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Extracellular Vesicles as Drug Delivery Systems for Future Melanoma Therapeutic Approaches †

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Abstract: There is increasing evidence regarding the use of tumor cell-derived extracellular vesicles (TEVs) as cytotoxic drug delivery systems due to their analogy to liposomes and their role in intercellular communication in tumor tissue [1]. Therefore, our research aimed to optimize melanoma cell-derived extracellular vesicles as delivery systems for doxorubicin (DOX) that can overcome the limitations of the clinically applied DOX formulations. To preserve the biological properties of TEVs, they were isolated by ultrafiltration followed by size-exclusion from a 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 and proteomic surface signature. 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 data have shown that PEG-coated TEVs encapsulating DOX (PEG- EV-DOX) were more efficient in inhibiting B16.F10 murine melanoma growth than clinically applied long-circulating liposomal DOX (LCL-DOX) and reduced significantly melanoma aggressiveness and tumor angiogenesis [2]. Thus, we proposed a novel combination therapy based on sequential administration of PEG-EV-DOX to selectively target melanoma cells and simvastatin incorporated in IL-13-functionalized long-circulating liposomes (IL-13-LCL-SIM) that ensures targeting of tumor microenvironment cells such as tumor-associated macrophages (TAMs). Our data suggested that this novel drug delivery strategy based on combined active targeting of both cancer cells and immune cells was able to induce a potent antitumor effect by disruption of the molecular communication between TAMs and melanoma cells [3].

Keywords: extracellular vesicles; liposomes; melanoma.

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Conflicts of Interest

The authors declare no conflict of interest.