Titanocene and Nucleic Acids: Analysis of a Fruitful Liaison

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Antitumor titanocene dichloride (Cp_2TiCl_2, Cp = cyclopentadienyl) and its derivatives are considered very promising in chemotherapy, attributable to their high activity in cancer cell studies and their low toxicity against healthy tissue. Though the precise mechanism of action has not been elucidated yet, the accumulation of the transition metal in the nucleus points towards DNA as one of the primary targets. Different analytical techniques and computational studies evidenced the interaction of metallocenes with oligonucleotides, but the exact ligand composition of the formed adducts and the underlying binding specificities remain unknown. Mass spectrometry constitutes an ideal tool to illuminate the ligand stoichiometries of the formed adduct. The ability to select and collisionally activate a certain metallocene-oligonucleotide complex further allows the specific localization of preferred binding sites.

In this study, positive nanoESI-MS/MS experiments were conducted on titanocene-nucleic acid adducts. Binding preferences were examined by competition experiments on DNA and RNA hexamers. Detailed elucidation of the binding pattern was performed by tandem mass spectrometric approaches comprising collisional activation and electron transfer. Furthermore, the influence of the transition metal coordination center on the gas-phase dissociation of the olignucleotides is discussed.