Structural studies on the interaction between human serum transferrin and cisplatin

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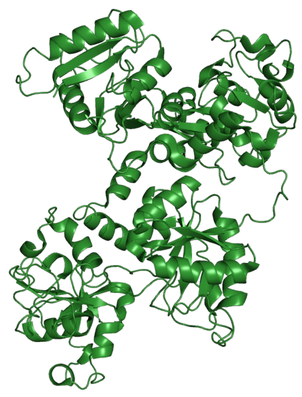
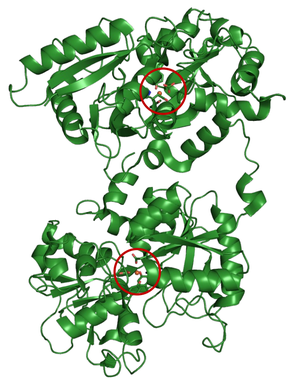
Background

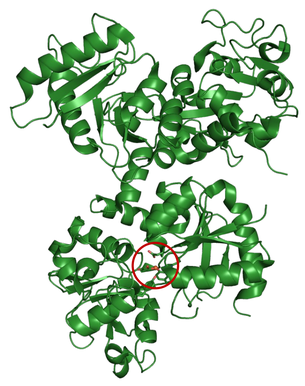
Human serum transferrin (hTF) is an 80 kDa single-chain protein formed by two lobes (N and C), each containing a Fe^{3+} binding site. Depending on the number of Fe^{3+} bound, hTF exists in different forms. In addition to the ***apo- and holo-hTF***, containing respectively no or two ferric ions, hTF can also occur in two ***monoferric forms***. In these latter, only one Fe^{3+} is bound either to N- (Fe_N-hTF) or C-lobe (Fe_C-hTF).



apo-hTF
PDB code 2HAV



holo-hTF
PDB code 3V83



Fe_C-hTF
PDB code 4X1B

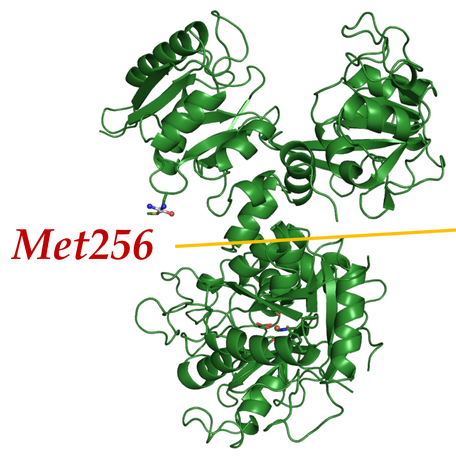
As a consequence of the ***over expression of transferrin receptor on cancer cells***, hTF has been proposed as a potential ***anticancer drug carrier***. It has also been demonstrated that hTF can bind the anticancer agent ***cisplatin ([cis-$Pt(NH_3)_2Cl_2$])*** and selectively deliver it to cancer cells. Although numerous studies have been conducted to determine the ***molecular mechanism of cisplatin binding to hTF***, there are still divergent opinions on the cisplatin binding sites of hTF. This is mainly due to the substantial lack of direct structural information on the adducts formed by cisplatin and the different hTF forms.

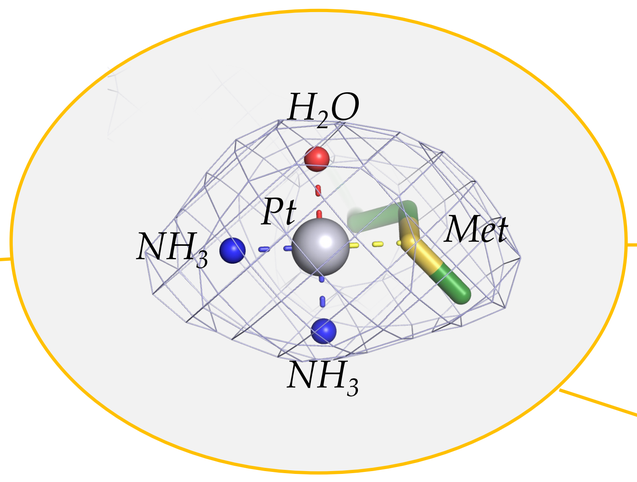
In this context, we recently solved, for the first time, the ***crystallographic structures*** of the adducts formed upon reaction of the cisplatin with ***apo-hTF*** or ***Fe_C-hTF***.

Results

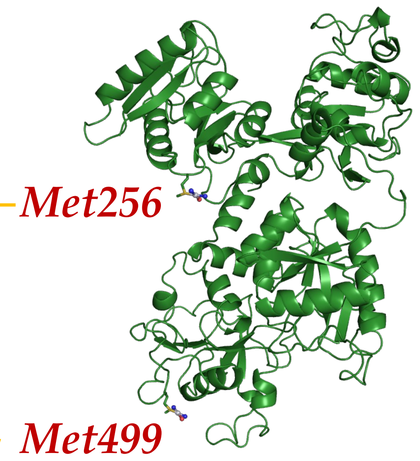
The binding of platin to the hTF involves ligation to the ***Sδ position of methionine residues***. The two structures show a ***different number of Pt-binding sites***. In particular, cisplatin binds Fe_C-hTF close to the side chain of ***Met256*** at the N-lobe. In the case of apo-hTF, Pt binds close to the side chains of ***Met256*** at the N-lobe and ***Met499*** at the C-lobe.

Fe_C-hTF/cisplatin adduct





apo-hTF/cisplatin adduct



To gain further independent information on the reactivity of the cisplatin towards the different forms of hTF, ICP MS experiments are ongoing.

Experimental details: apo-hTF and Fe_C-hTF crystals were equilibrated with solid cisplatin for few days and the data collections were performed at Elettra Sincrotrone Trieste. Atomic coordinates and structure factors for Fe_C-hTF/cisplatin adduct have been deposited with the Protein Data Bank under accession code 8BRC.

Conclusion

Considering the ability of hTF to transport both anticancer agents and radio-imaging agents, the two crystal structures of the hTF/cisplatin adducts can serve as excellent ***template to design new theranostic agents***. Moreover, it must be underlined that our structures enrich the still scarce repertoire of ***structures of hTF/metallodrugs adducts*** and provides ***useful data to understand the role of hTF in cisplatin cellular delivery***.

Part of these results has been published in *Inorg. Chem*. 2023, 62, 2, 675–678.