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Exosomes and HIV-1 Association in AIDS-Defining Patients

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Abstract

Exosomes are membranous nanovesicles of endocytic origin that help to facilitate cell-to-cell communication by transporting cellular cargo locally or systemically to a recipient cell. These are subsequently fused and internalised by recipient cells. Exosomes are secreted from all cell types in HIV-1 infected patients. Recent studies reveal that exosomes from various sources modulate the pathophysiology of HIV-1, and conversely, exosomes are also targeted by HIV-1 factors. Semen or plasma exosomes could suppress/inhibit HIV-1 replication in humans and rodent models. Exosomal cargo components could be used as a biomarker in HIV-1 patients and AIDS-defining patients. Exosome in semen and plasma is a useful tool for the diagnosis of HIV-1 and an alternative therapeutic tool for antiretroviral therapy.

Keywords: exosome, HIV-1, AIDS, semen, plasma

1. Introduction

Extracellular vesicles are membrane vesicles. The extracellular vesicles are secreted by most cell types of any living organism from archaea, bacteria, and eukarya. Extracellular vesicles are isolated from biological fluids such as blood, semen, cerebrospinal fluid, and saliva [1, 2]. Exosomes are formed by the fusion of multivesicular bodies (MVBs) with the cell membrane and then released into the extracellular space [3]. Exosomes are extracellular vesicles with a diameter of 30–100 nm. Exosomes are used in therapeutic applications like a delivery system. The exosomes and retroviral vectors are efficient transporters of biotransformation. The exosomes are used in immunotherapies and biotherapies. Exosomes and lentiviruses are excellent vehicles to carry encapsulated cargo with reduced immunogenicity with multiple cell types and tissue barriers, including the blood-brain barrier. The inherent properties of exosomes are to enclose nucleic acids, proteins, lipids, and chemical agents. Exosomes have been considered to carry the coding, and non-coding RNA (miRNA and siRNA) along with the lentiviral vectors which give a stable integration into target cells [4–9]. Some findings proposed that the human immune deficiency virus (HIV) particles like exosomes contribute to HIV pathogenesis, but the recent findings reported that

Figure 1.

A: View of an Multivesicular endosome (MVE) sparsely labelled with AuTf after a 20 min incubation at 37°C. note the apparent fusion of the MVE and the plasma membrane. This may represent incipient MVE exocytosis. Bar, 100 nm. $\times 107,000$. Fig. B: View of MVE exocytosis in an unfixed reticulocyte. This cell was incubated for 30 min with AuTf, subjected to a 20 min chase with unconjugated transferrin, and then quick-frozen without prior fixation and freeze-substituted. Bar, 200 nm. $\times 61,000$. Fig C: Freeze-fracture, deep-etch view of a large MVE filled with numerous inclusions. The remaining free lumen possesses a markedly lower protein concentration than the surrounding cytoplasm and is deeply etched. Bar, 200 nm. $\times 63,000$. Fig. D: View of an MVE lightly labelled by AuTf after a 20 min incubation at 37°C. AuTf (white dots) is bound to the walls of the MVE and is clustered heavily around the inclusions, making the outline of the individual gold beads difficult to discern. Bar, 100 nm. $\times 127,000$. All A, B, C, D figures are adopted from Harding et al. [11], figure source has permitted from the author).

the exosomes exert an effect on the replication of HIV [10]. The potential research on exosomes will be helpful in the vaccine or therapeutic design to treat HIV patients along with antiretroviral therapy. The exosome adopted picture is given in **Figure 1**.

