STUDIA UNIVERSITATIS BABEŞ-BOLYAI BIOLOGIA, 66, 1, 2021 (p. 13-14)

Novel combined therapy based on IL-13-PEG-LCL-SIM and PEG-EV-DOX to reduce murine melanoma aggresiveness *in vivo*

Giorgiana Negrea[1]✉, Valentin-Florian Rauca[1], Laura Pătraş[1], Lavinia Luput[1], Emilia Licărete[1], Vlad-Alexandru Toma[1,2], Bogdan Dume[1], Alina Porfire[3], Manuela Banciu[1] and Alina Sesărman[1]

[1] *Department of Molecular Biology and Biotechnology, Faculty of Biology and Geology, Babeş-Bolyai University, Cluj-Napoca, Romania;* [2] *Department of Experimental Biology and Biochemistry, Institute of Biological Research, branch of NIRDBS Bucharest, Cluj-Napoca, Romania;* [3]*Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania;*
✉***Corresponding author, E-mail:*** ***giorgiana.negrea@ubbcluj.ro.***

Abstract

Melanoma is one of the most aggressive type of cancer worldwide, which rapidly develops resistance to conventional treatments, resulting in metastasis and recurrence. This study aims to test the potential of IL-13-PEG-LCL-SIM and PEG-EVs-DOX to decrease the aggressiveness of B16.F10 murine melanoma by applying an innovative therapy that targets both tumor-associated-macrophages and cancer cells. Melanoma-bearing mice intravenously received the combined therapy, or the individually formulations of SIM or DOX. In order to detect the level of expression of HIF-1α, a key promoter of hypoxia and of Bcl-xL and Bax, apoptotic proteins, western blot analysis was performed. The concentration of malondialdehyde (MDA) in tumor lysates, a marker of oxidative damage, was assessed by HPLC. Our data showed a strong inhibition of tumor development for the group treated with the combined therapy. Also, there was a substantial decrease of expression of HIF-1α due to PEG-EVs-DOX therapy, which was not noticed in the case of combined therapy. However, the concentration of MDA was highly increased, indicating a disruption of intratumor ROS levels, that alters the balance needed for HIF-1α proper activity. Thus, our findings suggest that the combined active targeted therapy which was tested, strongly inhibits tumor growth. Additional studies must be performed to understand the actions of this new active therapy on other processes which maintain the tumor development, such as angiogenesis and inflammation.

Keywords: melanoma**,** targeted therapy, tumor microenvironment

Acknowledgements. This work was supported by UEFISCDI national project, PN-III-P4-ID-PCE-2016-0342, contract no: 91/2017, Project manager: Dr. Manuela Banciu, Babeş-Bolyai University, Cluj-Napoca, Romania.

References

Alupei, M. C., Licarete, E., Banciu, M., *et al*. (2015). Liposomal simvastatin inhibits tumor growth via targeting tumor-associated macrophages-mediated oxidative stress. *Can. Lett*., 356(2), 946–952.

Buranrat B., *et al*. (2017). Simvastatin potentiates doxorubicin activity against MCF7 breast cancer cells, *Onco. Let*. 14: 6243-6250.

Doublier, S., Belisario, D.C., *et al.* (2012). HIF-1 activation induces doxorubicin resistance in MCF7 3-D spheroids, *BMC Can*., 12(1).

Licărete, E., Rauca, V. F., Luput, L., Banciu, M., *et al*. (2020). Overcoming Intrinsic Doxorubicin Resistance in Melanoma by Anti-Angiogenic and Anti-Metastatic Effects of Liposomal Prednisolone Phosphate on Tumor Microenvironment. *International Journal of Molecular Sciences*, 21(8), 2968.

Liu, J., & Wang, Z. *et al.* (2015). Increased Oxidative Stress as a Selective Anticancer Therapy. *Oxid. Med. and Cell. Long*., 2015, 1–12, 2015.

Spampanato, C., De Maria, S., Sarnataro M., *et al.* (2012). Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of Bax and down-regulation of Bcl-2 gene expression. *Int. J. Oncol*. 40:935–941.