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A Comprehensive Review of Exosomes with Therapeutic Potential in Cancer and Coeliac Disease

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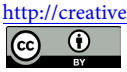

Abstract

The aim of this review was to evaluate the therapeutic potential of exosomes, extracellular vesicles secreted by cells. They have emerged as potential therapeutic transporters for several diseases. This review provides an overview of exosomes' therapeutic potential in cancer therapy and autoimmune conditions such as Coeliac Disease. The therapeutic effect is that the phospholipid-binding protein ANXA1 improves its anti-inflammatory properties. The review also analyzes the intricate processes of exosome production and composition ability to transport biomolecules such as proteins, microRNAs, and lipids, which promote intercellular communication and alter recipient cell behavior. Exosomes, linked to neurological disorders, cardiovascular disease, and cancer, present the means of targeted drug administration due to their innate specificity. Through genetic engineering and chemical modifications, exosomes can be tailored for specific purposes, demonstrating their versatility in targeted therapy. With ongoing research uncovering their therapeutic potential, exosomes present a promising frontier in novel medical treatments across various health conditions.

Keywords

Exosomes, Cancer, Coeliac Disease, Therapeutic Potential, Cell Communication, Anti-Inflammation

1. Introduction

A typical property all living cells have in common, whether prokaryotic or eu-

karyotic cells, is the release of extracellular vesicles. These vesicles are nature's delivery tool, carrying a variety of constituents from the cells that secreted them in the first place, such as proteins, metabolites, lipids, and nucleic acids, including microRNAs. One of the two classifications of these extracellular vesicles is exosomes, which play a very critical role in cell-to-cell communication. Exosomes are small vesicles ranging from 40 to 160 nm in diameter and form when the internalization of the plasma membrane leads to the formation of early endosomes, later maturing to form multivesicular bodies or MVBs for short. These MVBs then undergo internal budding or invagination to form the exosomes inside them [1]. MVBs can fuse with other vesicles and organelles in the cell, and the fusion of these MVBs (late endosomes) with the plasma membrane leads to the release of the exosomes into the extracellular space.

Since exosomes usually contain the cytosol of the original cell, they have many different cell constituents. These bioactive molecules, such as miRNA and proteins, play a significant role in cell communication and may alter their biological response. MicroRNAs bind to complementary sequences on messenger RNAs and can degrade or inhibit transcription, efficiently regulating the recipient cell's gene expression and behaviour. Cytosolic and cell surface proteins transport through the vesicles, which are heavily involved in cell signaling, tissue repair, homeostasis, and immune regulation. Exosomes are associated with various ailments and diseases, such as Alzheimer's, by inducing neuron apoptosis [2], inflammation in Cardiovascular Diseases [3], affecting intercellular communication leading to Liver failure [4] and most importantly-cancer by the intercellular transfer of oncogenic molecules [5].

2. Exosome Formation and Composition

Exosomes are formed from the plasma membrane by two internalization processes. The plasma membrane is lined with an essential receptor called the Transferrin Receptor, composed of two 95 kDa glycoprotein chains linked together by disulfide chains. This receptor plays a principal role in the analysis of exosome formation [6]. The first endocytosis of the lipid bilayer of the plasma membrane leads to the formation of the Early Sorting Endosome lined internally with the transferrin receptors as shown in **Figure 1**. The early endosome later matures into the late endosome, which undergoes the second internalization step, forming Intra Luminal Vesicles or ILF. The endosome containing the ILF is termed Multivesicular Bodies (MVB). During the secondary internalization step, the transferrin receptors are budded along with the vesicles from the limiting membrane; thus, the exosomes are lined externally with the receptors, making them excellent for marking [7]. The MVBs may be degraded if they fuse with lysosomes or autophagosomes; however, their fusion with the cell's plasma membrane will release the ILF, leading to the formation of exosomes.

