Exosomes for Diseases Prevention

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Exosomes are nano-sized vesicles secreted by most cells that contain a variety of biological molecules, such as lipids, proteins and nucleic acids. They have been recognized as important mediators for long-distance cell-to-cell communication and are involved in a variety of biological processes. Exosomes have unique advantages, positioning them as highly effective drug delivery tools and providing a distinct means of delivering various therapeutic agents to target cells. In addition, as a new clinical diagnostic biomarker, exosomes play an important role in many aspects of human health and disease, including endocrinology, inflammation, cancer, and cardiovascular disease.

exosomes biomarkers drug delivery tools therapeutic target diseases

1. Introduction

Extracellular vesicles (EVs) are lipid bilayer-bound particles secreted by most living cells [1]. Although these molecules have long been considered mediators of cellular waste, the discovery of their involvement in intercellular communication is generating increasing interest in many biological fields [2]. In addition, EVs allow the selective transport of functional proteins, nucleic acids (DNA, miRNA, mRNA), lipids or small molecules while protecting them from enzymatic degradation by the environment and facilitating their intercellular uptake [3][4]. These vesicles have been found in almost all biological fluids that allow their transport, such as plasma [5] or urine [6]. These EVs can then be taken up by neighboring or more distant cells in which they mediate many physiological or pathological processes by modulating their phenotype. EVs are classified into three types based on their biogenesis, size and surface markers: apoptotic bodies, microvesicles and exosomes. Due to their endosomal origin, exosomes are considered to play a key role in biological processes in normal and pathological conditions. Because of their inherent characteristics, such as stability, biocompatibility and stealth ability, exosomes are considered an interesting target for disease treatment. Exosomes are involved in basic physiological processes such as neuronal communication [7], antigen presentation [8], immune responses [9], organ development [10] and reproductive performance [11] by transmitting microRNAs, proteins, long-chain noncoding RNAs, circular RNA and DNA to mediate signal transduction between adjacent or distal cells. These structures are also involved in pathological diseases, such as cancer progression [12], cardiovascular disease and [13], inflammation [14] and even facilitate viral infection [15] and prion transmission [16].

Exosomes have become a new drug delivery tool due to their many advantages compared with traditional delivery systems. Efficient loading of external drugs or molecules into exosomes is another demanding and challenging task [17]. Like synthetic nanoparticles, several methods, including direct mixing, incubation, sonication, vortexing,

remote loading, electroporation, and transfection, can be applied to load micro- and macromolecules into exosomes. For some hydrophobic drugs (e.g., curcumin), EVs can be loaded with the drugs by direct mixing [18]. Paclitaxel can be loaded by mixing and sonication [19][20]. Due to the presence of the lipid bilayer around the exosome perimeter, electroporation is widely applied to load nucleic acids (siRNAs) [21]. It has been reported that describe a vesicular stomatitis virus G (VSVG) pseudo typing-based approach to load EV membranes with the receptor-binding domain (RBD) of the viral spike protein, which can be used to deliver antiviral drugs against SARS-CoV-2 infection [22].

2. Involvement of Exosomes in Disease Immunopathology

2.1. Exosomes and Tumor Environment

In recent years, the role of exocrine circRNA in regulating tumor cell proliferation in various kinds of cancers has been identified. In colorectal cancer, circIFT80 promotes the development of colorectal cancer by entering exosomes, promotes DNA synthesis and inhibits apoptosis through the miRNA-1236-3p/HOXB7 axis [23]. The expression of circFMN2 in serum exosomes of patients with colorectal cancer is high and negatively correlated with the level of miRNA-1182. The combination of circFMN2 and miRNA-1182 can significantly promote the proliferation of colorectal cancer cells, which suggests that exocrine circFMN2 plays an important role in promoting the tumor growth of colorectal cancer [24].