2. The exosomes association with HIV-1 patient

The circulated exosomes in plasma are small and nanometre in size. Due to the small size, the exosomes are easily separated from human plasma through low density, differential ultracentrifugation, or ultrafiltration [12]. The exosomes are isolated from the semen for HIV-1 infection assays [13]. The exosomes in the host play an important role in HIV-1 infection, releasing intracellular and extracellular material and establishing cell-cell communication. The exosome study in HIV research is a hotspot because it has great significance in predicting acquired immunodeficiency syndrome (AIDS). The microparticles containing the chemokine receptor CCR5, the principal coreceptor for macrophage-tropic human immuno-deficiency virus-1 was released from the surface of the CCR5⁺ Chinese hamster ovary cells and peripheral blood mononuclear cells. It proves that intercellular communication is associated with the cellular membranes of the HIV-1 infection [14]. Exosomes utilise the primary and secondary host cells. The human T cell immunoglobulin mucin (TIM) proteins are used by retroviruses, such as HIV, for viral entry. The TIM1 proteins promote the infection

of multiple viruses, such as HIV, through virion-associated phosphatidylserine [15]. As AIDS is incurable by antiretroviral therapy, a hypothesis is explained that the 'Trojan exosomes' can be a novel approach to vaccine development [16].

HIV-1 patients in antiretroviral therapy may develop the risk of non-AIDS-defining-cancers (NADCs). The transactivation response RNA containing exosomes from the HIV-1 infected T cells promotes the growth and progression of particular NADCs. In the host, the HIV-infected T cell exosome enters through the epidermal growth factor receptor by stimulating ERK1/2 phosphorylation via the EGF/TLR3 dependent manner leading to NADCs [17]. HIV-1 infected patients are more likely aggressive to develop cervical cancer. The HIV-1-associated exosomes promote the growth and progression of cervical cancer in HIV-1 patients [18]. A study reported the presence of the transactivation response element (TAR) miRNA encoded by HIV-1 infected cells and patient sera. This TAR miRNA was isolated from the exosomes derived from the HIV-1 infected cells. From the study, it was observed that the HIV-1 RNA molecules within the exosome helped in the intercellular viral spread in infected host cells [19]. This TAR RNA stimulated the production of proinflammatory cytokines from exosomes derived from HIV-1 infected cells [20]. The stable epigenetic repression of the HIV-1 expression *in vivo* was observed by the exosome-mediated systematic delivery of therapeutic cargo [21]. An engineered exosome Tat protein was used as a new class of biologic product to activate the latently HIV-1 infected primary CD4⁺ lymphocytes [22]. A research study found that the *Mycobacterium tuberculosis* drug-resistant strains secreted from exosomes by macrophages reactivate HIV-1 induced through oxidative stress. Proteomic information on several host factors, such as galectins, HSP90, HIF-1 α in the *Mtb* specific reactivation, promotes the HIV-1 reactivation in the host. This study of this redox and bioenergetics basis of HIV-1 TB coinfection would be an effective therapeutic strategy [23].

Exosomes are nano-sized membrane vesicles released by fusion of the multivesicular body or the organelle of the endocytic pathway origin with the plasma membrane of the cells. The exosome biogenesis is an endosomal sorting complex required for transport (ESCRT) dependent or ESCRT independent. The endosomal pathways are not entirely separated but the different subpopulations of exosomes work synergistically in different cell types of machinery. The cell type or cellular machinery is an important factor that controls the secretion of exosomes [24]. The formation of the exosome is behind with multiple mechanisms. In the early endosome formation, the best mechanism involves the recruitment of the endosomal sorting complex required for transport (ESCRT) machinery to the ubiquitinated proteins. The ESCRT complex is made up of four protein complexes (ESCRT-0, -I, -II, and -III) along with accessory proteins (Alix, VPS4, and VTA-1). These protein complexes bind to the exosome cargos through the intraluminal vesicles (ILVs). One of the ESCRT-III complexes induces the inward budding and fission of the vesicles to form the microvesicular bodies [25–28]. The exosome cargos formation depends on the synthesis of ceramide as a mechanism to induce the vesicle curvature and budding [29]. The exosome formation depends on the synthesis of the tetraspanin-mediated organisation of specific proteins, such as the amyloidogenic protein and pre-melanosome protein [30, 31]. After the formation of exosomes, the exosomes played an important role in cellular functions such as cellular migration and invasion, immunity, normal development and adult physiology, fertilisation and mating behaviour, nervous system [24]. Exosomes and HIV-1 particles share important features in biogenesis, biophysical, molecular, and cellular uptake mechanisms. Both HIV-1 and exosomes are surrounded by a phospholipid bilayer in a size of 100–200 nm but their separation is a technical challenge by

