Bench to beside study of a targetable enzyme controlling aggressive prostate cancer

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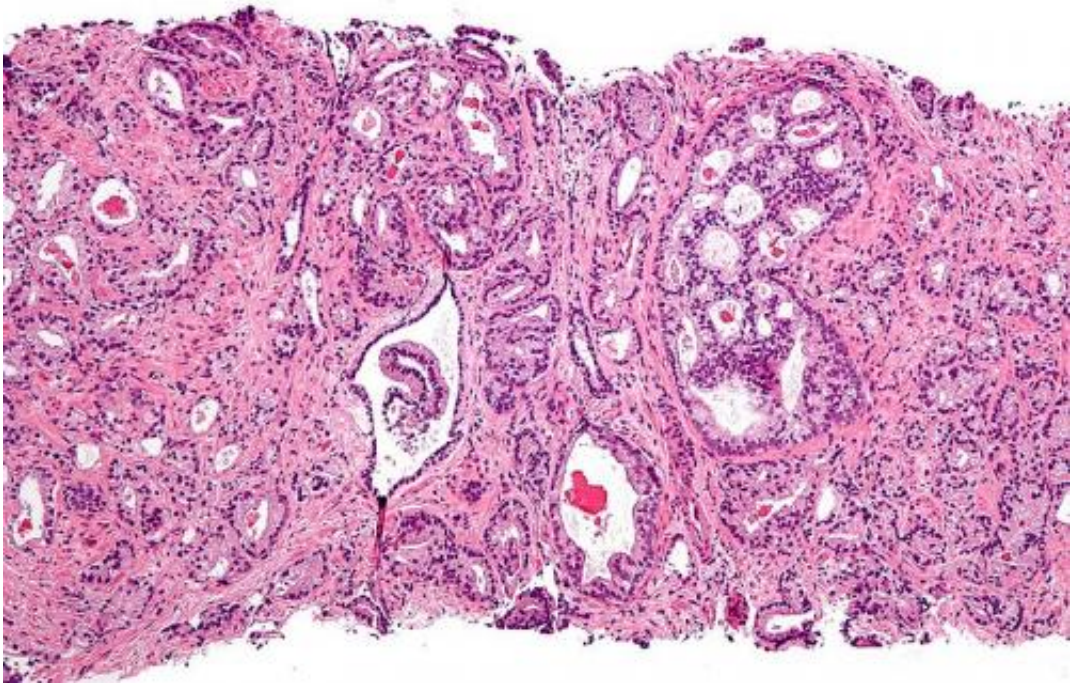

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Prostate cancer represents a major health challenge and there is currently no effective treatment once it has advanced to the aggressive, metastatic stage. A new has revealed a key cellular mechanism that contributes to aggressive prostate cancer, and supporting a new clinical trial. The study was published in the journal *Clinical Cancer Research.*

The research led by investigators at the Sidney Kimmel Cancer Center—Jefferson Health (SKCC) and their collaborators at Memorial Sloan Kettering Cancer Center, the University of California, San Francisco, and Celgene Corporation, focused on an enzyme called DNA-PK (DNA-dependent protein kinase), a pivotal component of the cellular machinery that controls both DNA repair and influences gene expression. The work was orchestrated by the laboratory of Karen E. Knudsen, Ph.D., EVP of Oncology Services and Enterprise Director of SKCC.

Previous studies showed that DNA-PK is excessively active in metastatic prostate cancer and that its hyper-activation is associated with a poor outcome in prostate cancer patients. "Our study further elucidates the functions of DNA-PK and identifies this protein as a master regulator of gene networks that promote aggressive cancer behaviors," says lead author Emanuela Dylgjeri.

A companion study in the same issue led by the laboratory of Felix Feng, MD, in collaboration with the Kundsen laboratory, identified DNA-PK as the most significantly associated kinase with metastatic progression of the disease. In an effort to understand how DNA-PK induces poor outcomes, the investigators found that DNA-PK modulates the expression of gene networks controlling a variety of important cancer-related cellular events, including a developmental process termed the epithelial-mesenchymal transition, the immune response, metabolic pathways (Dylgjeri et al.) and Wnt signaling (Kothari et al.).

The new findings suggest that targeting DNA-PK might allow the development of effective strategies to prevent or treat aggressive, late-stage prostate cancer. Data from the studies was used to develop a clinical trial combining standard-of-care with a first-in-man DNA-PK inhibitor. Early results of the trial have been promising, and the researchers have demonstrated in a laboratory setting that the combined

approach is more effective than either single treatment in eliciting anti-tumor effects. The clinical trial is still underway and has now entered the expansion phase of testing.

The newly published studies are focused on translating basic science findings from the laboratory to the clinic, but the investigators also plan to take the lessons learned in the clinic back to the laboratory. The results of the clinical trial will offer important clues and raise new questions that will guide the design of new experiments, with the ultimate goal of understanding how DNA-PK regulates specific cellular pathways to promote more aggressive cancer behavior. These studies in turn will aid in the development of more accurate genetic tests to detect advanced prostate cancer, identify the most appropriate course of treatment for individual patients, and predict treatment outcomes. Team leader Dr. Karen Knudsen envisions long-term practical outcomes of this research, saying "it is our hope to use the information gained by these studies to understand which prostate cancer patients might benefit the most from combination treatments with a DNA-PK inhibitor drug".

More information: Emanuela Dylgjeri, Christopher McNair, Jonathan F. Goodwin, Heather K. Raymon, Peter A. McCue, Ayesha A. Shafi, Benjamin E. Leiby, Renée de Leeuw, Vishal Kothari, Jennifer J. McCann, Amy C. Mandigo, Saswati N. Chand, Matthew J. Schiewer, Lucas J. Brand, Irina Vasilevskaya, Nicolas Gordon, Talya S. Laufer, Leonard G. Gomella, Costas D. Lallas, Edouard J. Trabulsi, Felix Y. Feng, Ellen H. Filvaroff, Kristin Hege, Dana Rathkopf and Karen E. Knudsen, "Pleiotropic impact of DNA-PK in cancer and implications for therapeutic strategies," *Clinical Cancer Research*, DOI: 10.1158/1078-0432.CCR-18-2207 , 2019. clincancerres.aacrjournals.org … 078-0432.CCR-18-2207

Vishal Kothari, Jonathan F Goodwin, Shuang G Zhao, Justin M Drake, Yi Yin, S. Laura Chang, Joseph R Evans, Kari Wilder-Romans, Kristina

Gabbara, Emanuela Dylgjeri, Jonathan Chou, Grace Sun, Scott A. Tomlins, Rohit Mehra, Kristen Hege, Ellen H. Filvaroff, Edward M. Schaeffer, R. Jeffrey Karnes, David A Quigley, Dana Rathkopf, Housheng H. He, Corey Speers, Daniel E. Spratt, Luke A Gilbert, Alan Ashworth, Arul M. Chinnaiyan, Ganesh V Raj, Karen E Knudsen and Felix Y. Feng, "DNA-dependent protein kinase drives prostate cancer progression through transcriptional regulation of the Wnt signaling pathway," *Clinical Cancer Research*, DOI: 10.1158/1078-0432.CCR-18-2387 , 2019. clincancerres.aacrjournals.org … 078-0432.CCR-18-2387