New Insights in the Mechanism of Action and Transport of Platinum Drugs

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Cisplatin (*cis*-[$PtCl_2(NH_3)_2$]), one of the most potent antitumor drugs currently in clinical use, is known to target DNA by forming bifunctional adducts [1]. Ancillary ligands can modulate the anticancer properties of this type of compounds and, as a result of their markedly different biological effects, only the *R,R* enantiomer of the [Pt(DACH)(oxalate)] complex has been approved for clinical use (DACH = 1,2-diaminocyclohexane) [2].

After cisplatin binding to the putative target, double-stranded DNA, a kinked structure, that is recognized by certain proteins, is formed [1]. The latter features depend upon the stereochemistry of the carrier ligands [3] and have direct consequences on cell viability and eventually leads to cell killing by apoptosis.

Apart from passive diffusion, a number of carrier-mediated import proteins have been identified, the main players being organic-cation transporters and the copper influx transporter CTR1. Moreover, ATPases involved in the removal of excess copper appear to play a role in the excretion/inactivation of platinum drugs. Also the copper chaperone Atox1 has been found to interact with platinum drugs at the same site as copper. Moreover, for longer contact time with platinum, Atox1 forms dimers similar to those formed by copper and which have been shown to be able to translocate to the nucleus and act as a transcription factor [4].

In the presentation new insights both in the cellular uptake of the drugs and in the processing of their adducts with DNA will be highlighted.

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