centrifugations. Exosomes are membrane-derived vesicles that harbour genomic, proteomic, and lipid cargos and also participate in the progression of HIV-1 pathogenesis. Exosomes derived from the HIV-1 infected dendritic cells were more infective than the cell-free HIV-1 or exosome-derived T cells. During HIV-1 infection, the exosomes

Categories of protein	Names
Tetraspanins	CD9, CD63, CD81, CD82, CD37, CD53
Heat shock proteins (HSP)	HSP90, HSP70, HSP27, HSP60
Cell adhesion	Integrins, Lactadherin, Intercellular Adhesion Molecule
Antigen presentation	Human leukocyte antigen I and II /peptide complexes
Multivesicular body Biogenesis	Tsg101, Alix, Vps, Rab proteins
Membrane transport	Lysosomal-associated membrane protein 1/2, CD13, PG regulatory-like protein
Signalling proteins	GTPase HRas, Ras-related protein, furloss, extracellular signal-regulated kinase, Src homology 2 domain phosphatase, GDP dissociation inhibitor, Syntenin-1, 14-3-3 Proteins, Transforming protein RhoA
Cytoskeleton components	Actins, Cofilin-1, Moesin, Myosin, Tubulins, Erzin, Radixin, Vimentin
Transcription and protein synthesis	Histone1, 2, 3, Ribosomal proteins, Ubiquitin, major vault protein, Complement factor 3
Metabolic enzymes	Fatty acid synthase Glyceraldehyde-3-phosphate dehydrogenase Phosphoglycerate kinase 1 Phosphoglycerate mutase 1 Pyruvate kinase isozymes M1/M2 ATP citrate lyase ATPase Glucose-6-phosphate isomerase Peroxiredoxin 1 Aspartate aminotransferase Aldehyde reductase
Trafficking and membrane fusion	Ras-related protein 5, 7 Annexins I, II, IV, V, VI Synaptosomal-associated protein Dynamin, Syntaxin-3
Antiapoptosis	Alix, Thioredoxin, Peroxidase
Growth factors and cytokine	Tumour necrosis factor- α , TNF receptors, Transforming growth factor- β
Death receptors	FasL, TNF-related apoptosis-inducing ligand
Iron transport	Transferrin receptor
Lipids	Lipid related enzymes
LTA4, LTB4, LTC4, PGE2, 15d-PGJ2, PGE2, PA, Ceramides, Cholesterol, Bis(monoacylglycero)phosphate, Phosphatidyl serine, Spingomyelin	LTA4 hydrolase, LTC4 synthase, COX-1, COX-2, PGE synthase, PLD2, DGK, nSMase2

Table 1.
Types of proteins and lipids in exosomes: The author has permitted the source [42].

from the dendritic cells contain fibronectin and galectin-3. In the T-cells exposed to exosomes cargo derived from HIV-1 infected dendritic cells, the gene expression of the pro-inflammatory cytokines IFN- γ , TNF- α , IL-1 β , and RANTES and activation of p38/Stat pathways was observed [32]. A class of proteins called 'Tetraspanins' provides a powerful approach to distinguish exosomes and HIV-1 infected cells during the progression of the disease [33]. The Epstein-Barr virus (EBV) that causes tumours in humans induces the transfer of viral oncoprotein, LMP1, and a virus-encoded miRNA through exosome [34]. Exosomes are involved in viral transmission and immune sensing in the host. Hepatitis-A and hepatitis-C viruses use exosomes for viral transmission and antibody-mediated immune responses in the host [35]. The cytomegalovirus, the herpes simplex virus, human papillomavirus, the respiratory syncytial virus was mediated exosome cargo of various molecules, such as dendritic cell-specific ICAM-3 grabbing nonintegrin (DC-SIGN) and MHC-I and II [36].

