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Synthesis and biological evaluation of novel classes of tyrosyl-DNA phosphodiesterase 1 inhibitors as anticancer drugs

Tyrosyl-DNA phosphodiesterase 1 (TDP1) is a promising target for antitumor therapy based on Top1 poison-mediated DNA damage. TDP1 plays an important role in removal stalled Top1-DNA covalent complexes, generated by DNA topoisomerase I (Top1) inhibitors, such as camptothecin and some other anticancer drugs. A mutation or genetic inactivation of Tdp1 can hypersensitise cells to camptothecin, whereas over-expression of the active Tdp1 protein has been shown to result in a significant reduction of camptothecin-induced DNA damages. Hence, inhibiting the activity of TDP1 can enhance the therapeutic effect of Top1 modulators for anticancer treatment. The row of novel types of compounds belonging to the different chemical classes were synthesized and tested as TDP1 inhibitors using an original oligonucleotide-based fluorescence assay. Some of them surpass world counterparts in efficiency in dozens of times. The study of cytotoxicity of these compounds revealed that all compounds possess moderate to low cytotoxicity. The absence of cytotoxicity is an advantage when used in combination with clinical Top1 inhibitors. Several inhibitors enhance cytotoxicity of camptothecin against tumor cell lines, sensitizing cells to its effects. We have chosen the least toxic inhibitors of Tdp1, possessing sensitizing effect, to test *in vivo*. We used mice with Lewis carcinoma to investigate the ability of Tdp1 inhibitors to sensitize tumor to the effect of topotecan (clinical camptothecin derivative). When using a combination of topotecan and Tdp1 inhibitor the primary tumor weight decreased by 30% and the number of lung metastases by 70% compared to a monotherapy with topotecan. Therefore, several new classes of very effective inhibitors of TDP1 were elaborated which are very prominent to improve cancer therapy based on TOP1 poison–mediated DNA damage.

Biography

Olga I Lavrik has completed her graduation from Novosibirsk State University and post-doctoral studies and PhD from Institute of Bioorganic Chemistry in Moscow. She is the director of Laboratory of Bioorganic Chemistry of enzymes in the Institute of Chemical Biology and Fundamental Medicine of Russian Academy of Sciences. She is the professor of Novosibirsk State University. She has worked as a Visiting Professor at NIEHS (NC), Institute Jacques Monod, France and University of Évry Val d'Essonne, France. She has published more than 300 papers in reputed journals and has been serving as an Editorial Board of *Journal of Molecular Biology and Biochemistry, Journal of Molecular Biology* and as a Reviewer of *Nucleic Acids Research, Journal of Medicinal Chemistry, Journal of Biological Chemistry, Oncology Letters* and other journals. She is a Member of Study Section of Russian Fund for Basic Research and Member of Federation of Biochemical Society. She is a Chancellor of European Environmental Mutagenesis and genomics Society. She is a State prize winner and correspondent member of Russian Academy of Sciences.

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