A study of the effects of cisplatin on nucleosomal DNA using magnetic tweezers

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The hallmark of cancerous cells is their incessant cell division, and they thus push and invade intact normal cells. Chemotherapeutic agents help to cure cancers by inducing apoptosis in the affected cells. Cisplatin, one of the most effective cytotoxic agents and displaying clinical activity against various tumors, has been widely used in cancer chemotherapy for decades. The well-known mechanism of cisplatin is that the drug binds and kinks DNA via crosslinking, which can lead to cell death. However, the working mechanism of cisplatin on the physiological condition has not been fully understood yet. In reality, cellular anionic species suppress cisplatin activity by forming non-reactive complexes with cisplatin. Besides, recent studies found several intriguing roles of histones in cisplatin's anti-cancer effect. Here, we reconstituted nucleosomes on a single DNA tether molecule under a physiological ionic condition by using a histone chaperone called NAP1. We then studied the effects of cisplatin on the reconstituted nucleosomal tether molecule under various ionic conditions via magnetic tweezers. Surprisingly, the reduced activity of cisplatin under physiological ionic conditions is still sufficient to eliminate the conformational flexibility and reversibility of nucleosomal DNA by fixing its condensed structure. The cisplatin-induced fastening of a nucleosomal DNA can therefore interfere with normal DNA metabolism. Our direct physical measurements shed new light on the understanding the mechanism of platinum-based anti-cancer drugs