proceedings

MDPI

Extended Abstract

Tdp1 Inhibition as a Promising Approach to New Anticancer Drugs †

Konstantin Volcho [1,*], Alexandra Zakharenko [2], Olga Luzina [1], Tatyana Khomenko [1], Evgeniy Suslov [1], Oksana Salomatina [1], Olga Zakharova [2], Nikolai Li-Zhulanov [1], Jóhannes Reynisson [3], Olga Lavrik [2] and Nariman Salakhutdinov [1]

[1] Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia
[2] Novosibirsk Institute of Chemical Biology and Fundamental Medicine, Novosibirsk 630090, Russia
[3] School of Chemical Sciences, University of Auckland, Auckland 1142, New Zealand
* Correspondence: volcho@nioch.nsc.ru
† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 7 August 2019

Keywords: anticancer agent; Tdp1 inhibitor; DNA repair enzyme; synthesis; usnic acid; pentathiepine; adamantane; molecular modeling; terpene; coumarin

---

The cytotoxic effects of chemotherapy and radiation that are clinically used to treat malignancies are directly related to their propensity to generate DNA damage. The capacity of cancer cells to recognize DNA damage and initiate DNA repair is a key mechanism for therapeutic resistance to chemotherapy. Therefore, the targeting of DNA repair enzymes can be used as a strategy to potentiate the cytotoxicity of the currently available DNA damaging agents toward cancer cells. PARP1 (poly ADP ribose polymerase 1, the enzyme involved in DNA repair) inhibitors such as olaparib, rucaparib, and niraparib are in clinical use already.

A new and very promising target for antitumor therapy is tyrosyl-DNA phosphodiesterase 1 (Tdp1). It plays a key role in the removal of DNA damage resulting from inhibition of topoisomerase 1 (Topo1) with camptothecin and its clinical derivatives irinotecan and topotecan. Furthermore, Tdp1 is known to be capable of removing the DNA damage induced by other anticancer drugs commonly used in clinical practice.

A set of very potent Tdp1 inhibitors was found by us among natural product derivatives. We designed new inhibitors using targeted modifications of terpenoids, coumarins, usnic acid, and other types of natural products. Moreover, we found that benzopentathiepine derivatives are very effective inhibitors of Tdp1. The ability of the inhibitors used in nontoxic concentrations to enhance the cytotoxicity of camptothecin and topotecan, the established topoisomerase 1 poison, was demonstrated. The significant increase in the antitumor and anti-metastatic effect of topotecan in mice in the presence of Tdp1 inhibitors was shown for the first time. Thus, Tdp1 inhibitors can be considered as a new type of drugs for antitumor therapy.