A new route for tackling treatment-resistant prostate cancer

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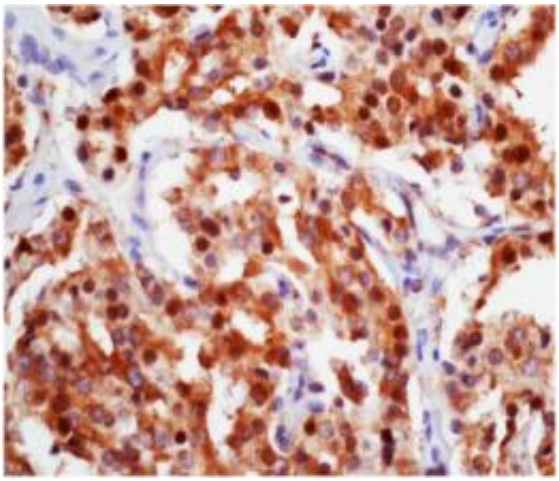

Scientists have identified what may be the Peyton Manning of prostate cancer. It's a protein called paxillin that's essential for the disease to execute its game plan - grow and spread throughout the body. In a study published in the Journal of Clinical Investigation, scientists found that paxillin controls cell growth in tumors that are sensitive to hormone therapy and in tumors that grow resistant to such treatment. Paxillin may be a new treatment target for men with advanced prostate cancer, a stage of the disease which usually proves lethal. Paxillin, in red, is much more prevalent in prostate cancer cells than normal prostate cells. Credit: University of Rochester Medical Center

Scientists have identified what may be the Peyton Manning of prostate cancer. It's a protein that's essential for the disease to execute its game plan: Grow and spread throughout the body.

Like any good quarterback, this protein has command over the entire field; not only does it control cell growth in tumors that are sensitive to hormone therapy, a common treatment for men with advanced disease, but also in tumors that grow resistant to such treatment – a dismal development that leaves men and their doctors with no good options to turn to.

In a study published in the *Journal of Clinical Investigation*, a team led by scientists from the University of Rochester Medical Center found that the protein paxillin is a major player in prostate cancer, the second most common form of cancer in men. Though in the very early stages, the discovery is an important first step towards developing a treatment for men whose cancer prevails even after the most aggressive treatment.

"The holy grail in prostate cancer is to figure out why cells stop responding to hormone therapy," said senior study author Stephen R. Hammes, M.D., Ph.D., chief of the Division of Endocrinology and Metabolism at the Medical Center. Initially, hormone therapy, which starves tumors of the hormones that fuel their growth, works well and may lead to remission. But, according to the American Cancer Society, nearly all prostate cancers treated with hormone therapy become resistant over a period of months or years and the cancer makes an unwelcome comeback.

"Somehow, tumors find a way to grow even when their main power source is choked off," noted Hammes, also the Louis S. Wolk Distinguished Professor in Medicine. "Our work is exciting because we've identified a protein pathway that controls growth even in the absence of hormones and provides a completely new treatment target for the disease."

Hammes and first author Aritro Sen, Ph.D., Research Assistant Professor in the Division of Endocrinology and Metabolism, knew from

their previous research that paxillin is important in prostate cancer, but they didn't know why or how.

They found that under certain conditions the protein, which normally hangs out in the cytoplasm or gel-like substance that fills a cell, actually goes into the nucleus – the cell's genetic powerhouse. There, it's an extremely commanding force, regulating signals that lead to the creation of cancer cells.

"This is the first time anyone's shown that paxillin goes into the nucleus and controls gene expression," said Sen. "When we eliminated this protein from prostate cancer cells their growth was significantly arrested, but what surprised us most was that this effect was identical in both hormone therapy-dependent as well as resistant prostate cancer cells."

In typical tumors stimulated by male hormones called androgens, paxillin partners with the hormones to turn on genes that lead to the creation of more cancer cells. Such tumors shrink, at least for a time, when subject to hormone therapy.

But for tumors that continue to grow despite hormone therapy – called castration-resistant prostate cancer – Hammes' team found that paxillin takes another route and connects with naturally occurring substances called growth factors to activate genes that produce more cancer cells.

Take paxillin out of the nucleus and growth comes to a halt: Without it, genes directed by androgens don't get turned on, nor do genes directed by growth factors.

"Lots of pathways are being examined as scientists look for what makes a prostate cancer cell become castration resistant, but ours is a completely novel approach," says Hammes of the paxillin-mediated pathway.

Sen adds, "We have now found a common factor that regulates both hormone-dependent and castration-resistant prostate cancer cells."

Edward M. Messing, M.D., chair of the Department of Urology at the Medical Center and a world-renowned expert in the diagnosis and treatment of prostate cancer, says "This is a potentially important observation since, as of now, most cancers eventually escape available means of inactivating androgens and their receptor. If paxillin proves to be a major new pathway, interfering with it may extend life or even cure men with far advanced prostate cancer, a stage of the disease which until now has always proved lethal."

The team conducted multiple tests to confirm the power of paxillin in prostate cancer. They found that paxillin is ramped up in tissue from human tumors, much more so than in normal cells. And in mice with human prostate cancer cells, getting rid of paxillin caused the tumors to grow more slowly.

Hammes says the next step is to figure out how to stop paxillin from getting into the nucleus, or to inhibit its activity once it's in the nucleus. "Paxillin has important functions in the cytoplasm, like helping cells communicate with each other to form organs and other structures," he noted. "If we can target paxillin in the nucleus where it mediates cancer cell growth, but leave it intact in the cytoplasm so it can continue to do the important work it does there, that would be the goal."

Like any targeted cancer therapy, the team wants to hurt the cells that are proliferating, and leave the healthy cells that are standing still alone, says Hammes.

Provided by University of Rochester Medical Center