

Abstract

DNA topoisomerases are the key enzymes involved in carrying out high precision DNA transactions inside the cells. In particular, Top1 relax DNA supercoiling generated by transcription, replication, and chromatin remodeling. To untwist the DNA, Top1 nicks one DNA strand by covalently linking its catalytic tyrosine residue to a 3'-phosphate, which allows the controlled rotation of the broken strand around the intact one. However, Top1 are detrimental to the cell when a wide variety of Top1-targeted drugs generate cytotoxic lesions (Top1cc) by trapping the enzymes in covalent complexes on the DNA. Repair of these Top1cc has been suggested as an important part of DNA metabolism. One of the key repair enzymes for Top1 is TDP1. TDP1 hydrolyzes phosphodiester bonds at a DNA 3'-end linked to a tyrosyl moiety. This type of linkage is found in Top1cc, and TDP1 is implicated in the repair of such complexes. Human TDP1 can also hydrolyze other 3'-end DNA alterations including 3'-phosphoglycolates and 3'-abasic sites indicating it may function as a general 3'-DNA phosphodiesterase and repair enzyme. Genetic inactivation of TDP1 in human causes the neurodegenerative disease spinocerebellar ataxia neuropathy 1 (SCAN1). TDP1 is also reported to be over expressed in cancer. The role of TDP1 in DNA repair is well established, however its regulation is poorly understood. Here, we describe novel mechanisms for TDP1 regulation and its unique role in mitochondrial DNA repair with implications for neurodegeneration and cancer.