Lynchpin molecule for the spread of cancer found

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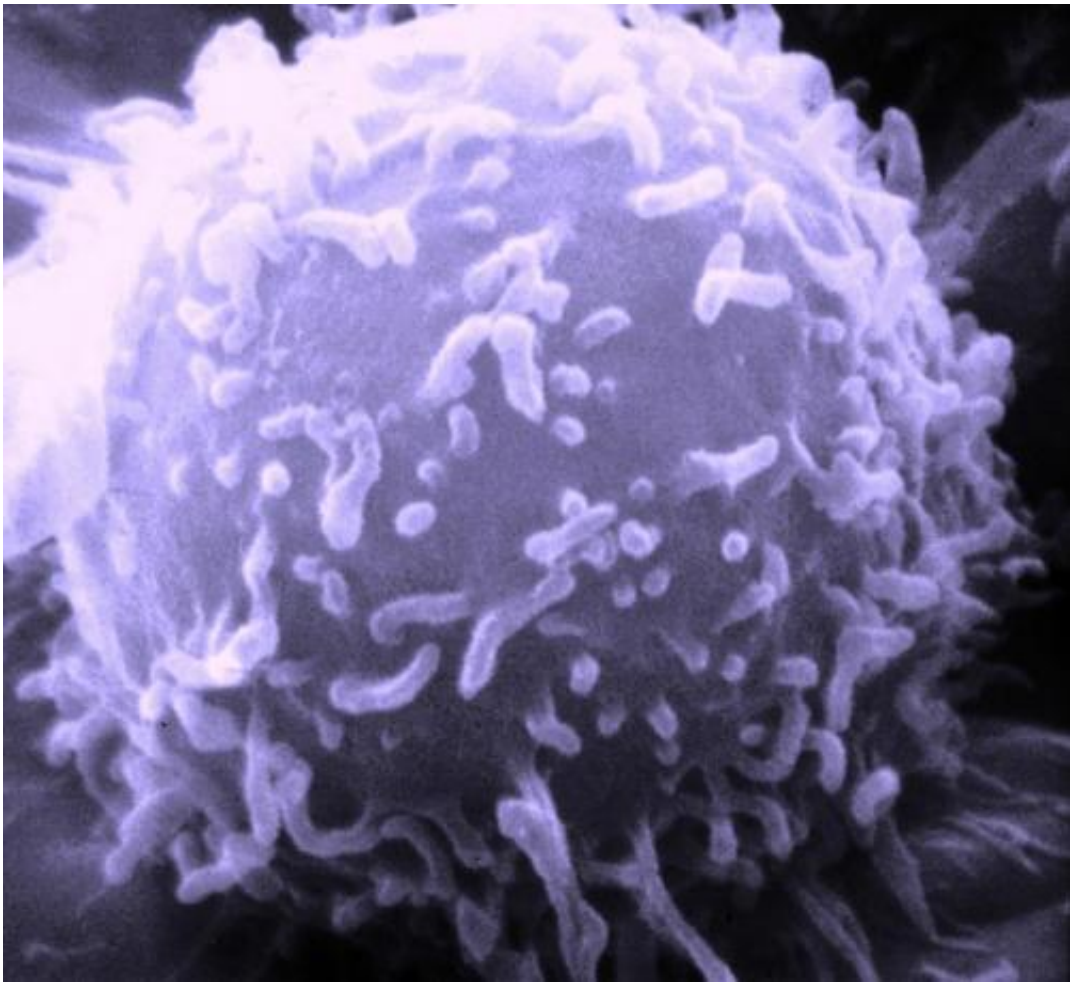

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Cancer is a disease of cell growth, but most tumors only become lethal once they metastasize or spread from their first location to sites throughout the body. For the first time, researchers at Thomas Jefferson University in Philadelphia report a single molecule that appears to be the central regulator driving metastasis in prostate cancer. The study, published online July 13th in *Cancer Cell,* offers a target for the development of a drug that could prevent metastasis in prostate cancer, and possibly other cancers as well.

"Finding a way to halt or prevent cancer metastasis has proven elusive. We discovered that a molecule called DNA-PKcs could give us a means of knocking out major pathways that control metastasis before it begins," says Karen Knudsen, Ph.D., Director of the Sidney Kimmel Cancer Center at Thomas Jefferson University, the Hilary Koprowski Professor and Chair of Cancer Biology, Professor of Urology, Radiation Oncology, and Medical Oncology at Jefferson.

