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Tyrosyl-DNA phosphodiesterase 1 (Tdp1) and its natural mutant SCAN1 inhibitors as prototypes of drugs

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Motivation and Aim: The ability of cancer cell to recognize DNA damage and initiate repair is the key mechanism of their resistance to chemotherapy. Therefore, the search of DNA repair enzymes inhibitors can serve as a strategy for the development of anticancer drugs. One of the most promising target enzymes for drug development is tyrosyl-DNA phosphodiesterase 1 (Tdp1) [1]. It plays an important role in the removal of DNA damage caused by topoisomerase 1 (Top1), its inhibitor camptothecin and anticancer drugs (camptothecin derivatives – topotecan and irinotecan) [2]. Thus, a Tdp1 inhibitors application can potentiate tumor cells to chemotherapy.

Furthermore, there is a natural mutant of Tdp1 (SCAN1), which is responsible for the development of neurodegenerative disease – a spinocerebellar ataxia syndrome with axonal neuropathy (SCAN1). SCAN1 phenotype does not appear until the second decade of life and is not associated with an increased risk of cancer or immunodeficiency states. Probably, pathology is caused by the accumulation of covalent intermediates SCAN1-DNA formed during the reaction [3]. Presumably, suppression of SCAN1 activity will prevent the progression of the disease.

Materials and methods: The Tdp1 and SCAN1 real-time activity measurements were carried out with fluorophore-quencher-coupled DNA-biosensor, previously designed in our laboratory [4]. Cell cytotoxicity was determined using standard MTT-test [5].

Results: We performed the screening of 34 compounds – derivatives of coumarin, β-carboline and leelamine. The most active derivatives have IC_{50} values of 0.1–1 mkM against Tdp1 and 3.5–10 mkM against SCAN1. SCAN1 inhibitors were found the first time. The compound showed low cytotoxicity (> 100 mkM) on A-549 and WI-38 cell lines.

Conclusion: Tdp1 and SCAN1 inhibitors can likely underlie the development of anticancer drugs and/or drugs preventing or slowing the progressive cerebellar ataxia to improve quality of life of SCAN1 patients.

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