Researchers reveal discovery of mechanism leading to drug resistance in prostate cancer

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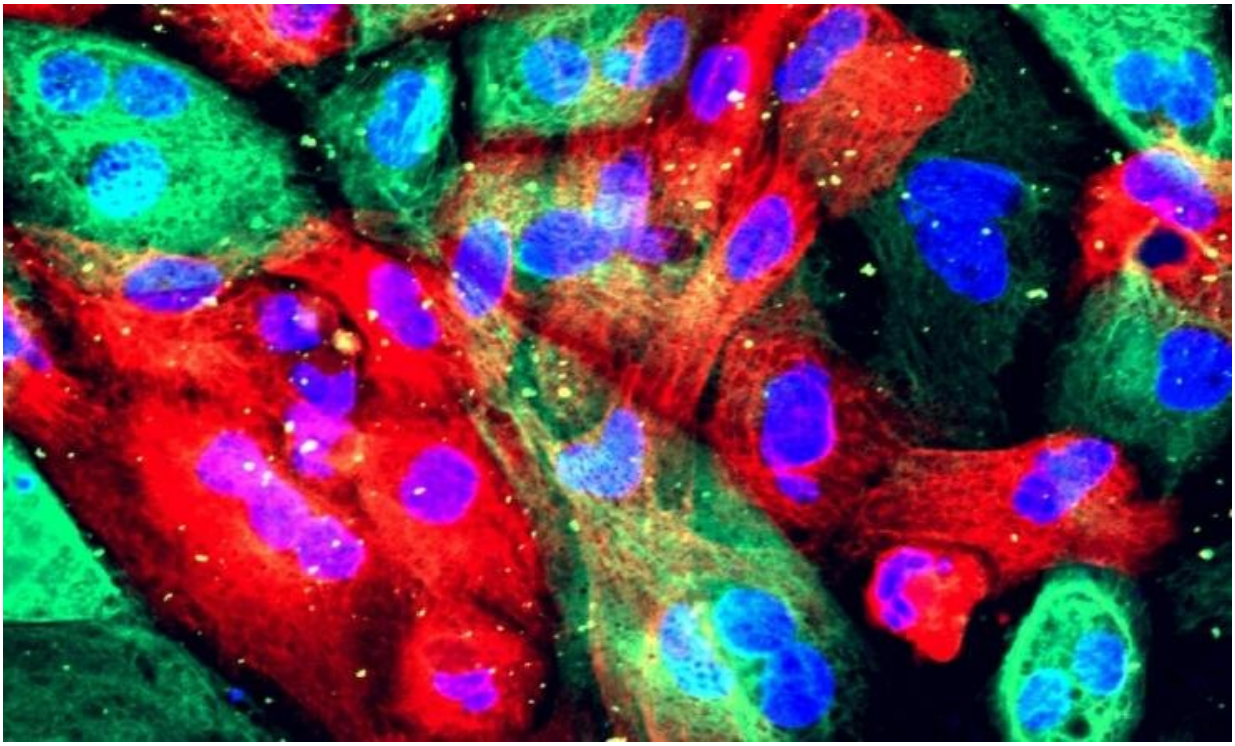

Prostate cancer cells. Credit: NIH Image Gallery

Prostate cancer is the most common cancer among men in the United States. Many patients can live long lives due to early detection and treatment with androgen deprivation therapy. However, despite the benefits of this therapy, almost all patients will eventually develop drug resistance and recurrent disease. In a new article published in *Science*

Translational Medicine, Moffitt Cancer Center researchers reveal a mechanism by which prostate cancer cells become resistant through molecular modification of the androgen receptor protein and identify a potential treatment approach that could overcome this resistance.

Androgen deprivation therapy has been the mainstay of prostate cancer treatment for decades. The goal of this therapy is to reduce the levels of hormones called androgens that stimulate prostate cancer cell growth through either surgical or medical approaches that target androgen receptor signaling. Androgen deprivation therapy greatly improves survival, but almost always leads to recurrent disease called castration-resistant prostate cancer. Scientists have discovered that resistance is primarily due to reactivation of androgen receptor signaling through different mechanisms, and they developed new drugs, such as enzalutamide and abiraterone, to overcome this resistance. Unfortunately, patients also eventually develop resistance to these drugs in a relatively short period of time. Several resistance mechanisms to these newer-generation drugs have been identified, but these modifications are not present in all patients, suggesting that additional resistance mechanisms exist.

The Moffitt research team, in collaboration with scientists at Washington University in St. Louis, wanted to identify alternative resistance mechanisms to enzalutamide and abiraterone in prostate cancer patients. They performed a series of laboratory experiments focused on the molecular modifications of the androgen receptor and its interactions with other proteins and DNA. They discovered that the androgen receptor becomes chemically modified at two distinct sites. First, a phosphate group is added to the androgen receptor protein by a protein called ACK1. This chemical modification permits a second modification, during which an acetyl chemical group is added. This modification occurs on a location of the androgen receptor that enables it to become active, even in the presence of enzalutamide. These

combined events result in a positive feedback loop during which the androgen receptor further increases levels of itself, as well as the ACK1 protein.

The researchers confirmed the importance of these molecular modifications in mouse experiments. They demonstrated that treatment of enzalutamide/abiraterone-resistant prostate tumors in mice with a Moffitt-designed ACK1 inhibitor called (R)-9b that targets ACK1 suppressed tumor growth, and reduced expression levels of ACK1, the androgen receptor and additional key genes regulated by the androgen receptor. Importantly, the researchers also showed that the expression level of ACK1 and the modified androgen receptor were higher in tissue samples from patients with prostate cancer than normal prostate tissue, and their expression increased throughout cancer progression.

"These combined observations suggest the importance of these androgen receptor modification events and protein interactions to the development of castration-resistant prostate cancer," said Nicholas Lawrence, Ph.D., study co-author and senior member of the Drug Discovery Department.

"Identification of an ACK1 kinase inhibitor that has the ability to thwart both the modifications, and the fact that an ACK1 inhibitor has not yet advanced to clinical trials, these data could open a new therapeutic modality for recurrent castration-resistant prostate cancer patients, a currently unfulfilled need," added Harshani Lawrence, Ph.D., study co-author and scientific director of Chemical Biology.

Drs. Nicholas and Harshani Lawrence, both medicinal chemists, are the inventors of (R)-9b.

More information: Mithila Sawant et al, Chronologically modified androgen receptor in recurrent castration-resistant prostate cancer and its therapeutic targeting, *Science Translational Medicine* (2022). DOI:

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