Exosomes-based cell-free cancer therapy: a novel strategy for targeted therapy

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ABSTRACT
Exosomes are cell-derived nano-sized, phospholipid vehicles that function to transport prodigious amounts of bioactive molecules to specific recipient tissues. Several hallmarks of cancer are impacted by this exosome-mediated cell-to-cell communication, including, remodeling the architecture of the extracellular matrix, endowing cancer cells with characteristics of drug resistance, or even modulating immune responses. Owing to their immunomodulatory potential and endogenous functionalities, exosomes may also be exploited in various innovative immunological approaches to activate adaptive and innate immune effector cells to mount an effective anticancer immunosurveillance. The review highlights the recent advances in state-of-the-art technologies and protocols for using exosomes as an effective and promising application for cancer immunotherapy.

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1. Introduction
Intercellular communications between neighboring and distant cells are crucial for survival of cells and responding to paracrine and endocrine signaling [1]. Cell to cell communication is also essential for tumorigenesis. Tumors are not isolated entities but involve a complex crosstalk between transformed and non-transformed cells to enhance tumor growth, progression, angiogenesis and metastasis [2]. Exchange of material between cells is essential for communication between cells and its survival. Extracellular vesicles (EVs), such as exosomes, are emerging as novel cell-cell communication mediators in physiological and pathological conditions [3]. Exosomes differs from other EVs such as microvesicles (MVs), and apoptotic bodies, on the basis of their biogenesis, release pathways, size, content and function (Table 1). While exosomes are formed by inward budding of the membrane of early endosomes, which then mature into multivesicular bodies (MVBs), MVs are formed by direct outward pinching or budding, of the cell’s plasma membrane, whereas apoptotic bodies are released by dying cells into the extracellular space [4]. Recent reports have highlighted the important role of tumor cell-derived exosomes in communication through the transfer of various biomolecules including proteins, lipids, DNA and RNA [5]. Exosomal cargo bares strong resemblance to the intracellular components of their parent cell. Real-time detection of these exosomal components could provide critical perceptive information in terms of diagnosis, prognosis and disease monitoring [6]. Clinically, exosomes functions as diagnostic biomarkers or even as a carrier of anticancer drugs. Exosomes are extremely stable and resistant against degradation enzymes such as RNases owing to their clathrin-coated membrane which makes them a lucrative tool for diagnosis and therapy [7]. The diverse application of exosomes is a result of their unique biological and pathophysiological characteristics. Over the recent years, there has been substantial evidence revealing the role of exosomes in immune regulation. This has further prompted related studies exploring these vesicles in various anti-cancer therapeutics, for instance as delivery agents or immune regulators [8]. Recent publications have unearthed major breakthroughs in exosome-based cancer therapy, which has galvanized momentous efforts to exploit them as a novel anticancer therapeutic agent [9]. In this review, I outline the biogenesis of exosomes, its role in immunomodulation and how these systems can be exploited as a potent therapeutic option.

2. Biogenesis of exosomes
Exosome biogenesis initiates within the endosomal system and is tightly regulated. Exosomes correspond to the intraluminal vesicles (ILVs) of MVBs. During the process of exosome biogenesis,
endosomal membrane invaginates to generate ILVs in the lumen of the MVBs [10]. In most cells, MVBs fuse with lysosomes where their content is degraded. However, MVBs can also directly fuse with the plasma membrane to release ILVs into the extracellular space. The ESCRT machinery is important in this process. It is composed of approximately ~30 proteins that are assembled into four complexes (numbered from ESCRT-0 to –3) The ESCRT-0 complex recruits proteins for internalization, whereas ESCRT-1 and –2 complexes determine the budding process and promote formation of ILVs and MVBs in the intracellular compartment [11]. In the final stage, ESCRT-3 complex along with ATPase VPS4, promotes membrane cleavage to free ILVs in the inner lumen space of MVBs [12]. Recently, an ESCRT-independent mechanism has been proposed suggesting that MVB biogenesis can occur without ESCRTs. Tetraspanins are exosomal transmembrane proteins, which are involved in releasing exosomes, independent of the ESCRT machinery. Fusion of MVBs with the plasma membrane releases ILVs as exosomes into the extracellular space. Exosome biogenesis partakes in unique cytosolic components including DNA, mRNA, miRNA and other non-coding RNAs from cell, depending on the physiological state of the parent cell. The ubiquitous production of exosomes by all cell types and their unique content has generated excitement for their potential as therapeutic tool [13].

