

QMMM Calculations on the Mechanism of Repair of 5'-Topoisomerase II-DNA Adducts

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Tyrosyl-DNA phosphodiesterase 2 (TDP2) catalyzes the hydrolysis of cytotoxic, dead-end complexes between DNA and the active site tyrosine residue of topoisomerase II created during the processes such as treatments with cancer chemotherapeutics. This catalytic reaction give rise to DNA with free 5' phosphate. Using the available X-ray crystal structures of the complex of TPD2 with DNA adducts as the starting conformations, we carried out molecular dynamics and QMMM calculations to study the mechanism of direct reversal of topoisomerase II adducts to 5'-phosphorylated DNA termini that could then be repaired through double strand break repair mechanism. Involvement of a single Mg²⁺ ion and the residues near the active site during the catalysis is investigated.