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Commentary on "Osteosarcoma from the Unknown to the Use of Exosomes as a Versatile and Dynamic Therapeutic Approach"

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Commentary

This commentary mentions to our published article that intends to describe the properties that turn exosomes (Exo) into an efficient, as well as safe nanovesicle for drug delivery and treatment of osteosarcoma (OS). Nowadays, the results of conventional treatments are still unsatisfactory, mainly, in patients with recurrent disease or metastatic [1,2]. Also, OS chemotherapy has two major challenges related to treatment toxicity and multiple drug resistance. Exo, a cell-derived nano-sized and a phospholipid vehicle, are capable of releasing the drug directly at the OS cells and decreasing the drug`s toxicity [3]. Furthermore, the incorporation of specific proteins or peptides on the Exo surface improves their targeting capability in several clinical applications [4]. In our article we can verify that Exo offer precious features such as safety and selectivity, that together with current nanoparticles in study may culminate in a better diagnosis [5], and treatment of pathologies, such as brain disorders and cancer [6], including OS [7]. In addition, Exo play important roles in different biological process, such as inflammation, cellular homeostasis, angiogenesis, apoptosis, intercellular signalling, antigen presentation and coagulation [8]. These roles are due to their capability to transfer lipids, RNA proteins as well as enzymes. For this reason, Exo can influence the pathological and physiological process in a variety of diseases, namely neurodegenerative diseases, cancer, autoimmune diseases, and infections [8]. The Exo of OS are responsible for regulating cytokines, either the expression or secretion, and their signalling pathways. This has been shown in some studies, where several aspects of the tumor, such as tumor growth, angiogenesis, metastasis, and evasion of the tumor cells from the host immune system, are regulated by Exo produced by the tumor itself [9]. Kansara and coworkers [10] found a significant relation between the inhibition of the gene Wif inhibitor 1, responsible for the expression of Wnt inhibitor, and the occurrence of OS in mice. This suggests that the incidence of OS may be increased by the activation of the Wnt expression. Some studies have suggested that the secretion of Exo and cell-catenin may be caused by the overexpression of CD9 and CD82. This has a major effect on the inhibition of the activity of the Wnt protein [11]. Therefore, Exo has a wide effect on the regulation of the cascade of Wnt signalling pathway, either indirectly or directly, and consequently on the cell function. Additionally, the investigators discovered that the receptor activator of nuclear factor Kappa-B (RANKL) in the Exo of the cells of OS have a major part in the osteoclast formation process and in the activation of metalloproteinases [12]. In 2020 a clinical trial was performed, whose purpose was to develop a microfluid chip technology to efficiently capture Exo for quantitative and qualitative analysis, marker screening, and establish a combination of Exo subgroup as a biomarker for the early diagnosis of OS lung metastasis (Clinicltrials.gov Identifier: NCT05101655). In our article we also refer the important role of Exo in distant metastasis as well as in chemotherapy resistance of OS. Shimbo et al. [13] showed that when the artificial miR-143 encapsulated in Exo was introduced into bone mesenchymal stem cells (MSCs), miR-143 had therapeutic efficacy on OS cells and significantly reduced metastases. Furthermore, they also demonstrated that Exo as a miRNA delivery nanosystems, was more efficient than other transfection processes in intercellular

Transport. Therefore, they demonstrated that Exo is a safe and effective carrier of synthetic miR-143 and is a functional drug delivery system in the treatment of OS. In another study, the investigators developed and explored the therapeutic potential of a nano-drug consisting of doxorubicin (Dox) in conjunction with Exo obtained from MSCs. Exo-Dox are nonimmunogenic, non-toxic, and may be programmed to increase the loading capacity and to direct to OS cells [14]. This article describes the several isolation, identification, and quantification techniques for Exo, as well as their advantages and disadvantages for a more complete and detailed reading. This article also presents several tables that summarize other recent studies on exosomal miRNAs in OS therapy, an overall view for targeted OS treatment as well as good biomarker for OS cells. More recently, the application of artificial intelligence, such as machine learning or bioinformatic tools, using Exo, have demonstrated promising results on the identification of predictive and prognostic markers for OS [15-17]. Although some new technologies are being developed in recent years, current methods used for the isolation and characterization of Exo are, often, used for prognostic and diagnostic purposes. OS is considered a chemotherapy-resistant tumor, however, in the future, due to the unique characteristics of Exo and the fact that this nanovesicle can easily be altered and improved, it could be the key for early diagnostic, treatment, and development of Exo as new nanosystem drug delivery of OS therapy.

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