**3. Immunosuppressive functions of tumor-derived exosomes**

The cargo of exosomes largely depends on the cell of origin and the activation status of that cell. Many studies have shown that cancer exosomes can deliver multiple signals to immune cells that induce immune tolerance toward the tumor cells. The immunosuppressive effects of exosomes ranges from reducing NK cell activity or dendritic cell (DC) differentiation [14,15], inducing T cell apoptosis mediated by FasL and PDL-1 [16] and inhibiting T cell and B cell proliferation [17]. Exosomes produced by hypoxic tumor cells are highly enriched in immunomodulatory proteins and chemokines including CSF-1, CCL2, FTH, FTL, IL-10 and TGFβ. Further, these tumor-derived exosomes (TEXs) potentiates M2-macrophage polarization and supports generation and infiltration of immunosuppressive Treg cells and even suppress proliferation of T cells, which in-turn favors tumor growth [18]. Expression of CD39 and CD73 on the surface of exosomes, dephosphorylates exogenous ATP and 5’AMP to form adenosine, thus contributing to rise the adenosine levels within the microenvironment which prevents proliferation of T cells. TEX impairs the capacity of circulating CD14+ monocytes to differentiate into functional DCs and to skew to differentiate immunosuppressive myeloid-derived suppressor cells [19].

**4. Immunostimulatory functions of exosomes**

Exosomes have direct antigen presentation capabilities, which were first observed by exosomes secreted by B cells. B-cell-derived exosomes carried MHC class I, MHC class II, co-stimulatory molecules (CD86) and adhesion molecules (ICAM-1) which suggested that such vesicles could directly stimulate CD4+ T-cell to elicit an antigen-specific response [20]. Thereafter various studies have shown the pivotal role exosomes plays in the stimulation of both adaptive and innate immune response. Exosomes isolated from antigen-presenting cells (APCs) expresses both MHC class I and II on their surface which could activate CD4+ T cells as well as CD8+ T-cell populations [21]. Exosomes released by DCs which are professional APCs could transfer MHC–peptide complexes directly to T cells activating the later [22]. Exosomes derived from macrophage and monocytes has been shown to play crucial roles in modulating the tumor microenvironment by inducing the production of pro-inflammatory cytokines [23]. These macrophage-derived exosomes augments inflammation by promoting granulocyte migration, enhanced DC maturation, promoting chemotaxis of neutrophil and promoting NK cell activity [24]. T cells also secrete these nano-sized vesicles which carry T-cell receptor (TCR) on their surface and can trigger interferon-γ (IFN-γ) and granzyme B production by naïve CD8+ T cells [25].

Exosomes thus have the potential to stimulate as well as suppress immune response depending on their source. Molecules carried by the exosomes on their surface as well as their internal components drive their functions. Various exciting concepts have emerged for developing exosomes as competent
drug delivery vehicles and utilizing them as cancer vaccines, which has produced enticing results in early-phase clinical trials.

5. Exosome-based drug-delivery system

Exosome-based delivery systems have high specificity and stability. Owing to their homing characteristics they can deliver their cargo to specific cells [26]. As exosomes are small and mostly self-derived, they bypass engulfment by macrophages, evade lysosomal degradation pathway and have a low immunogenic profile [27]. Exosomes have high stability in the blood that allows them to travel long distances within the body under both physiological and pathological conditions. Due to their hydrophilic core, they are suitable to carry water-soluble drugs [28]. There are several methods available for loading drugs into the exosomes, these strategies are mostly divided into two groups – pre-loading strategy and post-production loading strategy [29].

