cancer biomarker could define a new subtype of breast cancer as well as offer a potential way to treat it, say researchers at Washington University School of Medicine in St. Louis. Their findings will be published in the March 1 online early edition issue of the *Proceedings of the National Academy of Sciences*.

The research could further refine what recent breast cancer research has concluded: that breast cancer is not one disease, but many. So far, research has firmly established that at least five subtypes of breast cancer exist, each having distinct biological features, clinical outcomes and responses to traditional therapies.

The biomarker identified by the Washington University researchers is found frequently in breast cancers and especially in those that have poorer outcomes. It stems from overactivation of a gene called LRP6 (low-density lipoprotein receptor-related protein 6), which stimulates an important cell-growth signaling pathway. LRP6 can be inhibited by a protein discovered in the same laboratory, which could become an effective drug against the breast cancer type, the researchers say.

"We found increased expression of the LRP6 gene in about a quarter of breast cancer specimens we examined, and we think LRP6 overexpression could be a marker for a new class of breast cancer," says Guojun Bu, Ph.D., professor of pediatrics and of cell biology and physiology. "In addition, we found that this biomarker is often associated with breast cancers that are either harder to treat or more likely to recur. We already have an agent that seems to be effective against LRP6-overexpressing tumors, which could someday become a therapy for tumors that right now have few treatment options."

The research was conducted primarily by Chia-Chen Liu, a graduate student in the Bu lab, who is a fellow in the Cancer Biology Pathway Program at the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital.

The researchers' analysis of human breast cancer tissue samples found significant increases in LRP6 levels in 20 percent to 36 percent of the tumors. LRP6 was increased more frequently in ER (estrogen receptor)-negative or HER2 (human epidermal growth factor receptor 2)-negative samples. LRP6 was also increased more frequently in so-called triple-negative breast tumor samples, which test negative for ER, HER2 and PR (progesterone receptor).

In general, patients who have triple-negative breast cancers have an increased risk of disease recurrence after initial treatment and a poorer prognosis. Furthermore, although ER-positive and HER2-positive tumors can be targeted with specific therapies, ER-negative and HER2-negative tumors cannot. So it appears that LRP6 overexpression is often associated with tumors that are currently difficult to treat, says Bu.

Research in the lab had earlier discovered a protein that binds to and inhibits LRP6. This study showed that the protein, called Mesd (mesoderm development), was able to slow the growth of breast cancer cells in the laboratory and to inhibit mammary tumor growth in laboratory mice.

Importantly, mice treated with Mesd did not experience any of the known side effects, such as bone lesions, skin disorders or intestinal malfunctions, associated with inhibition of this growth pathway.

"Our work introduces Mesd as a promising antitumor agent that might be further developed for breast cancer therapy," Bu says. "It would be analogous to such successful breast cancer therapies as Herceptin (trastuzumab), which

specifically targets HER2-positive breast cancer."

The researchers also found that a small segment of Mesd has the same effect as the larger molecule. This segment, or peptide, is more stable than the whole protein molecule and can be easily synthesized.

More information: Liu C-C, Prior J, Piwnica-Worms D, Bu G. LRP6 overexpression defines a class of breast cancer subtype and is a target for therapy. Proceedings of the National Academy of Sciences. March 1, 2010 (advance online publication).

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