

From Mechanistic Study to the Design of Platinum-Based Anticancer Complexes

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Cisplatin is widely used for the treatment of different cancers. However, its severe toxicity such as nephrotoxicity and neurotoxicity, coupled with drug resistance developed with patients after initial treatments, has limited its wider clinical application. The toxic effects of platinum-based drugs have long been associated with its reactions with thiol-containing molecules such as glutathione γ -L-Glu-Cys-Gly (GSH). We have investigated the reactions of $[\text{Pt}(\text{L-MetH-S,N})\text{Cl}_2]$ with γ -glutathione (GSH) and L-cysteine (L-Cys) at different pH and different molar ratio. Polymeric species such as $[\text{Pt}_3(\mu\text{-SG-S})_4(\text{Met-S,N})_2]$ were detected and were stable for long hours. Interestingly, the thiols can also replace the S,N-chelated methionine from $[\text{Pt}(\text{L-Met-S,N})_2]$, and the *cis*-isomer of $[\text{Pt}(\text{L-Met-S,N})_2]$ was found more reactive than the *trans*-isomer.

Compounds with novel structural features, therefore, are required which could potentially provide different biological properties. Most of the structure-activity rules emerged from the initial studies by Rosenberg et al has recently been questioned. Many Pt (II) complexes which are *trans* in geometry, or charged, or having only one leaving group have been found active. In this talk we will first summarize our recent studies on the mechanism of reaction of platinum-based anticancer drugs, and then report the design of several new types of metal-based anticancer complexes, which will include: a) the mechanism of reaction of cisplatin and carboplatin with L-Methionine and L-Selenomethionine; b) chelate and ring-opening Pt(II) antitumor complexes; c) highly cytotoxic monofunctional Pt(II) complexes; d) polynuclear Pt(II) complexes with robust structural features.

Acknowledgment. The author gratefully acknowledges the support of the National Science Foundation of China and K.C. Wong Education Foundation, Hong Kong.

References

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