Understanding the immune-suppressive or immune-activating role of exosomes present in the tumor microenvironment can ultimately lead to the identification of exosome-based biomarkers of response and to the design of rational combinatorial therapies [25]. Programed death ligand 1 (PD-L1), also known as differentiation cluster 274 (CD274) or B7 homologue B7 homologue 1, is a type I transmembrane protein encoded by the CD274 gene, which is formed by immunoglobulin V-like and C-like extracellular domains [26]. PD-L1 is widely expressed in various cell types, mainly in tumor cells, monocytes, macrophages, natural killer (NK) cells, dendritic cells (DCs) and activated T cells. This molecule can also be expressed in immune privileged areas (such as the brain and cornea) and retinas [27]. Recently, cancer-derived exosomes were shown to transfer functional PD-L1 and inhibit immune responses [23]. Further, in melanoma patients receiving PD-1 blockade, exosomal PD-L1 levels correlated with tumor burden and response to therapy. It is unclear whether exosomal PD-L1 directly correlates with tumor or immune PD-L1 status, but it may have utility as a predictive biomarker for PD-1 blockade. PD-L1-containing exosomes may be both regulators and biomarkers of therapy resistance. In short, exosomal PD-L1 has a vital function in tumor metastasis, immune escape, and immunotherapy, but it is not clear whether the function of exosomal PD-L1 is cancer type-dependent. Further clarification of the role of exosomal PD-L1 in tumor progression will contribute to the early diagnosis and treatment of cancer (**Table 1**).

Table 1. Function of exosomal PD-L1 in tumor progression.

Type of Tumor	Source	Function	References
Colorectal cancer (CRC)	Serum and plasma	MiR-486-5p promotes the proliferation and migration of CRC cells by activating the signal pathways of pleomorphic adenomatoid gene 2 (PLAGL2), insulin-like growth factor 2 (IGF2) and β-catenin in vivo and in vitro.	[28]
Head and neck squamous cell carcinomas	Plasma	Downregulate CD69 expression on effector T cells to inhibit antitumor response	[29]
Prostate cancer	Tumor tissue	Suppress the function of T cells in the draining lymph node and block anti-PD-L1 antibodies	[30]
Melanoma	Plasma	Suppress the function of CD8 + T cells and cause failure of anti-PD-1 therapy	[23]

Exosomes can mediate molecular communication and substance transfer between primary tumor sites and distant metastatic sites. Exocrine bodies play an important role in tumor cell metastasis and invasion by regulating a series of cellular activities, including epithelial-mesenchymal transformation (epithelial-mesenchymal transition, EMT) [9]. The results of studies on circRNA and gastric cancer show that circNRIP1 can be transmitted between gastric cancer cells through exocrine bodies. In addition, miRNA-149-5p sponges components of the Akt1/mTOR signaling pathways, thus promoting gastric cancer cell metastasis [31]. Some exocrine circRNAs play an important role in the progression and metastasis of pancreatic cancer. Li et al. [32] found that exocrine circPED8A is highly expressed in pancreatic cancer and is related to lymphatic invasion, TNM stage and low survival rate. CircPDE8A can promote the growth of tumor cells by upregulating the expression of MET (one of the key oncogenes of epithelial tumors). In addition, circPDE8A secreted by tumor cells can be released into the blood circulation through exosomes to regulate MACC1 as a miRNA-338 sponge and promote invasive metastasis through MET/mitogen-activated protein kinase 1 (mitogen activated protein kinase-1-MAPK1) or the protein kinase B pathway. In addition, scholars [33] have found that exocrine circIARS secreted by pancreatic cancer cells is widely expressed in pancreatic cancer tissues, and its expression level is positively correlated with liver metastasis, vascular invasion and TNM stage (liver metastasis: paired 0.011; vascular invasion: paired 0.020; trans TNM: paired 0.023). CircIARS can enter human microvascular endothelial cells through exosomes derived from pancreatic cancer cells, downregulate the levels of miRNA-122 and tight junction protein-1 (zonula occludens-1), upregulate the levels of RhoA and RhoA-GTP, increase the expression of F-actin and adhesion plaques, increase endothelial monolayer permeability and promote tumor invasion and metastasis. In addition, related studies on colon cancer and cholangiocarcinoma have identified a role of exocrine circRNA in promoting tumor invasion and metastasis.

