Exosomes Diversity

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Contributor: Enrico Iaccino

Cells can communicate through special “messages in the bottle”, which are recorded in the bloodstream inside vesicles, namely exosomes. The exosomes are nanovesicles of 30–100 nm in diameter that carry functionally active biological material, such as proteins, messanger RNA (mRNAs), and micro RNA (miRNAs). Therefore, they are able to transfer specific signals from a parental cell of origin to the surrounding cells in the microenvironment and to distant organs through the circulatory and lymphatic stream. More and more interest is rising for the pathological role of exosomes produced by cancer cells and for their potential use in tumor monitoring and patient follow up. In particular, the exosomes could be an appropriate index of proliferation and cancer cell communication for monitoring the minimal residual disease, which cannot be easily detectable by common diagnostic and monitoring techniques. The lack of unequivocal markers for tumor-derived exosomes calls for new strategies for exosomes profile characterization aimed at the adoption of exosomes as an official tumor biomarker for tumor progression monitoring.

Keywords: exosomes ; liquid biopsy ; cancer ; extracellular vesicles

1. Introduction

Cells can communicate through special “messages in the bottle”, which are recorded in the bloodstream inside vesicles, namely exosomes. The exosomes are nanovesicles of 30–100 nm in diameter that carry functionally active biological material, such as proteins, messanger RNA (mRNAs), and micro RNA (miRNAs). Therefore, they are able to transfer specific signals from a parental cell of origin to the surrounding cells in the microenvironment and to distant organs through the circulatory and lymphatic stream. More and more interest is rising for the pathological role of exosomes produced by cancer cells and for their potential use in tumor monitoring and patient follow up. In particular, the exosomes could be an appropriate index of proliferation and cancer cell communication for monitoring the minimal residual disease, which cannot be easily detectable by common diagnostic and monitoring techniques. The lack of unequivocal markers for tumor-derived exosomes calls for new strategies for exosomes profile characterization aimed at the adoption of exosomes as an official tumor biomarker for tumor progression monitoring.

2. Exosomes: The Smallest Extracellular Vesicles

After the outstanding discovery of micro-vesicles as exfoliation of the ectoenzyme membrane by Eberhard G. Trams and colleagues in 1981 [1], the term “exosome” was used for the first time a few years later by Pan and Johnson, when referring to small endosome-derived vesicles [2]. Exosomes were produced and secreted by sheep reticulocytes during their maturation process while eliminating transferrin receptors (Tfr) as trash proteins [2]. Later, it was demonstrated that these nanovesicles could have an important role as mediators of physiological pathways, especially pathological processes.

Classified as small E.V. of endosomal origin, the exosomes are 30–100 nm diameter vesicles, which are physiologically produced by all cell types and secreted through an exocytosis process in blood, urine, cerebrospinal fluid, other body fluids, and the medium of in vitro cell cultures. Even though the mechanisms of synthesis and secretion of exosomes have not been completely clarified, the crucial roles of the Endosomal Sorting Complex Required for Transport (ESCRT) and the intracellular Ca^{2+} increase are commonly recognized to be required for the exosomes release [3]. Exosomes play an important role in cell-cell communications. In fact, the exosomes reach very distant target cells, in which they release their cargo, represented by proteins, DNA, RNA, microRNAs, cytokines, and lipids, influencing both physiological and pathological processes. The exosomes isolated from different tumor cell lines selectively target the tissues of origin when inoculated in animals. It has been observed, in fact, that exosomes isolated from liver cancer-targeted the liver in vivo [4] [5], while exosomes isolated from diffuse large B-cells Lymphoma (DLBCL) directly reached DLBCL cells [6]. Furthermore, the exosomes produced by esophageal cancer cells targeted parental cells, contributing to aggressiveness by promoting invasion and migration through a continuous transfer cycle [7].

3. The Role of Exosomes in Solid Tumors

Several reports support the pivotal role of exosomes in tumorigenesis, mediating the immune response, antigen presentation, cell migration, cell differentiation, tumor survival, tumor invasion, and angiogenesis [8]. It was recently demonstrated that exosomes play a crucial role in metastatic events stimulating TME [9], transforming neighboring cells, and promoting secondary neoplasms [10]. Cancer cells migrate away from the primary tumor and settle in a new body district by establishing a tumor niche supported by chemical mediators of inflammation, which in turn help to recreate the tumor microenvironment [11].

In this context, the components of innate immunity play a particular role, such as polarized M2 macrophages, capable of releasing pro-angiogenetic factors contributing to the self-renewal of the tumor and its relapse [12]. Under hypoxic conditions, cancer cells are able to modulate the microenvironment in order to enhance angiogenesis, resulting in an increase in metastatic potential [13]. EGFR-derived exosomes can adjust the liver microenvironment, thus promoting the formation of gastric cancer metastasis [14]. The role of exosomes in the formation of the tumor vessels has recently been hypothesized [15]. For example, glioma exosomes contain pro-angiogenic factors that can contribute to tumor vascularization [16]. Their role in neovascularization is carried out, thanks to crosstalk with endothelial cells. TDEs are, in fact, able to modulate endothelial cells, contributing to their proliferation and migration [17]. A markedly decreased expression of inflammatory markers was found in Glioma patients' exosomes, compatible with the effects of tumor-mediated immunosuppression [18].

Exosomes are capable of transferring metastatic potential to surrounding cells through the transfer of genetic information and/or pro-metastatic proteins [19]. Exosomes promote tumor growth and progression through a mechanism of inhibition of the immune system. In particular, several data show how exosomes are able to induce apoptosis of cytotoxic T-cells, inhibit the cytotoxicity of natural killer (N.K.) cells, or inhibit the differentiation of dendritic cells (D.C.) [20].

Interestingly, exosomes also induce drug-resistance in tumor cells due to their cargo in terms of multi-drug resistant protein release, tumor immune escape mechanisms, changes in apoptotic homeostasis, and tumor stroma interaction [21].

It has been shown that the treatment of a weak melanoma cell line (F1) with exosomes derived from the highly aggressive melanoma B16 cell line and with strong metastatic power, resulted in the expression of the metastatic marker met 72 in the F1 cell line, differently from untreated cells, showing that exosome treatment increased aggression of the weaker cell line [22]. In patients, melanoma derived exosomes were enriched in immunosuppressive proteins and inhibited CD69 expression, induced apoptosis, suppressed proliferation in CD8+ T cells, and down-regulated NKG2D expression in N.K. cells [23].

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