Drugs targeting chromosomal instability may fight a particular breast cancer subtype

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Another layer in breast cancer genetics has been peeled back. A team of researchers at Jefferson's Kimmel Cancer Center (KCC) led by Richard G. Pestell, M.D., PhD., FACP, Director of the KCC and Chair of the Department of Cancer Biology, have shown in a study published online Feb. 6 in the *Journal of Clinical Investigation* that the oncogene cyclin D1 may promote a genetic breakdown known as chromosomal instability (CIN). CIN is a known, yet poorly understood culprit in tumor progression.

The researchers used various in vitro and in vivo model systems to show that elevated levels of cyclin D1 promotes CIN and correlate with CIN in the luminal B breast cancer subtype. Cyclin D1 protein is elevated in breast, prostate, lung and gastrointestinal malignancies.

The findings suggest that shifting towards drugs targeting CIN may improve outcomes for patients diagnosed with luminal B subtype. Luminal B breast cancer has high proliferation rates and is considered a high grade malignancy.

Estrogen or progesterone receptor positive and HER2 positive cancers indicate luminal B, and about 10 percent of patients are diagnosed with it every year, though many do not respond well to treatment. The identification of CIN in luminal B provides a new therapeutic opportunity for these patients.

"Cyclin D1 has a well defined role in cell proliferation through

promoting DNA replication," says Dr. Pestell. "My team was the first to discover that cyclin D1 also has alternate functions, which include regulating gene transcription at the level of DNA. We were interested in discovering the function of DNA associated cyclin D1."

To help answer this, the researchers, including lead author Mathew C. Casimiro, Ph.D., of the Department of Cancer Biology at Thomas Jefferson University, first needed to directly access cyclin D1's role in gene regulation.

They applied an analysis known as ChIP sequencing to study the protein's interactions with genes that comprise the entire mouse genome, and found it occupied the regulatory region of genes governing chromosomal stability with high incidence.

They went on to show cyclin D1 promoted aneuploidy and chromosomal rearrangements typically found in cancers.

Faulty chromosomes—either too many or too few, or even ones that are the wrong shape or size—have been shown to be the crux of many cancers. However, a major question of cancer genetics is the mechanisms of CIN. What causes the breakdown in chromosomal stability?

As cyclin D1 expression is increased in the early phases of tumorigenesis, cyclin D1 may be an important inducer of CIN in tumors.

To analyze the association between CIN and cyclin D1 expression in the context of breast cancer, the team aligned an expression of a 70-gene set with the highest CIN score against over 2,000 breast cancer samples. They stratified the samples based on previously described subtypes and aligned them with cyclin D1 expression profiled across the dataset.

A significant correlation among CIN, cyclin D1 and the luminal B subtype was identified, and it was apparent that the relationship between these levels was subtype specific.

"Interestingly, previous studies have presented contradictory results," Dr. Pestell says. "Many studies have suggested a positive correlation between cyclin D1 expression and outcomes, while others have shown reduced survival. Here, we've dug deep, using a genome-wide analysis, and found that overexpression of the protein appears to be directly associated with the genes involved in CIN and this correlates with the luminal B subtype."

Drugs targeting chromosomal instability for cancer therapy have been explored, but a sub-stratification rationale for the luminal B subtype has not been established. The research presented in this study suggests such a target is worthy of further investigation.

"There is a big drive towards using targeting therapies for stratified breast cancers," says Dr. Casimiro. "What we are thinking is that there are a growing number of drugs that target aneuploidy, like AICAR and 17-AAG, that may be used as an adjuvant therapy in patients with luminal B breast cancer."

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