Metastasis is thought of as the last stage of cancer. The tumor undergoes a number of changes to its DNA - mutations - that make the cells more mobile, able to enter the bloodstream, and then also sticky enough to anchor down in a new location, such as the bone, the lungs, the liver or other organs, where new tumors start to grow. Although these processes are fairly well characterized, there appeared to be many non-overlapping pathways that ultimately lead to these traits.

Now, Dr. Knudsen and colleagues have shown that one molecule appears to be central to many of the processes required for a cancer to spread. That molecule is a DNA repair kinase called DNA-PKcs. The kinase rejoins broken or mutated DNA strands in a cancer cell, acting as a glue to the many broken pieces of DNA and keeping alive a cell that should normally self-destruct. In fact, previous studies had shown that DNA-PKcs was linked to treatment resistance in prostate cancer, in part because it would repair the usually lethal damage to tumors caused by

radiation therapy and other treatments. Importantly, Dr. Knudsen's work showed that DNA-PKcs has other, far-reaching roles in cancer.

The researchers showed that DNA-PKcs also appears act as a master regulator of signaling networks that turn on the entire program of metastatic processes. Specifically, the DNA-PKcs modulates the Rho/Rac enzyme, which allows many cancer cell types to become mobile, as well as a number of other gene networks involved in other steps in the metastatic cascade, such as cell migration and invasion.

In addition to experiments in prostate cancer cell lines, Dr. Knudsen and colleagues also showed that in mice carrying human models of prostate cancer, they could block the development of metastases by using agents that suppress DNA-PKcs production or function. And in mice with aggressive human tumors, an inhibitor of DNA-PKcs reduced overall tumor burden in metastatic sites.

In a final analysis that demonstrated the importance of DNA-PKcs in human disease, the researchers analyzed 232 samples from prostate cancer patients for the amount of DNA-PKcs those cells contained and compared those levels to the patients' medical records. They saw that a spike in the kinase levels was a strong predictor of developing metastases and poor outcomes in prostate cancer. They also showed that DNA-PKcs was much more active in human samples of castrate-resistant prostate cancer, an aggressive and treatment-resistant form of the disease.

"These results strongly suggest that DNA-PKcs is a master regulator of the pathways and signals that lead to the development of metastases in prostate cancer, and that high levels of DNA-PKcs could predict which early stage tumors may go on to metastasize," says Dr. Knudsen.

"The finding that DNA-PKcs is a likely driver of lethal disease states was unexpected, and the discovery was made possible by key

collaborations across academia and industry," explains Dr. Knudsen. Key collaborators on the study, in addition to leaders of the Sidney Kimmel Cancer Center's Prostate Program, included the laboratories of Felix Feng (University of Michigan), Scott Tomlins (University of Michigan), Owen Witte (UCLA), Cory Abate-Shen (Columbia University), Nima Sharifi (Cleveland Clinic) and Jeffrey Karnes (Mayo Clinic), and contributions from GenomeDx.

Although not all molecules are easily turned into drugs, at least one pharma company has already developed a drug that inhibits DNA-PKcs, and is currently testing it in a phase 1 study (NCT01353625). "We are enthusiastic about the next step of clinical assessment for testing DNA-PKcs inhibitors in the clinic. A new trial will commence shortly using the Celgene CC-115 DNA-PKcs inhibitor. This new trial will be for patients advancing on standard of care therapies, and will be available at multiple centers connected through the Prostate Cancer Clinical Trials Consortium, of which we are a member," explained Dr. Knudsen.

"Although the pathway to drug approval can take many years, this new trial will provide some insight into the effect of DNAP-PKcs inhibitors as anti-tumor agents. In parallel, using this kinase as a marker of severe disease may also help identify patients whose tumors will develop into aggressive metastatic disease, so that we can treat them with more aggressive therapy earlier," says Dr. Knudsen. "Given the role of DNA-PKcs in DNA repair as well as control of tumor metastasis, there will be challenges in clinical implementation, but this discovery unveils new opportunities for preventing or treating advanced disease."

More information: J. F. Goodwin et al., "DNA-PKcs mediated transcriptional regulation drives prostate cancer progression and metastasis," *Cancer Cell*, 2015.

Provided by Thomas Jefferson University