Adenine Recognition by Minor-Groove Targeted Platinum–Intercalator Conjugates: A New Technology with Applications in Chemotherapy and Gene Regulation

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The design of DNA-targeted sequence- and groove-specific small synthetic molecules continues to be one of the most challenging applications of chemistry in the life sciences. DNA-binding proteins and DNA-processing enzymes, which also interact with DNA in a sequence- and groove-specific manner, are mediators of the cytotoxic effect produced by many chemotherapies. One goal, therefore, is to target DNA-associated processes with high selectivity, especially those critical to cell proliferation and gene expression.

Platinum(II)-acridinylthiourea conjugates are a novel class of DNA-targeted cytotoxic agents that show promising activity in a broad range of solid tumor cell lines. Unlike cisplatin and its derivatives, PT-ACRAMTU ([PtCl(en)(ACRAMTU-*S*)]$(NO_3)_2$; en = ethane-1,2-diamine, ACRAMTU = 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea) does not induce purine-purine cross-links but associates with DNA through a combination of monofunctional platination of nucleobase nitrogen and intercalation of the acridine nonleaving group into the DNA base stack. The distinct base-pair step and groove recognition of the ACRAMTU moiety results in a DNA damage profile truly complementary to that of cisplatin. The most striking feature of PT-ACRAMTU proves to be its ability to covalently modify adenine-N3 in the minor groove of DNA, which is unprecedented in platinum antitumor chemistry. Various biophysical, high-resolution structural, and molecular biology methods have been applied to shed light on the DNA interactions of PT-ACRAMTU and the recognition of its (minor-groove) adducts by enzymes and proteins, such as TATA-binding protein (TBP), a key player in eukaryotic transcription initiation. New strategies that exploit the PT-ACRAMTU "technology" for the design of agents with improved sequence specificity will be discussed. This research is supported by the National Institutes of Health/National Cancer Institute.