The identification of cellular proteins to understand the composition of exosomes is done by using western blotting and fluorescence-activated cell sorting

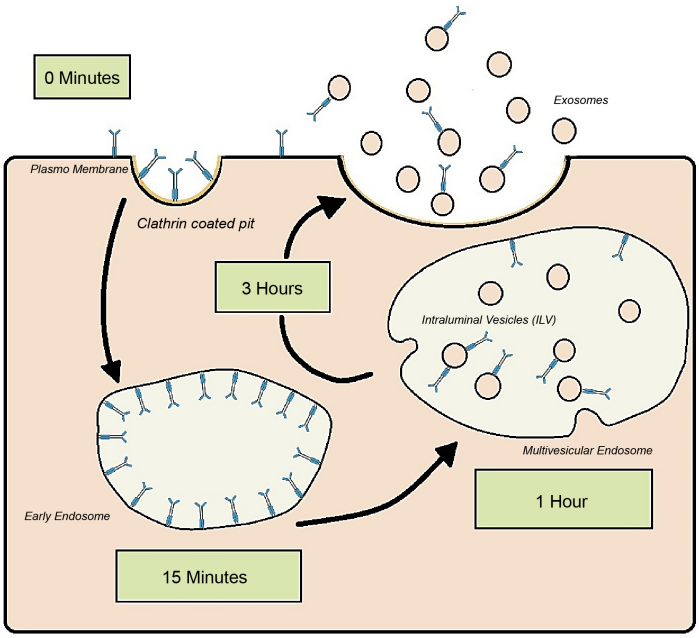

Figure 1. The internalization pathway of exosome formation, starting with the early endosomes which later mature into late endosomes. They undergo an internalization step to form ILVs. They are released upon fusion of the multivesicular endosomes with the cell's plasma membrane.

of beads lined with exosomes [8]. Different cytosolic proteins such as tubulin, actin, and actin-binding proteins such as cofilin are detected using exosomes secreted from a dendritic cell. Membrane proteins and proteins that help transport proteins, such as annexins and RAB proteins, were also observed. Protein kinases and heterotrimeric G proteins useful for signal transduction, enzymes such as peroxidases, enolase-1, pyruvate and lipid kinases, heat shock protein HSP70 and HSP90, and MHC class I and class II proteins, as well as tetraspanin proteins are observed.

Figure 2 shows an experiment conducted by Théry *et al*. [9] where the protein composition of dendritic cell-derived exosomes was analyzed. Essential proteins are identified through Western blotting and fluorescence-activated cell sorting, including MFG-E8, Mac-1, gag, CD9, Gi2α, hsc73, and annexin II. Additionally, their study highlighted the critical role of Major Histocompatibility Complex (MHC) proteins I and II in orchestrating immune responses. By examining exosomes from spleen-derived D1 cells and bone marrow dendritic cells (BMDCs), Théry *et al*. were able to deduce that the exosomes containing the MHC loaded with the tumor antigen peptides by CD4+ and CD8+ T-Cells, leading to their activation. Co-stimulatory signals by the DC-derived exosomes also improved the immune response.

3. Role of Exosome Proteins in Cell-Cell Communication

Exosomes are capable of binding to cells through receptor-ligand interactions by presenting antigens. They do not have to enter the cell to communicate with the

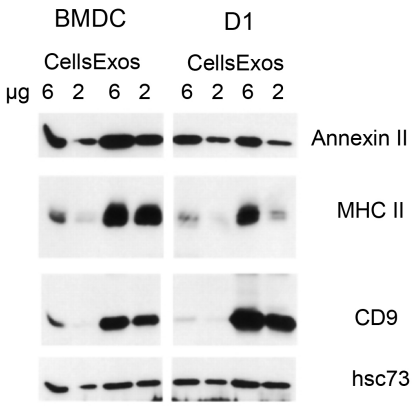

Figure 2. An experiment by Théry *et al.* (1999) which shows separation by SDS Page and subsequent Western Blotting using antibodies for the proteins.

acceptor cell. An example is found in exosomes containing MHC-peptide complexes, which can interact and activate T-cell receptors on T lymphocyte cells [10]. Exosomes can also play a part in developing tumor cells by communicating between cancer cells using proteins. EGFRvIII receptors are often exchanged between glioma cells, which can cause tumor progression [11]. Exosomes comprise a lipid bilayer membrane, similar to the plasma membrane from which they came. They can fuse to other plasma membranes and release their contents into the recipient cell. The recipient cell may also internalize the vesicle through endocytosis, after which it may either be degraded or recycled. Hemi-fusion stalk formation between the lipid bilayers is carried out by SNARE or Rab proteins. Integrins and adhesion molecules on the exosome also play a significant part in this fusion. The internalization rate usually decreases with a decrease in temperature and involves clathrin forming clathrin-coated vesicles [12]. Dynamin-2 is a protein that is heavily involved in internalization. Other exosome entry methods are lipid raft-associated internalization, phagocytosis, and micropinocytosis.