In pre-loading methods, the drug is initially loaded in the parental cells, and thus, the EVs produced by them are already pre-loaded with the desired drug. Such methodologies are particularly useful while loading oligonucleotides or proteins in the vesicles [30].

In post-loading methods, the drug is loaded in the EVs after their isolation. One such method is electroporation. By applying an electric field to a suspension of exosomes and the therapeutic cargo of choice, pores are created in the exosomes, thereby facilitating the movement of cargo into the lumen of the exosomes. Another method to load cargo into exosomes is sonication, where a mixture drug and exosome is sonicated resulting in effective drug loading into exosome [26,28].

6. Drawbacks of exosome-based drug-delivery systems

Many promising therapeutic candidates like various in-vitro synthesized nucleic acids and peptides are rather unstable after infusion within the patients and are rapidly removed from the system [31]. Exosomes can potentially avoid the phagocytosis by macrophages and degradation in lysosomes thus is used to carry these molecules. But the packaging of the cargo within exosomes in the desired quantity remains a challenge till date. Exosomes comprise heterogeneous components and may show immunogenicity based on its composition [32]. Further, loading and retention of drug was observed to be insufficient within exosomes. Poor pharmacokinetics of exosomes when loaded with bioactive agents was also observed. The involvement of exosomes in tumor progression, angiogenesis and metastasis is a huge concern. Exosomes is also known to carry caspase-3 that may inhibit cell death by apoptosis or enhance tumor cell survival by preventing accumulation of chemotherapeutic drugs [27].

7. Exosome-based immunotherapeutic vaccines

7.1. Dendritic cell-derived exosomes in cancer immunotherapy

Dendritic cell-derived exosomes (DEXs) retain crucial immunostimulatory properties of its parent cell which makes them the perfect candidate for their development as cancer vaccines. They possess various membrane proteins that further help them in targeting, docking and fusion with recipient cells [33]. The abundant presence of integrins and lactadherin on the surface of DEXs aids in their uptake by the recipient cells [34]. DEXs carry various immunostimulatory molecules such as, peptide/MHC complexes that can trigger antigen specific T cell response and co-stimulatory molecules like CD80, CD83, CD86, that contribute to the T cell priming and activation [35,36]. Furthermore, DEXs obtained from tumor peptide-exposed DCs could be used to prime tumor-specific cytotoxic T-lymphocyte (CTL) response to eliminate tumors in murine models [36]. DEXs could also induce the stimulation of CD8+ T cells against tumors [21]. DEXs are known to activate NK cells, induce NK group 2D ligands and the release of tumor necrosis factor (TNF) [37]. DEXs express BCL2-associated athanogene 6 on their surface, which enhanced NK cell cytokine release [38]. Additionally, TNF present within DEXs induces NK cell-mediated IFN-γ production [39]. DEXs can present antigen to T cells in direct or indirect ways. Indirect ways include ‘cross-dressing’ of APC surface with DEXs. They also transfer whole peptide-MHC complex to APC [21]. Interestingly, DEXs also has the capability to transfer MHC-peptide complex to the surface of tumor cells, making them susceptible to be targeted by the host T cells [40].

