Exosome-mediated drug resistance in cancer: the near future is here

Marco Giallombardo, Simona Taverna, Riccardo Alessandro, David Hong and Christian Rolfo

Ther Adv Med Oncol

2016, Vol. 8(5) 320–322

DOI: 10.1177/1758834016648276

Correspondence to:
Christian Rolfo, MD, PhD, MBAh
Phase I - Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital (UZA) and Center for Oncological Research (CORE) Antwerp University, Wilrijkstraat 10, 2650, Edegem, Antwerp, Belgium
christian.rolfo@uza.be

Marco Giallombardo, BSc, MSc
Phase I - Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital (UZA) and Center for Oncological Research (CORE) Antwerp University, Edegem, Antwerp, Belgium
Department of Biopathology and Medical Biotechnology, Biology and Genetics Section, University of Palermo, Palermo, Italy

Simona Taverna, PhD
Riccardo Alessandro, PhD
Department of Biopathology and Medical Biotechnology, Biology and Genetics Section, University of Palermo, Palermo, Italy

David Hong, MD
Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Drug resistance exerts a crucial role in several cancer treatments. Understanding the resistance mechanisms against different therapeutic agents can be helpful to determine the prognosis, but remains a tricky task. In this context, tumor-derived exosomes (TDEs) may give crucial answers about these resistance mechanisms. Exosomes are biological nanovesicles with an average size around 30–100 nm of diameter (Figure 1) that originate from the endocytic pathway by the inward budding of multivesicular bodies (MVB), and they function as cell-free messengers, involved in the cell–cell communication [Kowal *et al.* 2014]. It has been demonstrated that both cells in physiological and pathological conditions release exosomes and that exosomes are easily detected in several body fluids, such as plasma, serum, urine, saliva, etc. [Rolfo *et al.* 2014]. It has been demonstrated that TDEs contain different proteins, lipids, mRNAs and miRNAs and have pleiotropic functions in the tumor microenvironment, tumor growth and progression, immune escape, angiogenesis, invasion, and drug resistance [Kowal *et al.* 2014; Rolfo *et al.* 2014; Fontana *et al.* 2013].

Currently, there are three frequently described exosome-mediated drug resistance mechanisms: drug export via the exosome pathway, neutralization of antibody-based drugs and exosome-mediated transfer of miRNAs (Figure 2) [Chen *et al.* 2014b; Ciravolo *et al.* 2012; Corcoran *et al.* 2012; Safaei *et al.* 2005; Wei *et al.* 2014].

In a preclinical study, it was demonstrated that exosomes released from cisplatin-resistant ovarian carcinoma cells contained 2.6-fold more cisplatin respect to exosomes released from cisplatin-sensitive ovarian carcinoma cells, suggesting that cancer cells exploited the endocytic compartment as drug export vector [Safaei *et al.* 2005]. In addition, it was also described that cancer cells can release drugs or their metabolites

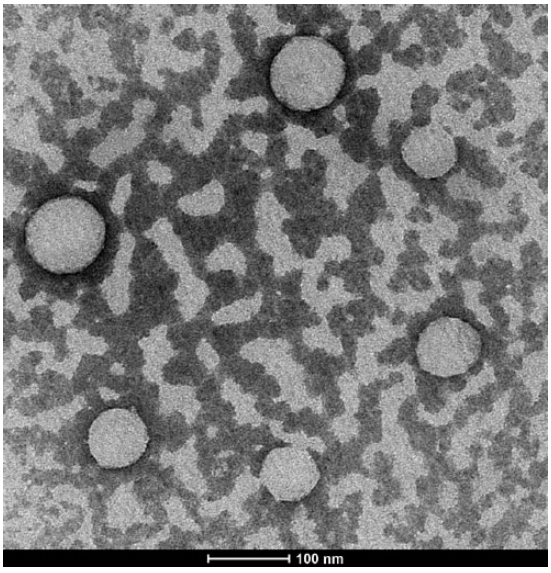

Figure 1. Image of exosomes, released in the plasma of a non-small cell lung cancer patient, performed through transmission electron microscopy analysis. This experiment was performed with UZA Hospital (Edegem, Belgium) ethical committee approval.

through exosomal pathway mediated by ABC transport. In this context, it was demonstrated in prostate cancer that exosomal transfer of multidrug resistance proteins such as multidrug resistance protein 1 (MDR-1/P-gp) could be related to docetaxel resistance [Corcoran *et al.* 2012]. Interestingly, an exosome-mediated transfer of MDR-1 from nonsensitive to sensitive breast cancer cells to docetaxel was observed, transferring docetaxel drug resistance to sensitive cells [Lv *et al.* 2014]. It was also described that mesenchymal stem cells derived exosomes could induce, both *in vivo* and *ex vivo*, 5-fluorouracil drug resistance in gastric cancer cells enhancing the expression of MDR-1, lung resistance protein (LRP) and multidrug resistance-related protein (MRP) through CaM-Ks/Raf/MEK/ERK pathway activation [Ji *et al.* 2015].