2.2. Exosomes and Digestive Environment

As one of the important functional vectors of gastric cancer (GC), exosomal RNA plays an important role in the initiation and development of gastric cancer by promoting cell-to-cell communication between gastric cancer cells and the microenvironment [34]. Relevant studies have shown that exosomes are an important part of the tumor

microenvironment in gastrointestinal cancer tissue and can promote the proliferation and metastasis of cancer cells, stimulate tumor angiogenesis, and inhibit the immune response of the host [35]. In addition, exosomes can effectively improve the accuracy and targeting of drug therapy for gastrointestinal cancer [36]. In conclusion, exosomes, especially exosome-derived miRNAs, play an important role in regulating the biological behavior of gastrointestinal cancer and have many advantages, such as good stability and convenient detection. *Helicobacter pylori* (Hp) infection is the most important factor leading to GC. Recent studies have shown that exosomes are associated with the occurrence of Hp-related diseases, having a tumor-promoting effect on tumor-associated macrophages, and promote GC progression [37]. Other studies have shown that exosomes in the conditioned medium of human gastric epithelial cells are involved in Hp infection [38]. This finding also shows that miRNA-155 exosomes from HP-infected macrophages can immunomodulate the inflammatory response and inhibit gastritis. Thus, exosomes play a key role in the diagnosis and treatment of gastrointestinal cancer.

2.3. Exosomes and Cardiovascular Diseases

Exocrine bodies are closely related to the occurrence and development of cardiovascular diseases such as hypertension, atherosclerosis, pulmonary hypertension, myocardial infarction, and myocardial hypertrophy. The cardiovascular system is an important site for intercellular transmission of exosomes. MicroRNA levels of exosomes related to cardiovascular disease, including miR-499, miR-133, miR-208, miR-192, miR-194, and miRNA-34a, are upregulated in patients with acute myocardial infarction and heart failure. Exosomes [39][40][41] can act on adjacent or remote target cells and mediate intercellular signal transduction. In addition, in pulmonary hypertension, researchers found that exosomes can ease pulmonary remodeling and reduce pulmonary hypertension by inhibiting high value-added pathways such as transcription factor-3 and inhibiting inflammation of monocytes [42].

2.4. Exosomes and Glioblastoma

Glioblastoma (GBM), also known as grade IV astrocytoma, is the most aggressive primary intracranial tumor of the adult brain [43]. Glioblastoma tumor cells release exosomes containing mRNA, miRNA and angiogenic proteins [12]. miRNAs have been found to function as regulatory molecules, acting as oncogenes or tumor suppressors and play prognostic roles in malignant transformation (including in GBM) and have been identified as novel therapeutic targets [44]. Previously, it had been shown that miR-125b overexpression decreased expression of cell cycle regulatory proteins such as CDK6 and CDC25A in U251 glioma cells, thereby preventing cell cycle arrest at the G1/S transition [45]. Another study showed that miR-181a, miR-181b and miR-181c act as tumor suppressors in GBM and contribute to the complexity of the pathological progression of glioma [46][47]. As with other cancers, miRNAs have great promise as prognostic biomarkers and therapeutic targets in GBM. miRNAs can function as potential oncogenes or tumor suppressors in gliomas [43].

