Study reveals molecular genetic mechanisms driving breast cancer progression

3 April 2015

Dr. W. Lee Kraus is the Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences. Credit: UT Southwestern

Researchers at UT Southwestern Medical Center have uncovered how the body's inflammatory response can alter how estrogen promotes the growth of breast cancer cells.

UT Southwestern researchers identified how a combination of signaling molecules inhibits the growth of breast cancer cells, improving clinical outcomes for some subtypes of breast cancers.

The combination—the steroid hormone estradiol and the proinflammatory cytokine tumor necrosis factor alpha (TNF?)—act to expand the number of sites where estrogen receptor alpha (ER?) can bind to the genome in breast cancer cells. The new sites of ER? binding turn new genes on and off, which alters the growth response of the breast cancer cells, inhibiting their growth and improving clinical outcomes in certain cases.

The newly identified gene set can be used as a biomarker that can help physicians determine who is at risk and how they might react to certain therapies.

"Our study uncovered the molecular mechanisms that alter the expression of the new set of genes in response to estradiol and TNF?, and identified potential target genes for future therapy," said senior author Dr. W. Lee Kraus, Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences, Professor of Obstetrics and Gynecology, and a member of the Harold C. Simmons Comprehensive Cancer Center. "Since the altered pattern of gene expression can predict outcomes in breast cancer, there are important diagnostic and prognostic implications."

The findings are published online and in the journal *Molecular Cell*.

Approximately 12.3 percent of women will be diagnosed with breast cancer at some point during their lifetime, and nearly 2.9 million women are living with breast cancer in the United States, according to statistics from the National Cancer Institute (NCI). About 232,670 new cases were reported in 2014, constituting about 14 percent of all new cancer cases. About 40,000 deaths were attributed to breast cancer in 2014.

Cancer cells release signals that can prompt the body to respond with an inflammatory response. As part of this response, TNF? is released and can impact the growth of the cancer cells. Previous studies suggested that inflammation might exacerbate the cancer, while the present study

suggests that, in some cases, it might actually promote a better outcome. The study revealed that, when present together, TNF? and estradiol cause ER?, a nuclear transcription factor that is present in about two-thirds of breast cancers (so-called ER+ cancers), to bind to new sites in the genome where the protein does not bind with either TNF? or estradiol alone. These new ER? binding sites allow altered gene expression and, for some subtypes of breast cancers, inhibit the growth of cancer cells.

Since the effect only happens when the two are combined, researchers can use the altered gene expression patterns as an indicator that both agents are at work in the cancer and as a biomarker that may help determine who might be more at risk and how they might react to therapy, said Dr. Kraus, Professor and Vice Chair for Basic Sciences in Obstetrics and Gynecology, Professor of Pharmacology, and holder of the Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences.

Provided by UT Southwestern Medical Center