Comparative MD simulations of wild type and T718A mutant in the DNA-human topoisomerase I complex - (session: Structural Genomics)

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Topoisomerase enzymes control the level of supercoiled DNA in cells transiently breaking one or two DNA strands. Recently, we carried out a Molecular Dynamics (MD) study of a reconstituted human topoisomerase I comprising the core and C-terminal domains, in covalent complex with a 22 base pair duplex DNA. The study provided useful information on the role of water in the protein-DNA recognition process and on the collective domain motions of the enzyme (Chillemi et al., 2001; Chillemi et al., 2003). Eukaryotic topo I is the cellular target of the anti-tumor drug camptothecin (CPT), which reversibly stabilizes the cleavable complex, an intermediate in the enzyme's catalytic cycle. Mutation of Thr718 to Ala produces a lethal phenotype that resembles CPT by stabilizing the covalent intermediate between topo I and DNA (Fiorani et al., 1999).

Here we present a MD simulation of human topo I comprising the core, the linker and the C-terminal domains (residues 203-765) in complex with a 22-base pair DNA duplex. Both the wild type enzyme and the human topo I T718A mutant were simulated for 2.2 nanoseconds. The simulations show strong modifications in the dynamics of mutated protein regions far from the mutation site and structural rearrangements of the active site residues that can explain the lethal phenotype of the mutant.

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