2.5. Exosomes, the Endocrine System and Cancer

Recent studies have shown that exosomes secreted by cytotoxic T (TC) cells contribute to tumor progression, angiogenesis and metastasis. Exosomes in liquid biopsies can reflect the overall molecular information of the

tumor and have natural advantages in the diagnosis of TC [48]. The advantage of miRNAs in diagnosis is that they are highly stable, protected by bilayer membranes, and contain key information related to the tumor biological response [49][48]. Lee et al. found that the levels of miR-146b and miR-222 in epithelioid cell (TPC-1) exosomes were higher than those in Nthy-ori3-1 (NTHY) cells, indicating that these two miRNAs may be biomarkers of follicular papillary thyroid carcinoma (PTC) recurrence [50]. Interestingly, another study detected plasma exosomes in PTC patients with or without lymph node metastasis, confirming that circulating exocrine miR-146b-5p and miR-322-3p have high diagnostic value in predicting lymph node melanoma metastasis (LNM) in patients with PTC [51]. Samsonov et al. compared patients with benign thyroid nodules and found that miR-31 expression was significantly upregulated in serum exocrine tissues of patients with PTC. [52] In addition, similar changes were found in miR-21 in the serum exocrine system of patients with follicular thyroid cancer (FTC). In addition, compared with that of FTC patients, the level of miR-21 in serum exosomes of PTC patients was lower, but the content of miR-181a-5p was significantly increased. Therefore, miRNAs in these exosomes can be used as diagnostic markers for PTC and FTC [53]. With the continuous improvement of high-throughput detection technology, more miRNAs have been found. Wang ZY et al. carried out plasma miRNA spectrum analysis in patients with PTC and healthy subjects and verified the experimental results. Among the candidate miRNAs, miR-346, miR-34a-5p and miR-10a-5p levels were upregulated in PTC plasma exosomes [54]. Pan Q isolated exocrine bodies from the plasma of patients with PTC and nodular goiter by small RNA sequencing and comprehensive analysis and identified a group of plasma exocrine miRNAs as candidate biomarkers for the diagnosis of thyroid nodules, among which miR-5189-3p was the best in the diagnosis of PTC. Dai D et al. found that miR-485-3p and miR4433a-5p may be used as biomarkers for the diagnosis of PTC. Plasma exocrine miR-485-3p can distinguish between high-risk and low-risk PTCs [55]. By analyzing exocrine bodies from different patients and screening a group of miRNAs in plasma exocrine bodies, Li MH et al. found that the combination of these miRNAs was more effective than any single marker in identifying PTC and thyroid nodules [56]. These results suggest that the comprehensive detection of various exocrine contents may be more advantageous.

2.6. Exosomes and the Urinary System

It has been reported that exocrine lncRNA-p21 inhibits the occurrence of prostate cancer and the expression of p53 transcriptional regulatory genes [57]. When binding to the DNA binding domain of glucocorticoid receptors, lncRNA-GAS5 inhibits antiapoptotic genes, thereby preventing prostate cancer [58]. However, renal EVs can also mediate several other pathological conditions, such as renal fibrosis and inflammation [59][60].

2.7. Exosomes in Metabolic Diseases

Metabolic syndrome (MetS), obesity and diabetes mellitus, are clinically classified as metabolic disorders [61]. Recently, extracellular vesicles (EVs) have been emerging as a novel way of cell-to-cell communication that transfers fundamental information between the cells through the transport of proteins and nucleic acids. EVs, released in the extracellular space, circulate via the various body fluids and modulate the cellular responses following their interaction with the near and far target cells. Clinical and experimental data support their role as biomarkers and bio-effectors in several diseases including metabolic syndrome [62]. New evidence shows that exosomes with flotillin immunomodulatory functions may be involved in the occurrence and development of

