A molecule worth its weight in gold to fight cancer

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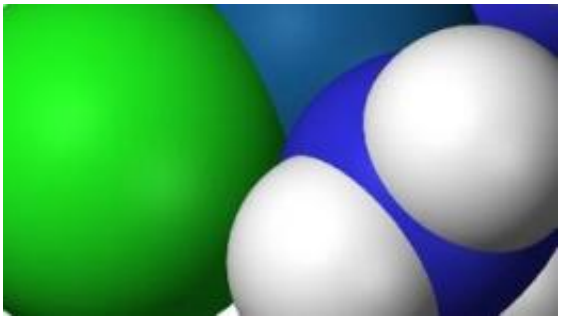

A part of the cisplatin molecule © Benjamin Mills

EPFL scientists have shown that inorganic, metal-containing molecules can be used to fight cancer. The discovery has opened up a whole new area of research.

Chemotherapy treatments often work by attacking the DNA of cancer cells. The therapy's effectiveness is often limited, however, because the cancer cells become resistant. In the cell, a protein known as PARP initiates a reaction that repairs the DNA damage the chemotherapy drugs have caused. To reduce this undesirable effect, doctors use complementary treatments. Angela Casini, a researcher in EPFL's Laboratory of Organometallic and Medicinal Chemistry, and Yury Tsybin of EPFL's Biomolecular Mass Spectrometry Laboratory have just shown how certain molecules can effectively inhibit the activity of this protein, whose normal job is, ironically, to protect DNA from attack.

Cancer treatments are designed to compromise the DNA of cancer cells. But once the DNA is damaged, the PARP protein jumps into action to protect the cell. It attaches itself to the damaged areas and launches a repair process. The EPFL researchers have shown that metal-based compounds alter the PARP protein, thus inhibiting its repair function. They first studied cisplatin, a chemotherapy drug containing platinum. This drug was already known for its anti-cancer effects, but not for its ability to fight side effects. Then they demonstrated the effectiveness of molecules containing gold. “These new results are very encouraging for getting around the resistance put up by the cancer cells,” says Casini.

Verifying an intuition

Casini followed her chemist’s intuition. “We hypothesized that molecules containing metal in their core were effective PARP inhibitors, based on the elemental chemical properties. But we still needed to verify this experimentally at the molecular level.”

Casini collaborated with Tsybin to run the experiments. They used a high-resolution mass spectrometer, a particularly precise apparatus that allowed them to measure particles in liquid solution, a necessary step in getting the metallic compound to interact with the DNA.

“To understand what interactions are taking place between the various molecules and how they combine, it’s important to know their exact mass, and the mass of their fragments. This allows us to deduce the reactions that are taking place,” explains Tsybin. This is how the scientists were able to figure out how the metallic compound affected the PARP protein.

New therapeutic possibilities

The chemists also hope to be able to open up new areas of research by

testing other metallic molecules. Applications for other therapies could be designed using their method. “It’s a gamble, because there’s nothing published on this,” explains Casini. But the huge efforts deployed to fight cancer are testimony to the importance of this particular battle.

More information: Metal-Based Inhibition of Poly(ADP-ribose) Polymerase – The Guardian Angel of DNA, Filipa Mendes, Michael Groessl, Alexey A. Nazarov, Yury O. Tsybin, Gianni Sava, Isabel Santos, Paul J. Dyson, and Angela Casini, *Journal of Medicinal Chemistry*.

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