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Team identifies blood biomarkers in drug-resistant cancer tumor cells

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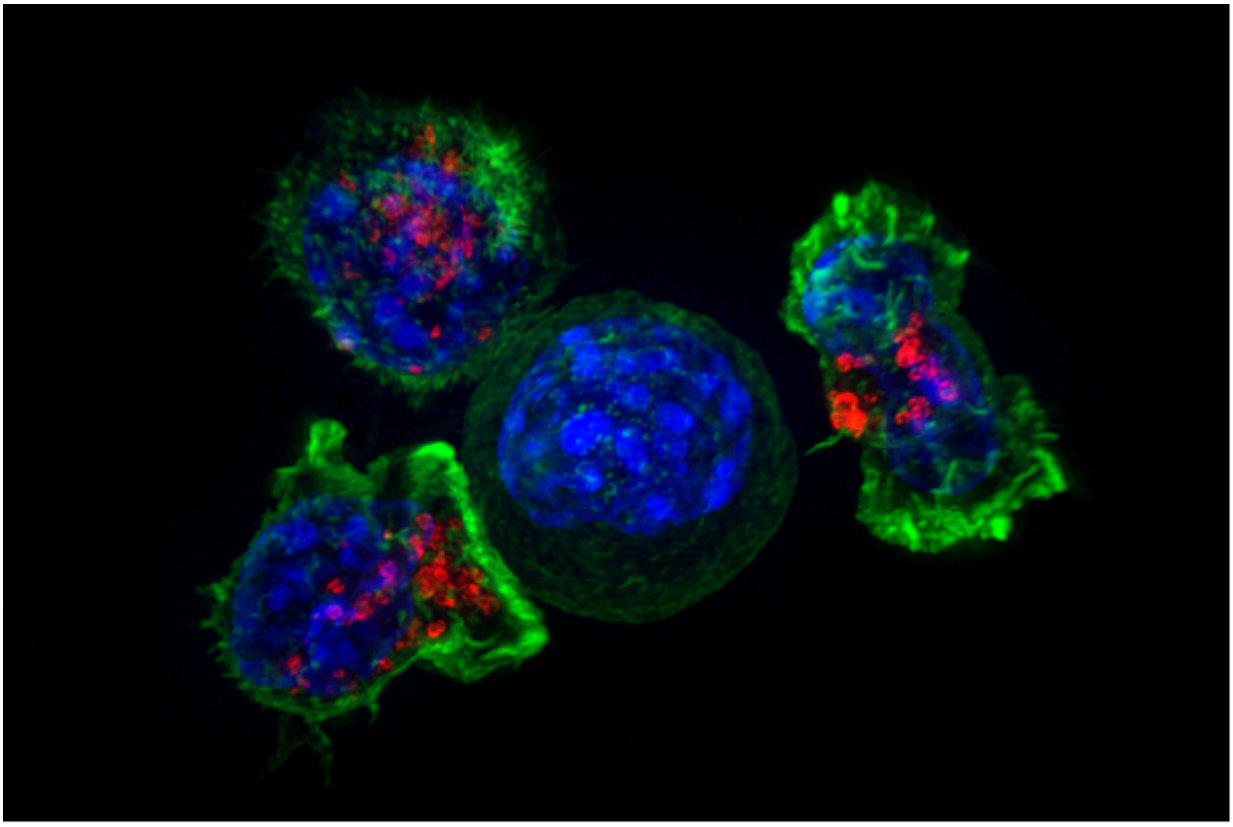

Killer T cells surround a cancer cell. Credit: NIH

While searching for a non-invasive way to detect prostate cancer cells circulating in blood, Duke Cancer Institute researchers have identified some blood markers associated with tumor resistance to two common

hormone therapies.

In a study published online this month in the journal *Clinical Cancer Research*, the Duke-led team reported that they isolated multiple key gene alterations in the circulating prostate tumor cells of patients who had developed resistance to abiraterone or enzalutamide.

Enzalutamide is a drug that blocks the male androgen receptor, and abiraterone is a drug that lowers testosterone levels. Both drugs are approved to treat hormone-resistant prostate cancer, but the tumors typically develop resistance within a few years.

The study, focusing on a small number of patients and using sophisticated blood analysis technology, demonstrated that circulating tumor cells detected in blood have the potential to reveal important genetic information that could guide treatments selection in the future, and suggest targets for new therapies.

"We have developed a method that allows us to examine the whole genome of rare circulating cancer cells in the blood, which is unique in each patient, and which can change over time during treatment," said senior author Andrew Armstrong, M.D., a medical oncologist and co-director of Genitourinary Clinical-Translational Research at the Duke Cancer Institute (DCI).

"Among the genomic changes in the patients' individual cancers, we were able to find key similarities between the cancer cells of men who have hormone-resistant prostate cancer," Armstrong said. "Our goal is to develop a 'liquid biopsy' that would be non-invasive, yet provide information that could guide clinical decisions."

Armstrong and colleagues from the DCI and the Duke Molecular Physiology Institute used a process called array-based comparative

genomic hybridization to analyze the genome of the circulating tumor cells of 16 men with advanced, treatment-resistant prostate cancer. The technique enabled them to determine which genes had extra copies and which regions were deleted.

Focusing both on genes that have previously been implicated in tumor progression, plus other genes important to cancer biology, the researchers found changes in multiple genetic pathways that appear to be in common among the men's circulating tumor cells.

"Our research provides evidence supporting the ability to measure gains and losses of large scale sections of the circulating tumor cells genome in men with prostate cancer," said co-author Simon Gregory, Ph.D., director of the Section of Genomics and Epigenetics in the Duke Molecular Physiology Institute. "We are now evaluating this method combined with higher resolution DNA mutational studies and measurements of RNA splice variants in CTCs to determine their clinical relevance to patients and treatment resistance."

Should these common alterations be similarly identified in larger studies, they could be used as biomarkers as part of a blood-based liquid biopsy to help determine what treatments would be most effective. The findings could also point to new targets for drug development.

One such large prospective clinical validation study is underway now at the Duke Cancer Institute, which is examining how the mutations develop in the context of enzalutamide or abiraterone therapy, and how the mutations relate to other key genetic events.

In addition to Armstrong and Gregory, study authors include Santosh Gupta, Jing Li, Gabor Kemeny, Rhonda L. Bitting, Joshua Beaver, Jason A. Somarelli and Kathryn E. Ware.

Provided by Duke University Medical Center