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Effect of Sequence Context in Platinum-DNA Structure

Debadeep Bhattacharyya, Candice L. King, Shantanu Sharma, Brenda Temple, Sharon L. Campbell, and Stephen G. Chaney

The structural basis for differential protein recognition of cisplatin (CP)-DNA and oxaliplatin (OX)-DNA adducts has not been determined and could be important for the design of more effective platinum anticancer agents. We have recently reported high resolution solution NMR structures of OX-GG, CP-GG adducts and undamaged DNA dodecamers in the AG*G*C (G* = G coordinated to platinum) sequence context. A comparison of the structures of these platinated-DNA adducts revealed that the conformation of CP and OX in the AG*G*C sequence is significantly different than that observed previously in other sequence contexts, which may relate to the increased mutagenicity of CP adducts in the AG*G*C sequence context. However, the experimental conditions were not identical in our structural study compared to previous studies. Thus, to confirm the effect of the sequence context in the conformation of platinated adducts, structural studies using multidimensional NMR spectroscopy of the OX-adducted dodecamer in the sequence context d(CCTCTG*G*TCTCC) d(GGAGACCAGAGG) were performed.

A comparison between the solution NMR structures of OX-TG*G*T and the OX-AG*G*C adducts solved in our laboratory also resulted in significant differences. The ^{1}H NMR study of the temperature dependence of the exchangeable protons of the OX-DNA adducts revealed an unprecedented dynamic motion for the 5′-flanking residue to the platinated adduct site in the T G*G*T sequence context. Compared to the OX-AG*G*C adduct, the OX-TG*G*T adduct exhibited less buckle, greater propeller twist, and less opening for the 5′- and 3′-G C base pairs. In addition, compared to the OX-AG*G*C adduct, the OX-TG*G*T adduct exhibited a greater roll, slide, and twist for the 5′-flanking base pair step and greater tilt and less twist for the 3′-flanking base-pair steps. In addition to the helical parameters, a greater chi angle value for the C4 and T20 residues of OX-TG*G*T adduct compared to those of the OX-AG*G*C adduct indicated a higher anti-character for the C4 and T20 residues of OX-TG*G*T adduct. The differences observed in the NMR structural features of OX-TG*G*T and OX-AG*G*C adducts highlight the importance of sequence context of DNA in explaining the discrimination shown for the translesion synthesis past the DNA-platinum adduct sites. We have also postulated that some of the differences in damage recognition protein binding and translesion synthesis past CP and OX adducts may be due to differences in the conformational flexibility of DNA containing those adducts. To test this postulate, we are currently performing a ten nanosecond unrestrained, fully solvated MD simulation of the OX-TG*G*T adduct along with those for the CP-DNA adduct and undamaged DNA in the same TG*G*T sequence context. These differences in the conformation and dynamic motion may help explain the effect of sequence context on the ability of damage recognition proteins to bind to Pt-DNA adducts. (Supported by NIH grant CA84480)