TOXIC POTENTIAL OF COMBINED SULFORAPHANE/*PSEUDOMONAS AERUGINOSA* MANNOSE SENSITIVE HEMAGGLUTININ TREATMENT IN CANCER PATIENTS

Dragica Božić[1*], Katarina Baralić[1], Katarina Živančević[1,2], Danijela Đukić-Ćosić[1]

[1]University of Belgrade – Faculty of Pharmacy, Department of Toxicology "Akademik Danilo Soldatović", Belgrade, Serbia
[2]University of Belgrade – Faculty of Biology, Institute of Physiology and Biochemistry "Ivan Djaja", Center for Laser Microscopy, Belgrade, Serbia

*djorgovanovic@pharmacy.bg.ac.rs

Sulforaphane (SFN) and *Pseudomonas aeruginosa* – mannose sensitive hemagglutinin (PA-MSHA) are known immune modulators with shown anti-tumor characteristics and ability to inhibit the growth and progression of cancer cells. However, the benefit/risk ratio of their combinational use is not fully explained and needs further investigation. Thus, this study aims to understand the potential of the given therapy mixture to induce side/toxic effects in cancer patients. With the help of in-depth *in silico* toxicogenomics analysis, we have previously demonstrated that SFN (1) and PA-MSHA (unpublished data) dysregulated 13 and 64 genes in cancer patients, among which 5 and 16 were repressed, while 8 and 48 were induced by the given molecule, respectively. A total of 21 downregulated and 56 upregulated genes were analyzed with computational tools such as ToppGene ToppFun (https://toppgene.cchmc.org/)
and REACTOME (https://reactome.org/PathwayBrowser/#/) to determine the most important Gene Ontology terms and molecular pathways influenced by SFN/PA-MSHA combination. As expected, this therapy approach can lead to dysregulation of cell cycle and p53 signalling pathway, but also acute kidney failure. On the other hand, the set of SFN/PA-MSHA upregulated genes were enriched for leukocyte activation, positive regulation of cell population proliferation, TNF and other cytokines signalling pathways, as well as inflammatory diseases such as psoriasis, ulcerative colitis, or Crohn disease. Thus, the combinational treatment of the given immune modulators might have the potential to cause severe adverse outcomes and should be used with caution in cancer patients with renal insufficiency or immune diseases.

References

1. Bozic, D., Baralić, K., Živančević, K., Miljaković, E.A., Ćurčić, M., Antonijević, B., Djordjević, A.B., Bulat, Z., Zhang, Y., Yang, L., Đukić-Ćosić, D. Predicting sulforaphane-induced adverse effects in colon cancer patients via *in silico* investigation. Biomedicine & Pharmacotherapy, 2022; 146: p.112598.

Acknowledgments

This research was supported by the Ministry of Education, Sciences and Technological Development of Republic of Serbia, International Serbia-China project: "Improving anti-cancer immunotherapy efficacy of CAR-T cells or PD-1/PD-L1 inhibitors by combining immune modulators" (451-03-1203/2021-09).

TOKSIČNI POTENCIJAL KOMBINOVANE PRIMENE SULFORAFANA I *PSEUDOMONAS AERUGINOSA* - HEMAGLUTININ OSETLJIV NA MANOZU KOD PACIJENATA OBOLELIH OD RAKA

Dragica Božić[1*], Katarina Baralić[1], Katarina Živančević[1,2], Danijela Đukić-Ćosić[1]

[1]Univerzitet u Beogradu – Farmaceutski Fakultet, Katedra za toksikologiju "Akademik Danilo Soldatović", Beograd, Srbija
[2]Univerzitet u Beogradu – Biološki Fakultet, Institut za Fiziologiju i Biohemiju "Ivan Djaja", Centar za Lasersku Mikroskopiju, Beograd, Srbija

*djorgovanovic@pharmacy.bg.ac.rs

Sulforafan (SFN) i *Pseudomonas aeruginosa* – hemaglutinin osetljiv na manozu (PA-MSHA) su imunomodulatori koji ispoljavaju antitumorske osobine i mogu da inhibiraju rast i progresiju ćelija raka. Međutim, odnos korist/rizik njihove kombinovane upotrebe nije u potpunosti razjašnjen zbog čega je potrebno detaljnije ispitati farmakološko-toksikološki profil ovakve kombinacije. Stoga, ova studija ima za cilj da razjasni potencijal kombinovane primene SFN/PA-MSHA da izazove neželjene/toksične efekte kod pacijenata obolelih od raka. Uz pomoć detaljne *in silico* tokiskogenomske analize podataka, prethodno smo pokazali da SFN (1) i PA-MSHA (nepublikovani podaci) utiču na ekspresiju 13 i 64 gena, među kojima je 5 i 16 inhibirano, dok je 8 i 48 indukovano datim molekulima, redom. Ukupno 21 inaktiviran gen i 56 gena čija je ekspresija stimulisana analizirano je pomoću računarskih alata kao što su *ToppGene ToppFun* (https://toppgene.cchmc.org/) i *REACTOME* (https://reactome.org/PathvaiBrovser/#/) kako bi bile utvrđene najznačajnije molekularne funkcije, biološke procese i molekularne puteve na koje utiče kombinacija SFN/PA-MSHA. Kao što je i očekivano, ovakav terapijski pristup može dovesti do disregulacije ćelijskog ciklusa i signalnog puta p53, ali i do akutnog zapaljenja bubrega. S druge strane, skup aktiviranih SFN/PA-MSHA gena je uključen u aktivaciju leukocita, pozitivnu regulaciju proliferacije ćelija, TNF i druge signalne puteve citokina, ali i inflamatorne bolesti kao što su psorijaza, ulcerozni kolitis ili Kronova bolest. Stoga, kombinovani tretman ispitivanih imunomodulatora može imati potencijal da izazove ozbiljne neželjene ishode zbog čega ga treba sa oprezom koristiti kod pacijenata sa bubrežnom insuficijencijom ili postojećim imunološkim oboljenjima.

Literatura

1. Bozic, D., Baralić, K., Živančević, K., Miljaković, E.A., Ćurčić, M., Antonijević, B., Djordjević, A.B., Bulat, Z., Zhang, Y., Yang, L., Đukić-Ćosić, D. Predicting sulforaphane-induced adverse effects in colon cancer patients via *in silico* investigation. Biomedicine & Pharmacotherapy, 2022; 146: p.112598.

Zahvalnica

Ovo istraživanje je podržalo Ministarstvo prosvete, nauke i tehnološkog razvoja Republike Srbije kroz međunarodni istraživačko-razvojni projekat između Republike Srbije i NR Kine: „Povećanje efikasnosti terapije karcinoma kombinacijom CAR-T ćelija ili PD-1/PD-L1 inhibitora pomoću imunomodulatora" (451-03-1203/2021-09).