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DNA-Pt Complex Interactions Investigated by Single-Molecule Force Spectroscopy and Surface-enhanced Raman Spectroscopy

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Abstract

Biomacromolecules have dynamic three-dimensional structures that are selective for interacting with other biological components in cellular function. For example, DNA is the major target of anti-cancer drugs in chemotherapy medications. Despite the broad clinical successes in cancer treatment, Platinum complexes exhibit severe side effects and acquired/intrinsic drug resistance due to off-target binding. Thus, an in-depth mechanistic understanding of DNA-Platinum complex interactions is required to support the rational design of new chemotherapy drugs that selectively bind to target DNA. Nevertheless, in the newly designed Platinum complexes, multiple binding modes with different kinetics are adopted to achieve better selectivity and binding affinity, significantly increasing the complexity of simultaneous molecular mechanisms. Therefore, it is challenging to distinguish and characterize different binding modes among heterogeneous DNA-Platinum complex interactions by traditional bulk studies that measure the average characteristics of large-scale molecular systems. By removing ensemble averaging, we utilized single-molecule techniques to investigate the individual binding behaviors between Platinum complex and DNA at the most fundamental level, in order to complement the traditional bulk observations and explain the detailed molecular mechanisms. The non-covalent interactions, in particular, intercalation, are monitored by single-molecule force spectroscopy. The covalent interactions are identified by surface-enhanced Raman spectroscopy. This multi-dimensional characterization can offer subtle details to understand the binding mechanisms between Platinum complexes and DNA, which would provide guidance for the development of selective anti-cancer drugs targeting specific DNA.

Besides, we are studying the protein folding of intrinsically disordered proteins to define the structural details at different intermediate stages, which is difficult to resolve by traditional methods in the bulk due to the pronounced conformational heterogeneity. The combination of single-molecule force spectroscopy and surface-enhanced Raman spectroscopy offers exclusive advantages when characterizing the dynamic conformational changes of intrinsically disordered proteins, providing mechanistic insight to extend the understanding of their functionality in the biological system.

Keywords: DNA-small molecule interaction, SERS, Raman spectroscopy, single-molecule force spectroscopy, protein folding.