Researchers discover a mechanism that could improve platinum-based cancer therapy

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Researchers have identified a protein that, when targeted, enables cisplatin-resistant cancer cells to become responsive to treatment. Cisplatin, and other similar platinum drugs, are incredibly effective at

killing rapidly growing cancer cells, which is why they have been used in treating cancers for over 45 years. However, these drugs are non-targeted and can cause debilitating toxic side effects, resulting in a diminished lifestyle, and patients in poor health are deemed ineligible for use.

In a study, published in *Cancer Research* researchers say they have discovered that the protein puromycin-sensitive aminopeptidase (NPEPPS) plays a role in regulating response to platinum chemotherapy in patients with bladder cancer.

"We found that this protein is a driver in resistance to platinum therapy. If we remove it experimentally or pharmacologically, we can re-sensitize the cancer cells to their pre-resistant level of response," says James Costello, Ph.D., co-corresponding author and associate professor at the University of Colorado Anschutz Medical Campus.

Costello and co-authors aimed to understand why most bladder cancer patients do not respond well to platinum-based drug regimens. By identifying the role NPEPPS plays, researchers were then able to genetically disrupt the function of NPEPPS, ultimately making cancer cells more responsive to platinum drugs.

"Our multi-omic assessment, including the use of tiny organoids derived from patients' bladder cancer samples, yielded findings that could make this effective treatment an option for many more patients," said Dan Theodorescu, MD, Ph.D., director of Cedars-Sinai Cancer, the PHASE ONE Foundation Distinguished Chair at Cedars-Sinai and co-corresponding author of the study.

Theodorescu added that the approach is an example of how precision medicine is leading the change in how cancer is treated by defining cancer vulnerabilities such as NPEPPS that can be targeted with small molecules and used in combination with cisplatin. Indeed, the

Theodorescu and Costello laboratories are doing just that.

"This novel therapeutic approach could allow the administration of lower platinum drug doses, potentially decreasing debilitating side effects while also making platinum-based therapies more effective," says Costello, also with the CU Cancer Center. He points to next steps in utilizing this new approach in hopes of expanding its use to other cancers.

"A high percentage of all cancer patients will see a platinum drug in their treatment. Our work opens the door for extending these findings to other cancer types. Our goal is to help platinum-based agents be more effective in many clinical settings."

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