The architecture of the exosome is very complex and contains proteins, nucleic acids, and lipids. Various databases are available for information on exosomal proteins, mRNA, MicroRNAs and lipids [37, 38]. The integrated database provides high-throughput datasets on vesicular components of prokaryotes, mammalian and nonmammalian eukaryotes extracellular vesicles [38]. An exosome contains several tetraspanins such as CD9, CD63, CD81, CD82 takes part in cell penetration, invasion and fusion events, heat shock proteins HSP70 and HSP90 involved in stress response in antigen binding and presentation, Alix, TSG101 proteins are involved in exosome release, annexins and Rab proteins are involved in membrane transport and fusion. The exosome biogenesis proteins Alix, flotillin, and TSG101 participate in exosome biogenesis. The proteins, such as TSG101, HSP70, CD81, and CD63, are highly enriched in exosomes and considered as the exosome marker proteins. Exosomes contain all types of RNA such as miRNA, ribosomal RNA, long non-coding RNA, piwi interacting RNA, transfer RNA, small nuclear and nucleolar RNA, etc. [39, 40]. Besides proteins and nucleic acids, the exosomes contain the lipids, such as phosphatidylserine, phosphatidic acid, arachidonic acid, cholesterol, and sphingomyelin. The human plasma and serum exosomes contain high-density lipoproteins (HDL), low/very low-density lipoproteins (LDL/VLDL), Apo AI, Apo-B100, etc. [41]. The various proteins and lipid components of the exosome are given in **Table 1**.

Exosomes contain receptors for virus entry. SARS-CoV-2 spreaders are contributed by exosomes as they transfer the receptors CD9 and ACE2 to recipient cells susceptible to the SARS-CoV-2. During the SARS-CoV-2 infection, the SARS-CoV-2 virus is directed into the exosome pathways and the components are packaged into exosomes for secretion [43].

3. Semen exosomes in HIV-1 patient

HIV-1 could transmit via the semen through sexual intercourse and is the leading cause of HIV-1 transmission worldwide during vaginal and rectal intercourse by human beings. The major route of transmission is the vaginal secretion during the sexual intercourse to the person who is involved in this period [44]. Exosomes play an important role in intracellular communication. Semen exosomes are epididymosomes and prostasomes. Epididymosomes and prostasomes are exosomes involved in the acquisition of fertilising ability, modulation of motility, maturation of spermatozoa and could be a possible biomarker in the early diagnosis of male infertility [45].

The identified proteins in the blood exosome and semen exosome are useful as a biomarker applicable to different fields of medicine, especially in reproduction and infectious diseases. The proteomic profiling of semen exosomes and blood exosomes from HIV-infected and uninfected individuals was compared. The compositional and functional variabilities were observed. Semen exosomes were enriched in clusterin protein compared with the blood exosome in HIV-infected and uninfected patients [46]. The antiretroviral activity of the human semen exosome was reported. The human semen exosome inhibits the HIV-1 replication, and it could be useful as a therapeutic purpose for HIV-1. Semen exosomes restrict HIV-1 transmission by vaginal cells. This study of the semen exosomes helps the development of the therapeutic diagnosis during the transmission of HIV-1 [13]. Semen and vaginal fluid exosomes of healthy individuals could inhibit the HIV-1 infection and block the transfer of HIV-1 into vaginal cells [47]. *In vitro* and *in vivo* study of HIV-1 infected, uninfected patients, ART naïve, ART patients' semen exosome were isolated and found the inhibition of replication of HIV-1 [48]. The semen exosomes in HIV-1 patients could be an option for the development of novel therapeutic biomarkers in the field of infertility and the diagnosis of AIDS.

