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Exosomes as versatile nanoscaled biocompartments in cancer therapy and/or resistance

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Summary

Cancer remains to be a major hurdle to global health. Exosomes as a versatile bio-derived platform, hold a bright prospect in nano-scaled delivery/targeting strategies. Shreds of evidence indicate that exosomes have a critical role in drug resistance in cancer cells through various mechanisms including shuttling of miRNAs, drug efflux transporters, and anti-apoptotic signaling. Exosomes' cargo, particularly miRNAs, may exert both resistance and in a few cases sensitivity to the anticancer agents in targeted cells. Therefore, the source and components of the exosomes should be carefully considered before any application. Our aim in this editorial is to further highlight the role of exosomes in the development of resistance to therapy in cancer cells. As a new chapter for drug delivery, the challenges should be elucidated before exosomes emerge as novel nanoplatforms for cancer therapy.

Authors' Biosketch

Jaleh Barar (PharmD, Ph.D.) is a Full Professor at the Faculty of Pharmacy, Tabriz University of Medical Sciences. Professor Barar is working on various aspects of pharmaceutical cell biology with particular emphasis on the development of novel drug delivery/targeting systems. She has published over 170 research and review articles in peer-reviewed journals and co-authored in 17 book chapters. Dr Barar is listed among top 1% of world scientists based on ESI ranking system.

Yalda Rahbar Saadat received her Ph.D. from Tabriz University of Medical Sciences. Her primary research interests lie in the area of cancer, with emphasis on targeting vital signaling pathways employing probiotics, postbiotics, and nutraceuticals. Her recent researches focus on various types of extracellular vesicles.

Cancer represents the leading cause of death worldwide. Among conventional therapeutic approaches, chemotherapy is considered an effective treatment against cancer; nevertheless, chemoresistance development is a major concern that contributes to cancer progression and deterioration via metastasis, tumor recurrence.[1] Two main pathways are involved in chemoresistance: intrinsic and extrinsic pathways. Intrinsic pathways are present in recipient cells before any drug treatment, however, extrinsic pathways are developed following the treatment procedure.[2] Various factors are associated with chemoresistance including increased drug efflux pumps, resistance to apoptosis, DNA repair defects, and mutations affecting drug targets.[1]

Exosomes are nanoscale lipid bilayer membrane vesicles sized 30–100 nm, secreted from almost all cell types, and are involved in cellular communication and signaling.[3] They encompass a variety of biomolecules such as proteins, lipids, DNA, RNA, and non-coding RNAs. It is well established that exosomes, serve as valuable cancer prognostic, therapeutic factors as well as efficient drug targeting/delivery vehicles.

Exosomes can modulate the biological activity of the recipient cells by transferring biomolecules. For instance, they may induce chemoresistance via exporting proteins which improve cancer cell survival and DNA repair. Additionally, in the donor cells, chemoresistance occurs through reducing the intracellular drug concentration as well as discarding proapoptotic proteins (i.e., caspases).[2,4,5]

Since exosomes carry a diverse pool of biomolecules, (e.g. miRNAs), through cargo exchange among cancer cells, they may be implicated in the modulation of the response to cancer therapy.[6] Numerous lines of evidence have reported that tumor-derived exosomes

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encompass specific miRNAs which are responsible for chemoresistance or chemosensitivity.[1] Exosomal miRNAs may trigger chemoresistance through various mechanisms such as autophagy, angiogenesis, and inflammation. Further, they can be involved in hypoxia induction through blocking apoptotic pathways, altering cell cycle, and increased oxidative stress.[1,7] Hypoxia, on the other hand further enhance the chemoresistance phenomena through different pathways such as disturbing the drug delivery and efficiency in the hypoxic or acidic condition or inducing adaptation in cancer cells.[2] Thus HIF-1α overexpression in most human solid tumors often is correlated with the tumor's resistance to chemotherapy.[8] Further, it has been proposed that exosomes are able to alter the anti- and pro- apoptotic homeostasis in the cells, leading to DNA repair.[5]

Various exosomal miRNAs also elaborate on the chemoresistance through cancer stem cells (CSCs) self-renewal capacity. Elevated levels of exosomes rich in oncogenic miRNA are detected in CSCs and their transfer to other cells exert a critical role in tumor progression and anticancer drug resistance.[6,9] Additionally, exosomes derived from cancer-associated fibroblast and tumor-associated macrophage could contribute to the chemoresistance.[10]

Another molecular pathway by which exosomes can cause drug resistance is transporting not only the drugs, but also, drug exporters, (i.e., P-glycoproteins, multidrug-resistant protein-1, and ABC subfamily G member 2). For instance, in various cancer models, transfer of aforementioned efflux pumps via exosomes results in drug-resistant phenotype in recipient cancer cells.[3]

Exosomal delivery of prosurvival factors is an additional molecular mechanism of chemoresistance that alters the apoptotic balance and cell viability in the receiver cells. For instance, exosomal delivery of hepatocyte growth factor and survivin (as prosurvival proteins) induce chemoresistance in recipient cells through activation of diverse signaling pathways.[2]

The growing number of evidence suggested the detrimental role of exosomes in cancer therapy via induction of chemoresistance. Hence, developing new strategies (i.e., blocking exosome biogenesis/secretion, and exosomes' depletion from circulation) to combat the inhibitory activities seems indispensable. However, few studies have been focused on the beneficial role of exosomes, that may lead to chemosensitivity via transferring multiple drug resistance efflux pumps out of cancer cells.

Given the widespread interest on the biomedical application of exosomes, it would be an immense necessity to provide comprehensive insights into the content and final fate of these biovesicles. Consequently, the cost-benefit analysis of engineering the natural exosomes could provide increased efficacy *in-vivo*. It is envisioned that advancement in this field will pave the path for a new era of effective/potent platform for cancer therapy and/or diagnosis.

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Ethical statement
None to be declared.

Competing interests
None.

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