Univerza v Ljubljani

Medicinska fakulteta

Javna agencija za raziskovalno dejavnost Republike Slovenije

Research project N1-0234

Modern chemical and biochemical approaches towards identification of anticancer and drug resistance preventing steroidal agents

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Funding: 1. 1. 2022 – 31. 10. 2025

Project group: SICRIS

Project description:

Hormone-dependent cancers such as breast, endometrial (EC) and ovarian (OC) cancers account for more than one-third of all cancers in women. The pathophysiology of these cancers involves estrogen-dependent receptor-mediated cell proliferation associated with increased number of mutations. Current treatment of EC primarily involves surgery and chemotherapy or hormone therapy (estrogen deprivation), which are not optimal and result in estrogen-refractory disease. After surgery, first-line combined chemotherapy for OC includes platinum-based drugs and taxanes. However, more than 80-85% of OC patients develop drug resistance, resulting in a high mortality rate. This high mortality rate due to drug resistance highlights the importance of novel therapeutic strategies. HSD17B1 represents an established target for new estrogen-deprivation therapies, while the enzymes AKR1C1, AKR1C2 and AKR1C3 represent targets for the treatment of chemoresistance. In the current project estrane based compounds synthetized in the collaborative group of Dr. Erzsébet Mernyák from the Department of Organic Chemistry, University of Szeged, Hungary, will be investigated as inhibitors of established drug targets and as anticancer agents. We will use recombinant enzymes and model cell lines of endometrial and chemoresistant ovarian cancer together with state-of-the-art approaches to study cell proliferation, invasion and migration in real time. The aims of the project are to examine effects of these compounds: i) on the recombinant enzymes HSD17B1, AKR1C1, AKR1C2 and AKR1C3; ii) on proliferation, invasion and migration of model cell lines in real time and iii) on chemoresistance reversal. The project will use spectrophotometric and HPLC based methods to evaluate enzyme inhibition, state-of-the-art methods to study proliferation, invasion and migration of model cell lines in real time and evaluation of drug sensitivity. Novel therapeutic strategies for chemoresistant cancers are urgently needed, and in this regard, our project will contribute to identification of novel lead compounds as potential anticancer and drug resistance preventing agents to combat cancer and prevent drug resistance.

The phases of the project and their realization:

Months 1-24: Examination of the effects of estrane derivatives on the recombinant enzymes

Months 12-24: Studies of the effects of estrane derivatives on model cell lines

Months 24-36: Investigation of the effects of estrane derivatives on chemoresistance reversal

Bibliography: SICRIS