Circumventing the renal toxicity associated with cisplatin treatment

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Cisplatin is widely used as a chemotherapeutic agent for the treatment of various solid tumors, including bladder, ovarian, and esophageal tumors. However, on metabolism by an enzyme called "cysteine conjugate beta-

lyase 1 (CCBL1)," it gets converted to "thiol-cisplatin," a highly active toxic metabolite. Though cisplatin treatment is associated with other side effects, this metabolite is known to cause kidney damage, and is thus, a major dose-limiting side effect of cisplatin treatment.

As a remedial measure, aggressive or intravenous short duration administration of saline and mannitol are considered as a standard of care. However, these hydration regimens often require hospitalization in many cases.

To improve the standard of care, a team of researchers from Japan have now found that the inhibition of the CCBL1-mediated metabolism of cisplatin by the aromatic ketone 2',4',6'-trihydroxyacetophenone (THA) can reduce cisplatin toxicity without affecting the drug's potency. This study was led by Associate Professor Hidetsugu Fujigaki of the Fujita Health University and published in *Molecular Cancer Therapeutics*.

Speaking about the study, Associate Professor Hidetsugu Fujigaki and a co-author, Nao Sukeda, a Master's student from Fujita Health University's Graduate School of Health Sciences say, "Using a high-throughput screening assay, we identified THA as an inhibitor of CCBL1. THA inhibited human CCBL1 β-elimination activity in a concentration-dependent manner."

To this end, the researchers first screened compound libraries for possible inhibitors of CCBL1, the enzyme responsible for the synthesis of cisplatin's toxic metabolite. This screening yielded THA, a naturally occurring compound from the Curcuma comosa rhizome, a plant of the ginger family, as an inhibitor of CCBL1 aminotransferase activity. They found THA to be an inhibitor of CCBL1 activity when testing with recombinant human CCBL1.

Investigating further, the researchers examined the protective in vitro

and in vivo effects of THA on cisplatin-induced kidney damage using a variety of experimental techniques. For instance, they demonstrated that THA decreased the toxicity of cisplatin in healthy kidney cells derived from pigs that produced human CCBL1. Moreover, the researchers also observed that THA did not interfere with cisplatin's ability to reduce the proliferation of human- and murine- derived cancerous cells.

Explaining further, Professor Kuniaki Saito from Fujita Health University's Graduate School of Health Sciences says, "Upon examining the preventive effect of THA on cisplatin-induced nephrotoxicity, we noticed that THA attenuated the effect of cisplatin on the viability of confluent renal tubular cells but did not interfere with cisplatin-induced reduction in the proliferation of tumor cell lines including murine lung cancer and human breast cancer cells."

Next, the researchers observed that mice pre-treated with THA showed a significant reduction in cisplatin-induced pathological increases in blood urea nitrogen, creatinine, cell damage score, and kidney cell damage. Importantly, this THA pre-treatment also did not interfere with or adversely affect the anti-tumor efficacy of cisplatin in tumor-bearing mice.

"These effects might be attributed to the inhibition of the CCBL1-mediated formation of thiol-cisplatin. Our results suggest that THA might prevent cisplatin-induced nephrotoxicity and potentially provide a new strategy for patients receiving cisplatin-based cancer treatments," explains Associate Professor Fujigaki.

Going forward, the researchers believe that THA could facilitate the use of cisplatin in patients with compromised kidney function. Though further clinical trials are warranted, the researchers believe that THA pre-treatment is likely to improve the quality of life in patients undergoing cisplatin-based cancer treatment.

More information: Nao Sukeda et al, Identification of 2',4',6'-trihydroxyacetophenone as promising cysteine conjugate beta-lyase inhibitor for preventing cisplatin-induced nephrotoxicity, *Molecular Cancer Therapeutics* (2023). DOI: 10.1158/1535-7163.MCT-22-0564