7.2. TEXs in cancer immunotherapy

TEX has the ability to suppress immune response in various ways, but this property is subjected to the dose of injection and the route of administration. TEX contains tumor-associated antigens which could be presented directly on the surface of tumor cells or via the recipient APCs triggering immune response against the tumor [41]. TEXs also carry HSP70, MHC-I molecules, that are considered to be a source of specific stimulus for the immune
response against cancer [33]. Various studies have further established TEXs as an effective cancer vaccine. TEX triggers anti-tumor responses more efficiently than irradiated tumor cells, apoptotic bodies or lysate of cancer cells. Rao et al. demonstrated that hepatocellular carcinoma cell-derived exosomes, elicited a stronger DC-mediated immune response than cell lysates both in vitro and in vivo [42]. TEX also contains other immunostimulatory molecules like CD80, OX40, OX40L, CD70, along with MHC molecules and various tumor associated antigens [43]. TEX-derived HSP70 functions as an endogenous danger signal, promoting NK cell activation and cancer cell lysis via granzyme B. Furthermore, exosomal EGFRvIII and transforming growth factor-beta (TGF-β) along with various other tumor antigens drives both T and B cell response [16,44].

7.3. Mesenchymal stem cell-derived exosomes in immunotherapy

Mesenchymal stem cells (MSCs) have emerged as a potential solution for tissue repair and wound healing. It has a scalable capacity to mass produce exosomes [45]. MSC-exosomes express galectin-1. Galectin-1 is known to induce apoptosis of activated T cells. Furthermore, MSC could also pack miRNA into exosomes that suppress tumor migration and invasion. MSC-derived exosomes could transfer extracellular miR-143 to osteosarcoma cells, which significantly reduced the migration of osteosarcoma cells. Moreover, secretion of miR-23b by MSC-derived exosomes contributes to cell cycle suppression and dormancy in breast cancer cells, which results in inhibition of migration and invasion of breast cancer cells [45,46]. Exosomes derived from MSCs also induces secretion of IL-6, IFN-γ, TNF-α, and activation of B cells, T cells and APCs. Similarly, HoxB4 contained with MSC-derived exosomes has been shown to affect DC maturation and promote T-cell proliferation, differentiation and activation through WNT signaling [47].

7.4. CTLs and CAR-T cells derived exosomes

CAR-based adoptive immunotherapies use genetically modified T lymphocytes to provide both tumor targeting effects and effective anti-tumor immune responses. However, in solid tumors, CAR-T therapy has not achieved the clinical success that has been observed in hematological malignancies due to limitations in cell-to-cell contact between CAR-T cells and tumor cells within the tumor microenvironment, which is an essential prerequisite for its anticancer strategy. Furthermore, following activation by the corresponding target cells CAR-T cells release a large number of cytokines. In addition to killing tumor cells, these excessive cytokine causes various clinical symptoms like headache, nausea, rash, hypotension and shortness of breath. This cytokine storm or cytokine release syndrome (CRS) is often associated with CAR-T cells therapy. Interestingly, CAR-T cell-derived exosomes, which are released from CAR-T cells, hold immense therapeutic potential for attacking cancer cells [48]. To a certain extent CAR-T cell-induced toxicity like CRS can be controlled using CAR-T cell-derived exosomes. Uncontrolled CAR-T cell expansion in vivo can be prevented by administering CAR-T cell exosomes instead thereby preventing CRS. Similarly, CAR-T cell-derived exosomes can cross the blood-tumor barrier much easily due to its nanoscale size and deliver anti-tumor agents to the tumor cells whereas CAR-T cells may face difficulties in penetrating the extracellular matrix. The targeting specificity of CAR-T cells are preserved in CAR-T cell-derived exosomes. Exosomes secreted by CAR-T cells contains specific engineered CAR structure thus retaining the targeting feature of parent cells [49,50]. Similarly, exosomes derived from CTLs also contains specific molecules derived from CTLs and ensures unidirectional delivery of lethal compounds like perforin, granzymes and lysosomal enzymes to the target cell. The production of CTL-derived exosomes is further promoted by TCR activation [49]. The use of CAR-T cell derived exosomes as a therapeutic strategy is at its nascent stage and requires a well-designed preclinical studies to characterize CAR-T cell-derived exosomes prior to applying them in any clinical setting.

