TUMOR-DERIVED EXTRACELLULAR VESICLES AS DRUG DELIVERY SYSTEMS FOR FUTURE CANCER THERAPIES

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Tumor cell-derived extracellular vesicles (TEVs) mediated bidirectional transfer of functional molecules between cancer cells and cells belonging to the tumor microenvironment (TME) and strongly support tumor progression. Thus, current mass spectrometry-based proteomic analyses have shown that TEVs harbor specific proteins that may enable not only targeting of specific cell types but also regulation of different protumor processes such as angiogenesis, inflammation, cellular invasiveness, and evasion of immune surveillance. Besides TEVs functions in the creation of favorable TME for cancer progression, there is increasing evidence regarding their use as cytotoxic drug delivery systems due to their essential role in intercellular communication and their analogy to liposomes. Therefore, our research aimed to optimize melanoma cell-derived extracellular vesicles as delivery systems for doxorubicin (DOX) that can overcome limitations of the clinically applied DOX formulations. To preserve the biological properties of TEVs, ultrafiltration followed by size-exclusion chromatography were used to isolate the vesicles from culture medium of B16.F10 murine melanoma cells cultured under metabolic stress conditions. Our data suggested that TEVs met all requirements to be used as drug delivery systems in terms of physical properties as well as proteomic surface signature. Moreover, gene ontology enrichment analysis suggested that nano-sized vesicles isolated belong to exosomes as well as microvesicles. We also identified several membrane proteins that ensure targeting of cancer cells and TME cells such as immune cells. However, since previous *in vivo* studies demonstrated that most of the TEVs administered intravenously were rapidly cleared by innate immune system cells, melanoma cell-derived extracellular vesicles were further "sterically stabilized" with poly(ethylene glycol) (PEG). Our preliminary data have shown that PEG-coated TEVs encapsulating DOX (PEG-EV-DOX) are more efficient to inhibit B16.F10 murine melanoma growth than clinically applied long-circulating liposomal DOX (LCL-DOX). Moreover, molecular analyses of the tumor tissues after different treatments suggested that melanoma-targeted properties of PEG-EV-DOX might reduce significantly melanoma aggressiveness as the expression of markers involved in tumor angiogenesis and invasiveness was suppressed.

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Reference:

1. Patras L and Banciu M., *Curr Pharm Des*. 25,17 (2019).
2. Patras L, *et al*., *Cancer Biol Ther*. 23(1) (2022).

Short Curriculum Vitae:

Manuela Banciu is Professor at the Department of Molecular Biology and Biotechnology, Faculty of Biology and Geology, Babes-Bolyai University of Cluj-Napoca, Romania. She has got a PhD at the Department of Pharmaceutics, Utrecht University, The Netherlands in 2007. At present she has been leading the group of Nanomedicine. The main topics of the research developed within this group are focused on the development of the tumor-targeted therapeutic strategies based on “re-education” of immune cells belonging to tumor microenvironment to fight against cancer and the elucidation of the molecular mechanisms of action involved in the antitumor activities of the treatments tested.