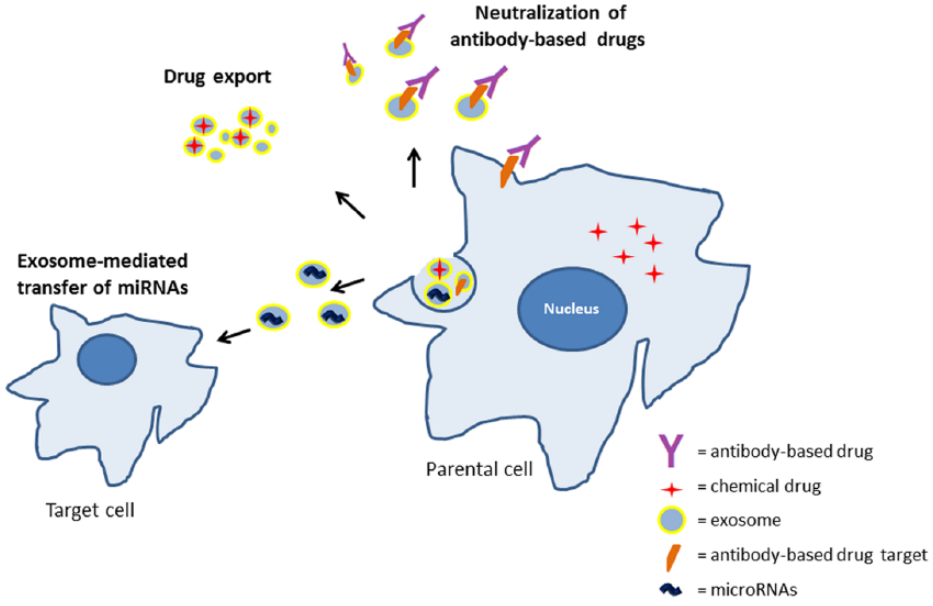

Figure 2. Overview of three well-described exosome-mediated drug-resistance mechanisms.

The idea to discover the mechanisms that lead to early antibody-based drug resistance in cancer cells is very attractive. In this field, Ciravolo and colleagues described that, both *in vitro* and *in vivo*, TDEs are involved into neutralizing antibody-based drugs: HER2-overexpressing breast carcinoma cell lines released TDEs containing HER2 protein that could bind the anti-HER2 antibody trastuzumab. This interaction leads to a decrease in the real amount of antibody-based drug that can interact with cancer cells and eventually decreased the overall effect of trastuzumab [Ciravolo *et al.* 2012].

During the last few years, there is a lot of interest in drug resistance by exosome-mediated transfer of miRNAs. Currently, several studies indicate that TDEs function also as a genetic exchange vector in the tumor microenviroment. Several *in vitro* studies suggest that breast cancer cells resistant to different drugs (docetaxel–adriamycin–tamoxifen) may transfer the resistance to sensitive cells in part by exosomal miRNAs exchange [Chen *et al.* 2014a, 2014b; Wei *et al.* 2014]. Similar results were obtained in ovarian cancer preclinical studies, it was demonstrated that a cisplatin-resistant ovarian cancer cell line transfers the resistance to sensitive cells by exosomal exchange of biologically active miR-21-3p, which targeted the NAV3 gene [Pink *et al.* 2015]. Moreover, the role of exosomal miRNAs in drug resistance mediated by the cross-talk with the tumor microenviroment in neuroblastoma (NBL) was investigated. In a preclinical study, Challagundla and colleagues demonstrated that exosomes released from the NBL cell line transferred the oncomiR-21 to human monocytes. This genetic information exchange led monocytes to transcribe oncomiR-155 in a NF-κB-dependent pathway and, interestingly, monocytes released exosomes containing miR-155 that was, in turn, internalized by NBL cells. One of described target of miR-155 is TERF1, a telomerase inhibitor; silencing of TERF1 mRNAs caused alterations of telomerase activity, which could lead to an increased resistance to DNA-damage induced by cisplatin [Challagundla *et al.* 2015]. Furthermore, other exosomal proteins lead to a drug-resistant phenotype changes in the target cells, for example, it has been demonstrated that PTEN is released in exosomes thus exerting biological functions in target cells [Putz *et al.* 2012]. Moreover, it has been described that the loss of function of PTEN increases resistance to chemotherapeutic and sensitivity to mTOR inhibitors in breast cancer and, then, PTEN exosomal transfer could be exploited as a transfer mechanism of drug resistance changes [Steelman *et al.* 2008].

