Multiple Inhibitor Co-crystal Structures of the Human Topoisomerase I Covalent DNA Complex bound to a Series of Structurally Diverse Anti-cancer Compounds

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Topoisomerases are ubiquitous enzymes that relieve the torsional stress of DNA generated by nuclear processes such as replication and transcription. All topoisomerases act through a conserved tyrosine residue to cleave the DNA phosphodiester backbone and form a covalent phosphotyrosine intermediate. After cleavage, the broken DNA strand can rotate around the unbroken strand to either wind or un-wind DNA. The phosphodiester backbone is restored in a reversal of the transesterification reaction.

The transient top1-DNA covalent complex is a validated target for the development of anti-cancer compounds. Several structurally diverse families of chemical compounds have been discovered which specifically bind to and trap the transient top1-DNA covalent complex, which eventually results in cell death.

We report the X-ray crystal structures of the human top1-DNA complex bound with representative members of several families of anti-cancer compounds including: camptothecins, homo-camptothecins, indenoisoquinolines, indolocarbazoles and minor groove binding top1 poisons. Two distinct binding sites are identified, one for intercalating compounds such as camptothecin, and another for minor groove binding ligands. The planar nature of the intercalating compounds allows them to stack between DNA base pairs at the site of single-strand cleavage. These new X-ray structures will aid the rational design of completely novel structural classes of anticancer drugs.

Keywords: topoisomerase I, camptothecin, DNA complex