autoimmune diabetes. For one thing, islet-derived exosomes can activate the immune system and cause an autoimmune response [63]. For another, exocrine bodies originating from the immune system may lead to dysfunction and beta cell death [64]. Another study showed that exosomes released by human urine-derived stem cells can prevent podocyte apoptosis and promote cell survival and angiogenesis in rats with T1DM [65]. In addition to T1DM, exosomes also play a role in other autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome [66]. One result showed that exosomes from adipose stem cells (ADSCs) improved insulin sensitivity and hepatic steatosis, and reduced obesity, when injected into obese mice [67]. Furthermore, AT macrophages (ATM) exosomes from obese mice have been shown to induce systemic insulin resistance and glucose intolerance in lean mice, and these factors are ameliorated in obese mice when ATM exosomes from lean mice are treated in obese mice [68]. MiR-155 is a repressor of the adipogenic transcription factor peroxisome proliferator-activated receptor γ (PPARγ) and has been suggested to be a key mediator of the effect of ATM exosomes on insulin resistance [68]. Taken together, these studies highlight the potential importance of exosome-mediated crossover between key metabolic tissues in regulating metabolism under physiological and pathophysiological conditions [69]. MiR-197, miR-23a, and miR-509-5p have now been identified as potential contributors to dyslipidemia in metabolic syndrome. In addition, a reasonable association between miR-27a and miR-320a and patients with metabolic syndrome and type 2 diabetes has also been found [70]. Therefore, EVs could be new biomarkers predictive of metabolic pathologies and new exploitable structures in therapy [71] (**Table 2**).

Table 2. The targets of exosomes in diseases.

Disease	Exosomal miRNAs	Target or Pathway	References
Acute myeloid leukemia	Exosomes with MICA/B (MHC I chain-related proteins A and B)	By downregulating NKG2D receptor expression	[72]
Brain cancer	Brain endothelial cells	Rhodamine 123, PTX, DOX	[73]
Breast cancer	MiR-365 in macrophage-derived exosomes	The triphospho-nucleotide pool, the enzyme cytidine deaminase	[74]
Leukemia	MiR-210	CD107a	[75]
Lung cancer	MiR-494	Suppresses PTEN (PTEN (phosphatase and tensin homolog deleted on chromosome ten), it is located at 10q23.3 and the transcriptional product is 515 kb mRNA).	[76]
Colorectal cancer	MiR-31-5p in (tumor-derived exosomes) TDEs	LATS2	[77]

Disease	Exosomal miRNAs	Target or Pathway	References
Nasopharyngeal cancer	MiR-24-3p	ND	[78]
Esophageal cancer	MiR-21 in TDEs	PDCD4	[79]
Head and neck cancer	MiR-196a in cancer associate fibroblasts (CAF)- derived exosomes	CDKN1B and ING5	[80]
Pancreatic cancer	MiR-106b in CAFs-derived exosomes	TP53INP1	[81]

t immune system [82]; because of the similarity of exocrine biogenetic pathways (ESCRT-dependent and independent), their fate (endocytosis, endocytosis and receptor-mediated uptake by target cells) and viral uptake, packaging and release are comparable to those of relatives [83]. Viral infection stimulates host cells to secrete exocrine bodies, which act as pathogen-related molecular models, carry inflammatory mediators, and cause inflammation [84]. HCV mRNA in exosomes induces secretion of interferon alpha (IFN alpha) from macrophages, and exosomes from C3/36 cells infected with Zika virus induce expression of tumor necrosis factor alpha (TNF alpha) from monocytes and cause endothelial damage to induce intravascular coagulation and inflammation. Exosomes from Kaposi sarcoma-associated herpesvirus also cause endothelial damage and induce the expression of IL6 [85]. Exosomes from virus-infected cells also cause apoptosis of immune cells. The 2019 coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019. It is believed that COVID-19 may be transmitted from person to person through droplets, fecal transmission and direct contact with aerosols. A relatively high basic fecundity (R 0) value estimated between 2.2 and 5.7 caused the virus to spread rapidly, resulting in a pandemic [86]. COVID-19 is a highly contagious respiratory syndrome that can cause multiple organ failure and may lead to death in a small number of infections. The virus can replicate in a variety of cells expressing ACE2, including nasal epithelium, nasopharynx, upper respiratory tract, type II lung cells in the lung, gastrointestinal tract, immune cells and endothelial cells [87][88]. Recent data have shown that lipid metabolism, including cholesterol metabolism [89], is involved in the pathogenesis of COVID-19, raising the question of whether exosomes are involved in the pathogenesis of SARS-CoV-2 infection. Consistent with this idea, SARS-CoV-2 protein interaction group analysis revealed interaction with Rab protein, which is part of the ESCRT pathway involved in exocrine biogenesis. In short, exosomes from virus-infected cells can cause tissue damage by activating inflammation and cytotoxicity. For example, HIV infection induces secretion of exosomes that are enriched in viral Nef protein [90]. Likewise, Epstein–Barr virus (EBV)-infected cells secrete exosomes enriched with galectin 9 that cause apoptosis of cytotoxic T cells specific to EBV-infected cells [91] (**Table 3**).

