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TOP1, TDP1 and PARP1 inhibition: coupling and association

Dyrkheeva N.*, Zakharenko A., Lavrik O.
Institute of Chemical Biology and Fundamental Medicine, SB RAS, Novosibirsk, Russia
** dyrkheeva.n.s@gmail.com*

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DNA topoisomerase 1 (TOP1) is an enzyme that has evolved to resolve topological problems in DNA catalyzing DNA supercoil relaxation via transient single-stranded breaks in DNA. There are clinically used antitumor drug compounds that stabilize the TOP1-DNA covalent complex formed during the normal catalytic event. These TOP1 poisons, for example topotecan and irinotecan, are commonly used to treat ovarian, colon, and small cell lung cancers [1]. Tyrosyl-DNA-phosphodiesterase 1 (TDP1) is a DNA repair enzyme that purifies the 3'-end single-stranded breaks of DNA from covalent adducts of various origins, including those formed under the action of topotecan and irinotecan. Thus, TDP1 could be one of the factors of resistance of tumor cells to these drugs [2]. Poly(ADP-ribose)polymerase 1 (PARP1) is an enzyme that, through post-translational modification of poly(ADP-ribosyl)ation, controls different processes in the cell, including DNA repair, maintenance of genome integrity, cell death, and others. Among these processes could be the repair of TOP1-DNA stalled complex caused by topotecan and irinotecan [3]. Olaparib is a PARP inhibitor indicated to treat breast cancer, ovarian cancer, fallopian tube cancer, peritoneal cancer, pancreatic cancer, and prostate cancer [4].

Our team discovered a number of TDP1 and PARP1 inhibitors among derivatives of natural biologically active compounds [5-7]. The anticancer effect of TOP1 inhibitors can be enhanced by the simultaneous inhibition of PARP1, and TDP1 [5, 8]. TDP1 inhibitors may sensitize tumor cells to the action of TOP1 poisons, thereby potentiating their effects. Some of the TDP1 inhibitors we found have a pronounced sensitizing effect on the cytotoxic effect of topotecan *in vitro* and antitumor *in vivo* [5].

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