Doubling up on advanced prostate cancer with PARP inhibitors

October 9 2012

Targeting dual roles of PARP-1 may slow cancer growth and progression, Jefferson's Kimmel Cancer Center researchers say. Credit: TJU

A newly discovered function of PARP-1 could be the key to more effective therapeutics to treat advanced prostate cancer patients, a recent preclinical study published in *Cancer Discovery* by Jefferson's Kimmel Cancer Center researchers suggests.

The team, led by Karen E. Knudsen, Ph.D., Professor in the Departments of Cancer Biology, Urology, & Radiation Oncology at Thomas Jefferson University, found that functions of PARP-1 not only include DNA damage repair but also androgen receptor (AR) regulation in advanced prostate cancer growth and progression. PARP inhibition in various models was found to suppress AR activity, which fuels prostate growth.

Researchers believe that the dual functions of PARP-1—as both a regulator of AR as well as critical for DNA damage repair—could be leveraged for therapeutic benefit. PARP inhibitors could slow down advanced-stage prostate cancer and shrink tumors, the team surmises.

"We hope to capitalize on this previously unknown function in PARP-1 in prostate cancer," said Dr. Knudsen. "Our data show that PARP-1 plays a major role in controlling AR function and that, when suppressed with inhibitors, enhanced anti-tumor effects of castration and delayed onset to castration resistance. "

"This is the basis to support a clinical trial investigating PARP-1 inhibitors in patients with advanced disease," she added.

Today, PARP-1 is seen as a valuable target because of its involvement in DNA damage repair for cancer cells. The therapy has been successful when combined with DNA-damaging drugs because it heightens the apoptotic activity of these drugs. In other words, it helps halt tumor growth by stopping DNA repair in various cancers.

Prostate cancer is dependent on AR activity for growth and survival, and is largely resistant to standard chemotherapy. AR-directed therapies are the first-line intervention for patients with advanced disease; however, recurrent tumors arise when AR is reactivated, a common occurrence in the castrate-resistant stage of the disease.

Therefore, there is a dire need to develop means to suppress the AR function in these patients. With this new role defined, PARP inhibitors targeting both functions could sensitize prostate cancer cells to DNA damage, and potentially improve the efficacy of AR-directed therapies in these patients, the researchers suggest in the paper.

Almost 40 percent of men with prostate cancer progress into an

advanced stage, termed castrate-resistant prostate cancer, where chemotherapy and other therapies have little to no effect.

Using various in vitro and in vivo model systems, the researchers found that PARP-1 activity is required for AR function and is increased in castrate-resistant prostate cancer. Additionally, inhibiting PARP-1 suppressed proliferation of cultured, primary human tumor specimens in a state-of-the-art system.

"These findings introduce a paradigm shift with regard to PARP-1 in prostate cancer," said Dr. Knudsen, "and provide the basis for new therapies that could help a whole population of cancer patients who have little options."

Dr. Knudsen recently received a two-year Challenge Award worth $1 million from the Prostate Cancer Foundation (PCF) for her work with PARP-1 and prostate cancer, and attended PCF's 10th annual fundraiser in Philadelphia.

More information: cancerdiscovery.aacrjournals.o … 2-0120.full.pdf+html

Provided by Thomas Jefferson University