How Does the Antitumor Drug Get to the Cell Nucleus?

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Platinum complexes such as the well-known cisplatin are powerful antitumor medications. They cross the cell membrane and reach the nucleus, where they attach to DNA and stop cell growth. But how does cisplatin get to the nucleus? Italian researchers have now proven that a copper transport protein may play a critical role. In the journal *Angewandte Chemie*, they present their hypothesis about the transport mechanism.

It has always been assumed that cisplatin simply passes through the cell membrane; however, growing evidence indicates that a copper transporter is involved. Ctr1 is a membrane-dwelling protein that brings copper into cells.

It consists of three helical segments that sit in the membrane, one end protruding into the cell, the other on the outside. Three such molecules lodge together to form a channel-like structure. The end that sticks out of the cell and the interior of the “channel” contain many sulfur-containing methionine groups, which are important for binding copper.

A team led by Giovanni Natile at the University of Bari (Italy) has now proven that this structural element also plays a role in binding platinum. The researchers produced a synthetic peptide with a structure very similar to the extracellular end of the copper transport protein. Cisplatin is a complex with a central platinum ion and four ligands: two neighboring amino groups and two neighboring chloride ions. The peptide displaces all four of these ligands and binds to the platinum ion

itself.

As is the case for copper, the transport protein seems to bind the platinum atom from cisplatin by replacing all other ligands bound to the metal ion. The next step could be the traversal of a ligand-free “naked” platinum atom through the channel and into the cytosol of the cell. However, this contradicts other experiments that have demonstrated that treated tumor cells do not contain bare platinum, but rather undegraded cisplatin—accumulated in certain organelles.

Natile and his co-workers have proposed an interesting hypothesis to explain these observations: After an initial interaction between a few cisplatin molecules and the methionine-rich extracellular end of the copper transporter, the platinum ion does not pass through the channel, but instead stabilizes the trimeric channel structure.

This sets in motion a mechanism called endocytosis, in which the cell membrane encircles the transporter and forms a little interior bubble filled with the outer medium. This medium contains some intact cisplatin. The bubble then migrates to the interior of the cell and comes into contact with the organelles, including the nucleus.

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