Intracellular Signalling.

After being taken up by recipient cells, exosomes often undergo degradation by lysosomes, autophagosomes, or recycling. However, their constituents are typically not degraded and activate inside the new cell. For instance, Transforming Growth Factor β-1 (TGFβ-1) carried by exosomes isn't degraded by the acidic pH; instead, it becomes activated and induces cellular changes [13]. Since most experiments use membrane receptor and lipid labeling, to analyze the exosome transport, it is difficult to understand the fate of the constituents inside the vesicles, in this case, the proteins. Exosomes have been studied to regulate both adaptive and innate immune responses. The exosomes secreted by pathogenic cells usually present these pathogenic antigens associated with MHC proteins to interact with the recipient cell's T-lymphocytes [1]. For tumor cells, various tumor antigens are associated with MHC to interact with T-cells. These antigens

thus regulate different immune responses within the cell. However, in some cases, these tumor cell-secreted exosomes may lead to immunosuppressive reactions [14].

In neural cells, they facilitate the transfer of the synaptotagmin four protein from presynaptic to postsynaptic cells, causing a backward signal travel [15]. Different neurogenerative diseases such as Creutzfeldt-Jakob disease and Mad Cow disease may be caused by the exosome transfer of scrapie prions (denoted as PrPsc) to normal functioning cells [16]. The transfer of CCR5 receptors via exosomes secreted by monocytes to endothelial cells can facilitate HIV-1 infection [17].

Exosomes that contain tumor-promoting molecules or proteins, as well as nucleic acids, may induce tumors in cells by preventing apoptosis, macrophage polarization, radioresistance, immune cell exhaustion, T-cell cytotoxicity [18] or providing resistance to different chemotherapeutic drugs. For instance, when exosomes extracted from irradiated lung cancer cells were analyzed, they exhibited upregulated expression of essential protein-coding genes, including ALDOA and ALDH3A1. This increase promotes faster growth of lung cancer cells by inducing glycolysis. Thus, exosome constituents can have an increased impact on the cell expression and response of the recipient cells.

4. Discussion

4.1. Role of Exosomes in Therapy

The field of drug delivery has undergone significant advancements in recent years as researchers explore various strategies to enhance targeted drug transport. Ideally, transport materials with a small volume, large surface area, good recipient cell response, and high affinity to the drugs are ideal [19]. The vesicle must also have an appropriate biodegradability potential, which does not affect the efficacy of the adjoined drug. Exosomes are naturally secreted in the human body and have a high specificity, so they are suitable for use. The gene of interest in parent cells may be upregulated, as in the upregulation of the transmembrane domain of the platelet-derived growth factor receptor (PDGFR) in cells for breast cancer therapy [20]. Alternatively, the parent cells may be cultured and incubated with the therapeutic agent to produce the modified exosomes, such as incubating mouse brain epithelial cells with the anti-inflammatory agent curcumin [21]. Small hydrophobic agents can diffuse into the parent cells due to the lipid bilayer membrane of the cells. Electroporation, or less commonly sonication, increases cellular membrane permeability in cases where hydrophilic agents such as small interfering RNA (siRNA) are used as cargo [22]. Genetic engineering of the surface peptides, such as PDGFR, is linked with single-chain variable fragments of HIV-1. Env-specific antibodies result in these exosomes' targeted delivery to the HIV-1 infected cells [23]. Chemically engineered exosomes may also be used to regulate the efficacy of the exosomes, such as the addition of aminoethylanisamide-polyethylene glycol (AA-PEG) with paclitaxel (PTX) loaded

exosomes to increase the effectiveness of the chemotherapeutic agent [24].

Research has shown that exosomes from cancer cells prefer to fuse with other cancer cells [25]. Chemotherapeutic agents like cisplatin, sorafenib, 5 fluorouracil, and oxiplatin can be used by exosomes along with other helper agents, such as the miRNA-27 inhibitor for different cancer types such as colon cancer [26]. They can induce cell cycle arrest and cell death in rapidly proliferating tumor cells. Exosomes from cancer stem cells in pancreatic cancer contain miRNA-210, which can carry out gemcitabine resistance in these cancer cells by activating the mTOR signaling [27]. In a novel pursuit of using exosomes for targeted therapy, they may be used in treating neurological disorders such as Alzheimer's [22] and ischemic stroke [28]. Exosomes can penetrate the blood-brain barrier in both disease and healthy conditions. According to Ghosh *et al*. [29], exosomes derived from mesenchymal stem cells (MSCs) secrete neuroprotective factors which promote normal neurological function, a critical factor in their potential utilization for post-traumatic brain injury. MHC, when interacting with the parenchymal cells in the brain, causes a decrease in the expression of axon inhibitory molecules. Neurodegenerative diseases have also been linked to proinflammatory factors.

