Protein that suppresses androgen receptors could improve prostate cancer diagnosis, treatment

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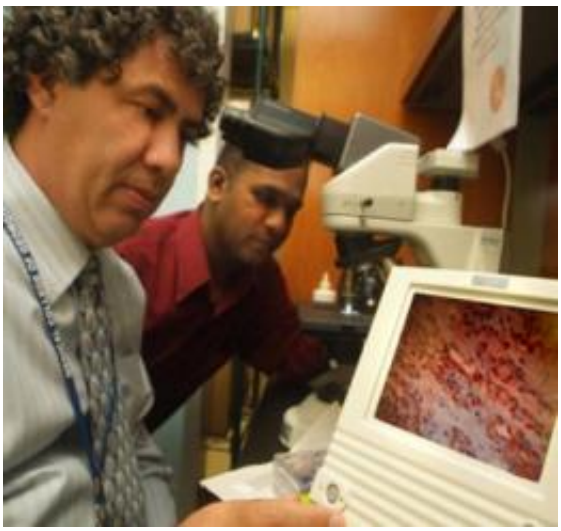

Drs. Yehia Daaka (left) and Vijayabaskar Lakshmikanthan are from the Medical College of Georgia. Credit: Medical College of Georgia

A protein that helps regulate expression of androgen receptors could prove a new focal point for staging and treating testosterone-fueled prostate cancer, Medical College of Georgia researchers say.

Levels of the protein, βarrestin2, are lower in some prostate cancer cells than in normal prostate cells while expression of testosterone-fed androgen receptors is higher, they report in *Proceedings of the National*

Academy of Sciences Online Early Edition this week.

"An increase in the number of androgen receptors is believed responsible for prostate cancer progression in men with advanced disease," says the study's corresponding author, Dr. Yehia Daaka, Distinguished Chair in Oncologic Pathology in the MCG School of Medicine.

With increased numbers of androgen receptors, prostate cancer can make use of the limited testosterone available after a diseased prostate gland is removed or after testosterone production is blocked by drug therapy. In fact, the increased number of androgen receptors may mutate so they can start feeding off other steroids or even growth factors, Dr. Daaka says.

These wily skills help explain why cancer returns despite initially promising treatment results.

"It is clear that signaling by the androgen receptor is paramount for not only the initiation but also the progression of the disease, including escape to a hormone-refractory disease," he says. Moves androgen receptors make to support cancer growth make it "unbeatable at this point," for some patients.

However increased levels of βarrestin2 appear to halt the potentially deadly increase in androgen receptor expression, the MCG research team has found.

Androgen receptors have co-factors that can activate or repress their activity. "You could make the leap and say perhaps prostate cancer initiation and progression may be regulated by expression or non-expression of these co-factors," says Dr. Daaka, a Georgia Cancer Coalition Distinguished Cancer Scholar.

Their studies in human tissue - both in culture and transplanted into mice - show this appears the case for βarrestin2. First the team identified βarrestin2 as cofactor for androgen receptors. Next they found a reciprocal relationship: androgen receptor expression is low when βarrestin2 expression increases. That's the scenario in healthy prostate cells while the exact opposite is true in some prostate cancer. When they forced increased expression of βarrestin2, androgen receptor expression and activity went down.

βarrestin2 locks up an androgen receptor by binding to it, then the pair bind to yet another protein, ubiquitin ligase, which tags the receptor as waste and the trio make their way to the cell's garbage dump. "The neat thing about it is βarrestin2 inhibits or blunts the androgen receptor by promoting its degradation. So it disappears," Dr. Daaka says.

His future studies include determining what happens when βarrestin2 expression is further decreased in the face of prostate cancer. These studies will also help determine how big a player βarrestin2 is in prostate cancer progression, says Dr. Daaka, noting that numerous other corepressors and activators of androgen receptors are known.

Since all the happenings occur inside prostate cells, the findings don't point toward a new blood or urine test for prostate cancer but could lead to new ways to stage prostate cancer from the first biopsy. In fact, Dr. Daaka and his team already are collecting samples from patients whose cancer has been staged to see if specific levels of βarrestin2 expression correlate with different stages of disease.

Another goal is to develop a small molecule that can get inside a patient's cell and mimic βarrestin2's ability to suppress androgen receptor expression and so restore healthy levels found in prostate cells.

Prostate cancer falls behind skin cancer as the second most common

cancer in men and more than 192,000 new cases will be diagnosed this year in the United States, according to the American Cancer Society.

Source: Medical College of Georgia