Anti-Cancer Compound Could Help Overcome Resistant Prostate Tumors

Combined with a targeted nanoparticle, Platin-L disrupts cancer cell DNA and metabolism and could provide another tool to treat prostate cancer.

Shanta Dhar, Ph.D.

Researchers at Sylvester Comprehensive Cancer Center in the University of Miami Miller School of Medicine have shown that a compound called Platin-L disrupts tumor cell DNA and fatty acid oxidation, a critical metabolic process that fuels both prostate tumor growth and resistance to common chemotherapy drugs, such as cisplatin. In addition, the team showed Platin-L can be readily attached to targeted nanoparticles, which makes the compound orally available and could increase its safety and efficacy. The study was published in the journal ACS Central Science.

“Cisplatin has been used effectively to treat many different cancers, but unfortunately, prostate cancer resists this drug,” said Shanta Dhar, Ph.D., associate professor of biochemistry and molecular biology, assistant director of technology and innovation at Sylvester and senior author on the study. “We believe Platin-L can circumvent these resistance mechanisms.”
Tumor Resistance

Prostate tumors are generally treated with anti-hormone therapies, which can become ineffective over time. If not for tumor resistance, cisplatin would be a logical second-line treatment. The team sought to overcome this with Platin-L, which is a prodrug — a compound that only becomes the actual drug when metabolized in the body.

In the study, the researchers treated both patient prostate tumor samples and cisplatin-resistant preclinical models with Platin-L. These experiments showed the prodrug forces cancer cells to abandon their main energy source, fatty acid oxidation, both starving them and sensitizing them to cisplatin chemotherapy. In addition, the Platin-L destroyed both mitochondrial and nuclear DNA. This combined metabolic and DNA disruption successfully destroyed prostate cancer cells.

“We know that when this compound binds to a mitochondrial protein (called CPT1A), it inhibits fat metabolism and is eventually transported to the mitochondria, where it damages mitochondrial DNA and helps overcome resistance,” said Dr. Dhar. “We are also making prostate cancer cells choose a less favorable metabolic pathway, which is insufficient to their needs, making it difficult for them to survive.”

Flexible Nanoparticles

These nanoparticles target a protein called prostate-specific membrane antigen (PSMA), which is highly expressed in prostate tumors.

“We made a dual-targeted nanoparticle,” said Dr. Dhar. “The
first targeting is needed to get it through the gut barrier, and the second targeting takes it to the prostate. The beauty is, now we can deliver a chemotherapeutic orally, which is usually never done. And by targeting the prostate, we can reduce kidney and liver toxicity and the risk of peripheral neuropathy.”

This promising discovery could give prostate cancer patients new treatment options, but first, it will have to advance through clinical development. Dr. Dhar and colleagues at Sylvester are investigating potential industry partners to carry this work forward.

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