TOXICOLOGICAL ASPECT OF IMMUNOMODULATORS: FRIEND OR FOE IN INCREASING THE EFFECTIVENESS OF CANCER IMMUNOTHERAPY

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Malignant diseases world incidence is constantly increasing and it is assumed that combining immunomodulators with immunotherapy would improve cancer therapy effectiveness. We present a research-development project of international cooperation with the People's Republic of China entitled "Increasing the effectiveness of cancer immunotherapy with a combination of CAR-T cells or PD-1/PD-L1 inhibitors using immunomodulators", led by Faculty of Pharmacy, University of Belgrade. Sulforaphane (SFN), isothiocyanate from cabbage vegetables, and a type of inactivated bacterium *Pseudomonas aeruginosa* (PA-MSHA) have been recognized as immunomodulators with high immune system stimulating potential, i.e. antitumor effect. However, there are few data on their individual safe use, and no data on the potential side/harmful effects of their combination, especially in patients with malignant diseases and significant immune system impairment. The Chinese team is investigating the effectiveness of improving immunotherapy with combination of immunomodulators, with their first published results proving SFN positive effect when administered with CAR-T cells (1), while Serbian team aims to examine toxicological profiles of single and/or combined SFN and PA MSHA, *in silico*, *in vitro* and *in vivo* on two experimental models - zebrafish and rat. The project will specifically examine adverse effects potential of single and/or combined use of the tested immunomodulators or lack of their efficacy in cancer patients, especially colon cancer. The first *in silico* results of the Serbian team indicated benefit/risk of SFN in patients with colon cancer depending on individual genes expression and identified gene set which change may indicate a positive or negative effect of immunomodulators (2).

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TOKSIKOLOŠKI ASPEKT IMUNOMODULATORA: PRIJATELJ ILI NEPRIJATELJ U POVEĆANJU EFIKASNOSTI IMUNOTERAPIJE KARCINOMA

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Incidenca malignih oboljenja u svetu je u stalnom porastu i pretpostavlja se da bi kombinacija imunomodulatora sa imunoterapijom poboljšala efikasnost terapije kod pacijenata obolelih od raka. Ovaj rad prezentuje istraživačko-razvojni projekat međunarodne saradnje sa NR Kinom pod nazivom „Povećanje efikasnosti imunoterapije karcinoma kombinacijom CAR-T ćelija ili PD-1/PD-L1 inhibitora pomoću imunomodulatora” čiji je nosilac Farmaceutski fakultet Univerziteta u Beogradu. Sulforafan (SFN), izotiocijanat iz kupusastog povrća, i vrsta inaktivisane bakterije *Pseudomonas aeruginosa* (PA-MSHA) prepoznati su kao imunomodulatori sa velikim stimulativnim potencijalom imunskog sistema, odnosno antitumorskim efektom. Međutim, malo je podataka o njihovoj pojedinačnoj bezbednoj primeni, dok nema podataka o potencijalnim neželjenim i štetnim efektima njihove kombinovane primene, posebno kod pacijenata obolelih od malignih bolesti sa značajno narušenim imunskim sistemom. Kineski tim ispituje efikasnost poboljašanja imunoterapije kombinacijom sa imunomodulatorima, pri čemu je njihovim prvim publikovanim rezultatima dokazano pozitivno dejstvo SFN kada se primenjuje sa CAR-T ćelijama (1), dok je zadatak srpskog tima da ispita toksikolški profile pojedinačne ili kombinovane primene SFN i PA-MSHA *in silico*, *in vitro* i *in vivo* na dva eksperimentalna modela – zebrica i pacova. Projekat će posebno ispitati potencijal za pojavu štetnih efekata pojedinačne i/ili kombinovane primene ispitivanih imunomodulatora ili pak izostanak efikasnosti terapije kod pacijenata sa rakom, posebno rakom debelog creva. Prvi *in silico* rezultati srpskog istraživačkog tima ukazuju da korist ili rizik primene SFN kod pacijenata sa rakom debelog creva zavisi od ekspresije pojedinih gena kod pacijenta i identifikuje setove gena čija promena može ukazati na pozitivan ili čak negativan efekat primene imunomodulatora (2).

Literatura

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