4. Plasma exosomes in HIV-1 patient

Exosomes play an important role in pathogenesis in HIV-1 patients. The exosomes in HIV-1 patients and their relationship in immune and oxidative stress response have been documented [49]. Exosome plasma proteomic profiles were identified and characterised in HIV patients of alcohol drinkers and cigarette smokers. The exosome proteins, such as hemopexin and properdin, could be used as a potential biomarker for physiological effects that may arise in HIV-infected individuals tobacco and alcohol abusers [50]. Exosome-associated most cytokines were observed in the HIV-1 infected patients. The exosomes purified from HIV-positive patients induced the CD38 expression in naive and central memory CD4⁺ and CD⁺ T cells leads to inflammation and viral propagation [12]. The expression levels of miR21 were lower in the plasma-derived exosome of HIV-1 elite controller with decreasing CD4 T cell count [51].

5. Exosome and HIV-associated neurological disorders (HANDS)

In the HIV-1-associated neurocognitive disorders, the HIV-exosomes accelerate the dysfunction of primary human brain microvascular endothelial cells (HBMVECs) by inducing mitochondrial hyperfusion. HIV-1 exosome increases the mitochondrial hyperfusion due to loss of phosphorylated dynamin-related protein1 (p-DRP1). HIV-exosomes dysregulate the mitochondrial function could adversely change the effect of the brain microvascular endothelium [52]. The important role of exosomes in HAND has been reported to lead to a disease like Alzheimer's. The HIV patients on ART are the main cause of the deposition of Beta-amyloid (A β) leads to dementia. The neuroinflammation is induced by HIV proteins, such as Tat, gp120, and Nef. Exosomes serve as a link between HIV and Alzheimer's disease by packaging and transporting the toxic proteins [53]. The exosome played an important role in signaling in the central nervous system and acts as a potential vehicle to deliver various therapeutics to treat HIV neuroinflammation [54]. The exosomes played an important

role in transporting cargo in many neurological disorders, such as mental disorders, brain injury, abnormal neuronal development, neurodegenerative diseases, epilepsy, stroke, and brain cancer [55].

6. Exosomes used as therapy

Exosomes in semen and plasma could be used as a biomarker for the diagnosis of HIV-1 patients. Exosomes could be used as an immunological and oxidative stress marker in HIV patients. Exosomes either promote or inhibit HIV-1 pathogenesis in the human body. The exosomes could be used as a diagnostic biomarker, therapeutic tool for successful implementation, and clinical application in HIV-1 patients [56]. Plasma neuronal exosomes are used as biomarkers in HIV-associated neurological disorders and Alzheimer's disease [57]. In a recent study, the researchers used the exosome-based strategy to block HIV in mice in a block and lock approach [58].

7. Conclusion

The exosome formation and secretion after a retrovirus infection is a very complex process. Further study of the virally complex microvesicles will clarify their role in infection. The main function of the exosome in semen and plasma is immune activation, immune suppression, transfer of functional miRNA, intracellular and intercellular communication. The exosome study will manage the broad biological and medical implications towards the pathogenesis of HIV-1 infected individuals. The current understanding of the exosome biology and function with regards to the HIV-1 infection is in early-stage now. The role of exosomes in the host-HIV-1 infections can open a new era of understanding of disease mechanisms, therapeutic interventions, and future diagnostic purposes in the field of medical science research.

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Conflict of interest

No conflict of interest by the authors.

Key points

1. The exosomes are nanovesicles derived from various cell types under the physiological or pathological conditions of the body of human beings.
2. Basically, exosomes carry the host and pathogen-derived genomic, proteomic, lipidomic materials. The exosomes exchange information between the cells during the progression of AIDS.

3. Exosomes in the HIV-1 patients have the dual activity that could inhibit HIV-1 infection or progress the HIV-1 infection within the host.
4. Exosomes may activate the resting CD4⁺T lymphocytes and, by activating these cells, lead to chronic infection.
5. The study of biological information in an exosome could be used as a marker in HIV-1 patients and could be helpful in diagnosis and treatment.
6. Semen exosomes are rich in nucleic acids and protein binding factors than blood exosomes.

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