Altogether, these findings suggest a crucial role for exosomes in drug resistance in several tumor types. Notable, in the liquid biopsy research field, it could be an attractive idea to analyze selected exosome groups among the total population in different

body fluids. Regrettably, especially in cancer patients, the challenge for a good discrimination of TDEs among the total exosome population in body fluids (such as in blood) is still open. However, it seems that the amount of TDEs is prevalent in the total exosome population [Milane *et al.* 2015]. The new era of liquid biopsies is growing very fast, and less-known components, such as exosomes, may also be exploited as a source of biomarkers. Could exosomal drug resistance biomarkers finally be used in clinical practice? Probably the near future is here, and after more research and validation, exosomal drug resistance biomarkers could lead to a more defined insight into resistance mechanisms against several targeted therapies in cancer.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Challagundla, K., Wise, P., Neviani, P., Chava, H., Murtadha, M., Xu, T. *et al.* (2015) Exosome-mediated transfer of microRNAs within the tumor microenvironment and neuroblastoma resistance to chemotherapy. *J Natl Cancer I* 107: djv135.

Chen, W., Cai, Y., Lv, M., Chen, L., Zhong, S., Ma, T. *et al.* (2014a) Exosomes from docetaxel-resistant breast cancer cells alter chemosensitivity by delivering microRNAs. *Tumour Biol* 35: 9649–9659.

Chen, W., Liu, X., Lv, M., Chen, L., Zhao, J., Zhong, S. *et al.* (2014b) Exosomes from drug-resistant breast cancer cells transmit chemoresistance by a horizontal transfer of microRNAs. *PLoS One* 9: e95240.

Ciravolo, V., Huber, V., Ghedini, G., Venturelli, E., Bianchi, F., Campiglio, M. *et al.* (2012) Potential role of HER2-overexpressing exosomes in countering trastuzumab-based therapy. *J Cell Physiol* 227: 658–667.

Corcoran, C., Rani, S., O'Brien, K., O'Neill, A., Prencipe, M., Sheikh, R. *et al.* (2012) Docetaxel-resistance in prostate cancer: evaluating associated phenotypic changes and potential for resistance transfer via exosomes. *PLoS One* 7: e50999.

Fontana, S., Saieva, L., Taverna, S. and Alessandro, R. (2013) Contribution of proteomics to understanding the role of tumor-derived exosomes in cancer progression: state of the art and new perspectives. *Proteomics* 13: 1581–1594.

Ji, R., Zhang, B., Zhang, X., Xue, J., Yuan, X., Yan, Y. *et al.* (2015) Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. *Cell Cycle* 14: 2473–2483.

Kowal, J., Tkach, M. and Théry, C. (2014) Biogenesis and secretion of exosomes. *Curr Opin Cell Biol* 29: 116–125.

Lv, M., Zhu, X., Chen, W., Zhong, S., Hu, Q., Ma, T. *et al.* (2014) Exosomes mediate drug resistance transfer in MCF-7 breast cancer cells and a probable mechanism is delivery of P-glycoprotein. *Tumor Biol* 35: 10773–10779.

Milane, L., Singh, A., Mattheolabakis, G., Suresh, M. and Amiji, M. (2015) Exosome mediated communication within the tumor microenvironment. *J Control Release* 219: 278–294.

Pink, R., Samuel, P., Massa, D., Caley, D., Brooks, S. and Carter, D. (2015) The passenger strand, miR-21-3p, plays a role in mediating cisplatin resistance in ovarian cancer cells. *Gynecol Oncol* 137: 143–151.

Putz, U., Howitt, J., Doan, A., Goh, C., Low, L., Silke, J. *et al.* (2012) The tumor suppressor PTEN is exported in exosomes and has phosphatase activity in recipient cells. *Sci Signal* 5: ra70–ra70.

Rolfo, C., Castiglia, M., Hong, D., Alessandro, R., Mertens, I., Baggerman, G. *et al.* (2014) Liquid biopsies in lung cancer: the new ambrosia of researchers. *Biochim Biophys Acta* 1846: 539–546.

Safaei, R., Larson, B., Cheng, T., Gibson, M., Otani, S., Naerdemann, W. *et al.* (2005) Abnormal lysosomal trafficking and enhanced exosomal export of cisplatin in drug-resistant human ovarian carcinoma cells. *Mol Cancer Ther* 4: 1595–1604.

Steelman, L., Navolanic, P., Sokolosky, M., Taylor, J., Lehmann, B., Chappell, W. *et al.* (2008) Suppression of PTEN function increases breast cancer chemotherapeutic drug resistance while conferring sensitivity to mTOR inhibitors. *Oncogene* 27: 4086–4095.

Wei, Y., Lai, X., Yu, S., Chen, S., Ma, Y., Zhang, Y. *et al.* (2014) Exosomal miR-221/222 enhances tamoxifen resistance in recipient ER-positive breast cancer cells. *Breast Cancer Res TR* 147: 423–431.