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Scientists find cell pathway driving a deadly sub-type of breast cancer

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An intra cellular pathway not previously linked to breast cancer is driving a sub-type of the disease that is highly lethal and disproportionately over-represented in African American women.

The pathway regulates how cells identify and destroy proteins and represents a class of genes called proteasome targeting complexes. The work shows that basal cancer cells degrade the tumor suppressor gene p27 by making a new type of proteasome targeting complex. The gene p27 is one of a handful of proteins that are expressed in normal cells and act to prevent rapid cell growth, which is indicative of cancer. Beyond chemotherapy, no specific therapeutic target has been identified for this sub-type of cancer, found in between 12 to 15 percent of breast cancers in the general population and up to 25 percent of cases in African American women.

"The mortality rates in this subgroup of cancer are very high," said Tim Lane, senior author of the paper and a researcher at UCLA's Jonsson Comprehensive Cancer Center. "The possibility that this new proteasome targeting complex might provide targets for therapeutic intervention is a completely new area for breast cancer research."

The research, done in animal models and human breast cancer cell lines, is published in the Nov. 15 issue of the journal *Genes and Development*.

Scientists have identified five to seven different sub-types of breast cancer. Basal-like breast cancers currently are among the most difficult

to treat.

Targeted therapeutics are available for several sub-types. Women with HER-2 positive breast cancers can receive Herceptin, which when paired with chemotherapy extends disease-free survival by more than 50 percent. HER-2 positive women used to have the worst prognoses before Herceptin was developed. They now have the best prognoses because the drug targets what's broken in the cancer cell that is driving the disease. Another sub-type includes women with Estrogen Receptor positive cancers. These patients have several drugs available, such as Tamoxifen, that suppress the actions of estrogen on breast cancer tissue and thus control the disease.

Next up, Lane and his team plan to use protein chemistry and genetic tools to uncover the molecular components that participate in this new proteasome targeting complex, which could identify alterations – like HER-2 - that can be targeted in cancer cells and leave the healthy cells alone. That would give patients with this aggressive cancer sub-type a more effective and less toxic option than chemotherapy.

"This research has the potential to identify clinically relevant markers of a large subgroup of human breast cancer and find a novel therapeutic target that could be exploited with appropriate pharmaceutical agents," said Lane, who is an associate professor of obstetrics and gynecology. "We need a new paradigm to think about how to treat these cancers."

Lane's research also showed that basal-like breast cancer cells are most like breast stem cells, which generate the tissues of the breast. One way they're alike is that they are resistant to chemotherapy and do not express mature breast markers like estrogen receptor. These features make basal-like breast cancers so difficult to treat.

Another mystery Lane and his team hope to focus on is why basal-like

breast cancers are over-represented in African American women. It could be related to genetic features in the patient, or to other complex factors such as access to effective early intervention, Lane said.

Lane is currently working to validate his work in human disease and identify all the key players in this molecular pathway.

"We're still missing a couple of the key players. We currently understand the shape and general features of the complex, but hope to find all the components in the next couple of years," Lane said. "It is a great time to be involved in this research."

Source: University of California - Los Angeles