Elucidating side effects of antineoplastic agent

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Cisplatin, an anticancer drug widely used for treating various types of tumor, can induce side effects in the short term. A team of French scientists, mostly from CNRS and the Universite de Nice has provided first in vitro evidence that this antitumor agent modifies the sensitivity of cellular pressure sensors. This completely novel mechanism could help to elucidate certain neurological side effects of cisplatin hitherto unexplained. These results could open potential avenues for improving the chemotherapeutic efficacy of cisplatin-based compounds. The researchers now plan to test them on animal models. Their work was published on 1st October 2010 in the journal *Cancer Research*.

Cisplatin is a platinum-based molecule widely used in the treatment of various forms of cancer in humans. Following intravenous administration, it penetrates the cells to form stable complexes with the DNA molecule, thereby preferentially killing tumor cells, which are the most vulnerable. In order to proliferate, cancer cells actually need to constantly replicate their DNA, which they can no longer do when it is complexed with cisplatin. However, this treatment has a major drawback. Within an hour or even half an hour following injection, some patients suffer from side effects: perception and hearing disorders, tinnitus and sometimes inner ear dysfunctions causing dizziness. The unpleasantness of these neurological effects can prompt patients to interrupt the treatment, despite its efficacy. A better understanding of these short-term side effects is therefore crucial.

Most research laboratories mainly focus on cisplatin's action on DNA.

However, such genotoxic effects cannot occur very rapidly: consequently, they do not explain the short-term side effects of cisplatin and other antineoplastic drugs of the same family. For this reason, the team of scientists headed by Laurent Counillon and Mallorie Poet decided to focus on another aspect of cisplatin: its already known action at the cell membrane level.

The researchers conducted their experiments in a model cell system. They discovered that cisplatin, independently of its action on DNA, is capable of modifying, within a few minutes, the architecture of a cell membrane: injecting this molecule into a cell changes the shape, morphology and tension of its membrane. Yet, the cell membrane contains numerous pressure- and stretch-sensitive proteins. These sensors regulate the pain threshold in peripheral nerve fibers and detect sound waves and “verticality” in the vestibular system of the ear . Pursuing their investigations, the scientists managed to demonstrate that cisplatin disrupts the functioning of these mechanosensitive sensors, which may trigger neurological effects. They have identified and described a novel mechanism through which this antitumor agent acts. This process could therefore explain the occurrence of cisplatin's short-term side effects. These results make it possible to envisage optimizing the efficacy of platinum-based anticancer treatments by combining them with compounds that reduce these short-term side effects. Researchers are now due to proceed with animal testing.

More information: *Nongenomic Effects of Cisplatin: Acute Inhibition of Mechanosensitive Transporters and Channels Q2 without Actin Remodeling*. Nina Milosavljevic, et al, *Cancer Research*, 1st October 2010

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