Table 3. Exosomes in the pathogenesis of viral infections.

Virus	Source	Function	References
Avian influenza (H5N1)	miR-483-3P	Increased production of proinflammatory cytokines in vascular endothelial cells	[92]

Virus	Source	Function	References
HIV	Nef	Susceptibility to infection and apoptosis of CD4 cells	[90][93]
KSHV	miRNA and others	IL6 production and cellular metabolism	[85]
Coronavirus	CD9	Proviral	[94]
EV-A71	Viral protein and nucleic acid	Virus spread	[95]

2.9. Exosomes in Transplantation

Transplantation is the treatment of choice for many terminal organ failures. However, it comes with an important risk of chronic rejection. Exosomes are key mediators of donor recognition by the host immune system through protein transfer of the preformed donor MHC-peptide complex in host APC that subsequently activates donor-specific T cells [96]. Moreover, studies focusing on blocking this phenomenon are increasing and show promise. However, exosomes derived from host immune cells have shown interesting capacities to modulate rejection, as in other pathological conditions. Exosome-based therapies are currently being studied to specifically silence the immune system toward the graft. Several cell types are candidates for sources of exosomes: mesenchymal stem cells, regulatory T cells, M2 macrophages and immature dendritic cells, which are well-known immunoregulatory cells [97][98][99][100].

2.10. Anti-Inflammatory and Antimicrobial Vesicles

Mesenchymal stem cells (MSCs) can interact with the immune system to prevent infection through both direct and indirect mechanisms [101]. MSCs, exosomes secreted by these cells can be used as complementary antimicrobial agents, as a substitute for or in combination with antibiotics under specific physiological conditions or specific priming conditions [102]. In particular, antimicrobial properties are associated with the paracrine of several antimicrobial peptides (AMP), which have a wide range of antimicrobial properties, as well as specific extracellular vesicle (EV) secretion, including the release of immunomodulatory factors MSCs that retain antimicrobial properties [103] and are considered safer than parental cell administration [104]. EVS as a cell-free agent and/or drug carrier may have therapeutic effects for sepsis [104] and may be developed as a superior drug delivery vehicle [105].

EV number, size and their biologically active material is altered in numerous inflammatory conditions and EV can alter the cellular functions of neutrophils, monocytes, macrophages and their precursor hematopoietic stem and progenitor cells (HSCs) [106]. Neutrophils can release at least two sub-classes of EV, termed: neutrophil derived trails (NDTRS), which are generated by integrin mediated interactions by migrating neutrophils in response to vascular wall forces and neutrophil derived microvesicles (NDMV), which are dependent on the PI3K pathway and released by membrane blebbing following neutrophil activation [107][108]. Mesenchymal stem cell (MSC) EV modulate neuroprotection during ischemic injury by inhibiting neutrophil recruitment and mediate similar protective effects to those observed with neutrophil depletion [109]. Monocyte-derived EV may provide utility as diagnostic biomarkers for the assessment of pathologies where monocyte phenotypes contribute to the inflammatory disease such as infection, dyslipidemia, diabetes, obesity and cardiovascular diseases [110]. In conclusion, EV, especially

exosomes, can be used as the carrier of K, which is expected to improve the therapeutic effect and reduce adverse reactions [111].

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