Cancer drug cisplatin found to bind like glue in cellular RNA

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An anti-cancer drug used extensively in chemotherapy binds pervasively to RNA -- up to 20-fold more than it does to DNA, a surprise finding that suggests new targeting approaches might be useful, according to University of Oregon researchers.

Medical researchers have long known that cisplatin, a platinum compound used to fight tumors in nearly 70 percent of all human cancers, attaches to DNA. Its attachment to RNA had been assumed to be a fleeting thing, says UO chemist Victoria J. DeRose, who decided to take a closer look due to recent discoveries of critical RNA-based cell processes.

"We're looking at RNA as a new drug target," she said. "We think this is an important discovery because we know that RNA is very different in tumors than it is in regular healthy cells. We thought that the platinum would bind to RNA, but that the RNA would just degrade and the platinum would be shunted out of the cell. In fact, we found that the platinum was retained on the RNA and also bound quickly, being found on the RNA as fast as one hour after treatment."

The National Institutes of Health-supported research is detailed in a paper placed online ahead of regular publication in *ACS* Chemical Biology, a journal of the American Chemical Society. Co-authors with DeRose, a member of the UO chemistry department and Institute of Molecular Biology, were UO doctoral students Alethia A. Hostetter and Maire F. Osborn.

The researchers applied cisplatin to rapidly dividing and RNA-rich yeast cells (Saccharomyces cerevisiae, a much-used eukaryotic model organism in biology). They then extracted the DNA and RNA from the treated cells and studied the density of platinum per nucleotide with mass spectrometry. Specific locations of the metal ions were further hunted down with detailed sequencing methods. They found that the platinum was two to three times denser on DNA but that there was a much higher whole-cell concentration on RNA. Moreover, the drug bound like glue to specific sections of RNA.

DeRose is now pursuing the ramifications of the findings. "Can this drug be made to be more or less reactive to specific RNAs?" she said. "Might we be able to go after these new targets and thereby reduce the drug's toxicity?"

While cisplatin is effective in reducing tumor size, its use often is halted because of toxicity issues, including renal insufficiency, tinnitus, anemia, gastrointestinal problems and nerve damage.

The extensive roles of RNA have come under intense scrutiny since completion of the human genome opened new windows on DNA, life's building blocks. It had been assumed that RNA was simply a messenger that coded for protein activity. New technologies, DeRose said, have shown that a vast amount of RNA performs an amazing level of different functions in gene expression, controlling it in specific ways during development or disease, particularly in cancer cells.

In this project, DeRose's team only explored cisplatin's binding on two forms of RNA: ribosomes, where the highest concentration of the drug was found; and messenger RNA. There are more areas to be looked at, said DeRose, whose group initially developed experience using and mapping platinum's activity as a mimic for other metals in her research on RNA enzymes.

DeRose is now planning work with UO colleague Hui Zong, a biologist studying how cancer emerges, to extend the research into mouse cells to see if the findings in yeast RNA hold up. An additional collaboration with UO chemist Michael Haley involves the creation of new platinum-based drugs with "reaction handles" that will allow researchers to easily pull the experimental drugs out of cells, while still attached to their biological targets. New developments in 'deep' RNA sequencing, available through the UO's Genomic Core Facilities, could then provide a much broader view of platinum's preferred resting sites in the cell.

Provided by University of Oregon