According to Sheng *et al*. [30], interleukin (IL)-1, an inflammatory cytokine found at elevated levels in the brains of Alzheimer's disease (AD) patients, could potentially play a significant role in its development. When Krstic *et al*. [31] stimulated the immune system of mice by administering polyriboinosinic-polyribocytidilic acid, it showed an increase in the levels of the proinflammatory cytokine IL-1β in both plasma and brain, along with elevated levels of IL-6 specifically in the brain. IL-6 has been shown to penetrate the blood-brain barrier (BBB), enabling it to enter the brain. This can cause persistent and chronic neuroinflammation, subsequently leading to neurodegenerative disorders [32]. Human umbilical cord-derived mesenchymal stem cells (hUC-MSC) have been shown to inhibit the release of IL-6 by targeting the PIK3R1 gene [33]. Thus, these exosomes are capable mediators of regulation that are efficient enough to be involved in cell signaling and communication.

4.2. Prospects of Harnessing Exosomes as Therapeutic Agents in Coeliac Disease: A Futuristic Outlook

Coeliac Disease, an autoimmune condition affecting the small intestine, may be treated using exosomes. An intolerance to gluten causes it, specifically wheat, barley, and rye prolamins. These grains, closely related to cereals, have a high composition of glutamine and proline. The interaction of these peptides with MHC class II molecules stimulates CD4+ T helper cells. The release of Th1 and Th2 cytokines promotes the growth of autoreactive B cell clones and mucosal damage [34], leading to the erosion of the villi of the small intestine, a condition known as villous atrophy [35].

The compatibility of exosomes with the phospholipid-binding protein-ANXA1 enhances the anti-inflammatory property by regulating the release of proinflam-

matory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-*α*) [36]. Formyl Peptide Receptors (FPRs), specifically FPR1 and FPR2/ALX, are G protein-coupled receptors expressed on the surface of immune cells, which interact with the peptide and induce an anti-inflammatory response.

Exosomes transport biomolecules such as proteins, lipids, metabolites, and microRNAs. They can communicate with recipient cells through receptor-ligand interactions, which minimizes the need for cellular entry. Despite their potential therapeutic applications, some limitations affect their use in clinical trials. One such limitation is the composition differences resulting from donor metabolic disorders, which limits their efficacy in regenerative medicine. Exosomes contribute to inflammation and metabolic dysregulation in diseases like metabolic syndrome and type 2 diabetes, accelerating the progression of the condition. Synovial fluid-derived exosomes may trigger inflammation and cartilage degeneration in joint diseases like osteoarthritis. Cancer-derived exosomes regulate the tumor microenvironment, promoting metastasis and chemotherapeutic resistance and affecting the immune response. In kidney failure, they may transport toxic substances, inducing inflammation and fibrosis. In addition, exosomes play a role in the disease progression in endometriosis by affecting cell invasion, angiogenesis, and infertility [37]. Despite the promising therapeutic potential, suitable doses and source selection remain essential for effective exosome-based treatments, considering their varied effects on pathological conditions.

5. Conclusion

Exosomes are primarily limited to diagnostic research for cancer, autoimmune, cardiovascular, and neurological diseases by playing a central role in biofluid biopsies. Their high biological stability and greater accuracy compared to conventional biomarkers are the basis for their use. Depending on their constituents, exosomes secreted by immune cells can activate or decrease immunological responses. They are designed to deliver therapeutic constituents such as proteins, siRNA, miRNA, and drugs to specific cells or organs. They also offer several natural advantages as therapeutic agents, including bypassing cellular barriers and low immunogenicity. While more studies are required to understand the therapeutic potential of exosomes completely, they present a promising opportunity for creating innovative treatments for various health conditions. The diverse attributes of exosomes highlight their potential as a valuable tool in future medical treatments.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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