Journal of Neuroimmune Pharmacology (2020) 15:487–500
https://doi.org/10.1007/s11481-019-09884-9

ORIGINAL ARTICLE

Macrophage-Derived Extracellular Vesicles as Drug Delivery Systems for Triple Negative Breast Cancer (TNBC) Therapy

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Received: 30 July 2019 / Accepted: 27 September 2019 / Published online: 13 November 2019

Abstract

Efficient targeted delivery of anticancer agents to TNBC cells remains one of the greatest challenges to developing therapies. The lack of tumor-specific markers, aggressive nature of the tumor, and unique propensity to recur and metastasize make TNBC tumors more difficult to treat than other subtypes. We propose to exploit natural ability of macrophages to target cancer cells by means of extracellular vesicles (EVs) as drug delivery vehicles for chemotherapeutic agents, paclitaxel (PTX) and doxorubicin (Dox). We demonstrated earlier that macrophage-derived EVs loaded with PTX (EV-PTX) and Dox (EV-Dox) target cancer cells and exhibited high anticancer efficacy in a mouse model of pulmonary metastases. Herein, we report a manufacture and characterization of novel EV-based drug formulations using different loading procedures that were optimized by varying pH, temperature, and sonication conditions. Selected EV-based formulations showed a high drug loading, efficient accumulation in TNBC cells in vitro, and pronounced anti-proliferation effect. Drug-loaded EVs target TNBC in vivo, including the orthotopic mouse T11 tumors in immune competent BALB/C mice, and human MDA-MB-231 tumors in athymic nu/nu mice, and abolished tumor growth. Overall, EV-based formulations can provide a novel solution to a currently unmet clinical need and reduce the morbidity and mortality of TNBC patients.

Keywords Doxorubicin · Drug delivery systems · Extracellular vesicles · Paclitaxel · Triple negative breast cancer

Introduction

TNBC is a highly aggressive and metastatic cancer that is characterized by minimal estrogen and progesterone receptors, as well as nominal human epidermal growth factor receptor 2 (HER2) expression (Mersin, Yildirim et al. 2008). The development, progression, and metastasis of TNBC are the leading cause among female mortality. The current standard of care revolves around the use of various neoadjuvant chemotherapeutics (Ren, Hao et al. 2019), including anthracyclines, taxanes, and platinum agents (Walsh, Shalaby et al. 2019), as well as poly(ADP-ribose) polymerases (PARP) inhibitors (Zhou, Ji et al. 2016), and immune checkpoint inhibitors (Cyprian, Akhtar et al. 2019). Chemotherapy remains the only adjuvant treatment for TNBC, but responses are usually brief and associated with progressive resistance, short survival, and systemic toxicities. Thus, the development of new effective delivery approaches and in particular, more effective chemotherapies, determines translational success of these antineoplastic drugs for TNBC.

A large proportion of chemotherapeutics have low aqueous solubility, consequently requiring the use of specialized nanosized delivery vehicles (e.g. micelles, liposomes, polymeric nanoparticles, or other types of nanoparticles) for parenteral administration. Much effort has been dedicated to the development of drug nanoformulations targeted to tumors, but these efforts have been met with limited success (Chandolu and Dass 2013). Nanoparticles are promising platforms for treating cancer, but mainstream nanoparticles target tumors

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11481-019-09884-9) contains supplementary material, which is available to authorized users.

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