8. Drawbacks of exosome-based immunotherapy vaccines

Most of the studies on exosome-based therapies showed results generated in pre-emptive settings and not in a pre-established tumor model. Various studies have highlighted the immunosuppressive role of TEXs which makes them less suitable for a tumor therapy system. Studies have shown impairment of T cell response to IL2 in the presences of TEX. They also promote and activate Tregs which in themselves are immunosuppressive in nature. Furthermore, TEXs has also shown to promote tumor invasion and accelerate metastasis in many studies [51]. In addition, clinical trials conducted using DEXs from autologous immature DC cultures improved NK cell response but increased T cell activity only in one patient out of five [52]. Delayed-type hypersensitivity response was also observed after the final immunization in a few patients. In the second phase 1 trial, DEXs also
failed to induce CD4$^+$ and CD8$^+$ T cell response. Therefore to overcome the above mentioned drawbacks, exosomes from IFN-γ-matured DCs were employed in phase 2 trials. Though the stimulation increased costimulatory molecules and ICAMs which led to a greater T cell activation, the successes was limited [51,53]. Thus, DEX showed restricted efficacy in initial clinical setting. Various factors may affect the efficacy of DEX therapy. A few of them are progressed stage of tumor, heterogeneity in patient cohorts, or the influence of other systemic and local immune regulatory mechanisms. The biggest caveat in exosome-based therapy is the industrial scale-up to produce homogeneous batch of exosomes for treatment. Addressing these issues will ensure wide-scale therapeutic applicability and acceptance of exosome-based therapy [30] (Figure 1).

**Conclusion**

Exosomes have enormous potential in providing a novel therapeutic area for delivery of different synthetic and biological molecules in cellular therapy. They are also important mediator of immune system, and their immunotherapeutic potential could be exploited in many ways. Though, initial mouse model studies have shown incredible results, clinical trials on tumor patients failed to achieve similar success in terms of their anti-cancer effect. Furthermore, current methods of exosomes isolation are expensive, and large-scale exosome isolation techniques are still to be developed. In addition, the entire composition of exosomes varies according to the cell type and the cellular environment. These complexities in composition of exosomes have shown both immunostimulatory and immunosuppressive effects, which are complex to comprehend and thus must be considered when employing exosomes for cancer immunotherapy. Despite the many obstacle exosome-based cancer therapy has shown promising results in various experimental setting, future research in this field will iron out the remaining hurdles. Synthetic exosome-mimics produced by cell extrusion or cell membrane-cloaked nanoparticles, can be used to significantly increase the production of exosomes. These exosome-mimics were observed to have almost identical zeta-potential, size distribution and morphology as compared to natural exosomes. They even possessed the immunocompatibility and stability of exosomes due to coating of the plasma membrane. Interestingly, cancer cell membrane-coated nanoparticles showed homing effect and therefore may serve as a potential anti-tumor drug delivery or immunotherapy vehicle. Incorporation of specific peptides or proteins on cell

**Figure 1.** A schematic representation showing immunosuppressive and immunostimulatory properties of exosomes isolated from tumor cells, MSCs, DCs and CTL/CAR-T cells and how exosomes from tumor cells and MSCs are be both immunostimulatory and immunosuppressive.
membranes could effectuate these exosome-mimics as a targeted drug delivery vehicle [30]. Artificial exosomes production could be easily scaled-up and homogeneity in the content of each batch of artificial exosomes produced will increase its therapeutic potential.

Combination of exosomes-based chemotherapeutic drug delivery to target the tumor cells and exosome-based immunotherapeutic vaccines to boost the immune response against the tumor might be a double-edged sword in cancer immunotherapy. The best way forward might be a refinement of the two methods where DEXs,TEXs or MSC-derived exosomes can be engineered to incorporate specific chemotherapeutic drugs, DNA, RNA or peptides which then can be used as a novel bio-carrier for targeted gene and drug delivery (Figure 2).

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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