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Reaction and selectivity of metallodrugs to zinc proteins

Metallodrugs, such as cisplatin, are widely used in clinic for cancer chemotherapy. It is well-known that DNA is the drug target of platinum antitumor agents; however, only small portion of intracellular platinum binds to DNA. Proteins are found to play important roles in the drug uptake, DNA repair and drug efflux, thus determine the drug efficacy and resistance. Metalloproteins are the majors targets of metallodrugs since the metal binding in metalloprotein could also be suitable to the coordination of emtallodrug. Sulfur containing proteins are kinetically more favorable than DNA in the reaction to platinum drugs. Copper proteins are highly reactive to cisplatin since Cu(I) and Pt(II) have similar binding preference in coordination chemistry. Moreover, a large number of zinc proteins, such as zinc-finger proteins (ZFPs), could also be potential binding targets of metallodrugs. The selectivity of metallodrugs on various zinc proteins are crucial for their drug efficacy and side-effects.

Sp1 is a transcription factor regulating the expression of a number oncogenes and is associated with cancer metastasis. We found that Sp1 is rather inert to cisplatin, but active to trans-PtTz an antitumor active trans-platinum complex. NAMI-A is a ruthenium-based anti-metastasis drug. Interestingly, NAMI-A selectively reacts with Sp1. This selectivity is rather different from cisplatin and arsenic trioxide. It is worth noting that the reaction of Sp1 with NAMI-A is significantly enhanced by GSH; which promotes the unfolding and aggregation of Sp1. Unexpectedly, the reduction of Ru(III) to Ru(II) reduced the reactivity of NAMI-A to Sp1.

Arsenic trioxide (ATO) is an effective drug used for the treatment of APL. The ring-finger protein PML is the drug target of ATO; however, the binding of ATO to ZFPs is associated with the toxicity of ATO. We found that ATO preferentially binds to PML, the drug target of APL. According to the target selection in the treatment of APL, we investigated ruthenium arene complexes in the reaction of PML protein. Results indicate that [(η6-p-bip)Ru(en)Cl][PF6] (Ru-1) can selectively react with PML, leading to the zinc-release and protein unfolding. The degradation of PML-RARα causes the differentiation of APL cells. Ru-1 also binds to DNA and triggers the apoptosis of APL cells. The other non-selective Ru(II) compound, though also highly reactive to PML, does not exhibit anti-APL activity. These findings suggest that the selectivity of metallodrugs is crucial for their therapeutic potency.

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