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Review

Cisplatin binding to proteins: A structural perspective

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ABSTRACT

The interactions of clinically established anticancer Pt-based drugs with proteins play crucial roles in Pt cellular uptake and biodistribution, as well as in determining side effects and resistance, thus affecting the overall pharmacological profile of this class of drugs. Here, we summarize a number of recent crystallographic studies of cisplatin/protein adducts that contribute unveiling the molecular basis for cisplatin-protein recognition. Details of each molecular structure are carefully and comparatively described; common trends and regularities occurring in the analyzed adducts are highlighted. Analysis of the structural features of its protein derivatives, integrated with selected results arising from the application of other biophysical methods on strictly

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related systems, allows an overall elucidation of the protein platination process and offers a more comprehensive understanding of the mode of action of cisplatin and its parent Pt-based drugs.

Abbreviations:
a.u., asymmetric unit
Atox-1, a copper chaperone protein
ATP7A, Menkes' disease protein
ATP7B, Wilson's disease protein
beSOD, superoxide dismutase from bovine erythrocyte
CA, carbon alpha atom
CD, circular dichroism
Cox17, Cytochrome c oxidase Copper Chaperone
Ctr1, Copper transport protein 1
Cyt c, horse heart cytochrome c
cyt c, cytochrome c
DMSO, dimethyl sulfoxide
DNA, deoxyribonucleic acid
ESI-MS, electrospray mass spectrometry
Grx, glutaredoxin
GSH, glutathione
HEWL, hen egg white lysozyme
HSA, human serum albumin
hSOD, human superoxide dismutase
MD, molecular dynamics
Na^+/K^+-ATPase, sodium/potassium pump dependent adenosine triphosphatase
ND1, atom of the side chain of His
NMR, nuclear magnetic resonance spectroscopy
ox*Pf*Grx-1, oxidized *Plasmodium falciparum* Glutaredoxin-1
Occupancy, proportion of sites filled by atoms
PAGE, polyacrylamide gel electrophoresis
PDB, protein data bank
PEG, polyethylen glycole
*Pf*Grx-1, *Plasmodium falciparum* glutaredoxin-1
Rmsd, root mean square deviation
RNase A, bovine pancreatic ribonuclease
SOD, superoxide dismutase
Space group, description of the symmetry of the crystal
ssRNA, single-stranded RNA
QM/MM, quantum mechanism/molecular mechanics
1 Å, 10^{-10} m

1. Introduction

Since the end of 1970s, cisplatin [*cis*-$Pt(Cl_2(NH_3)_2]$ (Fig. 1) has been widely used in the clinics for cancer therapeutics, in particular to treat and even cure a few solid tumors that manifest a high chemo-sensitivity toward platinum drugs, such as testicular and ovarian cancers [1–4].

The *in-vivo* molecular mechanism of cisplatin, which behaves as a classical *prodrug*, involves most probably its aquation and subsequent DNA binding [5–7]; in turn, Pt binding induces large structural modifications of the DNA double helix, ultimately leading to cancer cell apoptosis [4]. Although DNA is the commonly accepted primary target for cisplatin [8,9], interactions between cisplatin and a variety of intracellular biomolecules (in particular thiol-rich or His-rich) are also very important owing to the high reactivity and affinity of Pt compounds toward S- and N-donors [10]. Indeed, the process of protein-cisplatin recognition is reputed crucial in determining cisplatin transport, its cellular uptake, biodistribution and toxicity profile [11,12].

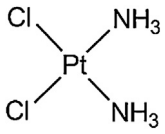

Fig. 1. Structure of cisplatin.

After injection into the bloodstream, most of the platinum (65 to 98%) deriving from cisplatin is associated with proteins [13], in particular to hemoglobin [14], serum albumin [15–17] and transferrin [18,19]. In addition, a significant portion of Pt is bound to γ-glutamyl-cysteine-glycine (glutathione, GSH) [20] and/or other cysteine-rich biomolecules [21] like a few small proteins of the metallothionein family [22]. Cisplatin may enter cells with the help of proteins belonging to the so called "copper trafficking" system