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Invited Mini Review

The complex role of extracellular vesicles in HIV infection

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During normal physiological and abnormal pathophysiological conditions, all cells release membrane vesicles, termed extracellular vesicles (EVs). Growing evidence has revealed that EVs act as important messengers in intercellular communication. EVs play emerging roles in cellular responses and the modulation of immune responses during virus infection. EVs contribute to triggering antiviral responses to restrict virus infection and replication. Conversely, the role of EVs in the facilitation of virus spread and pathogenesis has been widely documented. Depending on the cell of origin, EVs carry effector functions from one cell to the other by horizontal transfer of their bioactive cargoes, including DNA, RNA, proteins, lipids, and metabolites. The diverse constituents of EVs can reflect the altered states of cells or tissues during virus infection, thereby offering a diagnostic readout. The exchanges of cellular and/or viral components by EVs can inform the therapeutic potential of EVs for infectious diseases. This review discusses recent advances of EVs to explore the complex roles of EVs during virus infection and their therapeutic potential, focusing on HIV-1. [BMB Reports 2023; 56(6): 335-340]

INTRODUCTION

Extracellular vesicles

Extracellular vesicles, or EVs, are a heterogeneous population of vesicles enclosed by a lipid bilayer. They are released by both healthy and infected cells into the extracellular environment (1). EVs have been detected in different biological fluids, including saliva, cerebrospinal fluid, blood, urine, and breast milk. EVs were considered as cellular 'garbage bags' for eliminating unwanted compounds from the cell (2). However, recent studies have shown that EVs are more than just waste bags, and act as signaling vehicles between cells by carrying various biological active molecules, such as nucleic acids, proteins, and lipids (3). Although the term EVs is currently employed to describe all membrane vesicles that are secreted. However, these vesicles can be classified into two main groups: microvesicles and exosomes (1, 3). Microvesicles are formed through an outward budding process at the plasma membrane, and their size typically ranges from 50 nm to 1 μm (1, 3, 4). Exosomes are endosome-derived nanovesicles of about 30-150 nm (5). Although microvesicles and exosomes are formed at different locations, there is significant overlap in their intracellular mechanisms and sorting machinery, and both involve membrane-trafficking processes. Furthermore, EV generation pathways may differ by producing cells, therefore, this nomenclature of exosomes and microvesicles is still questionable.

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EV and virus infection

Recent studies identified EVs as exerting a variety of mechanisms during virus infection (3, 6, 7). Modified EVs that are released from infected cells can help to enhance viral replication and transmission by serving as vehicles for the transfer of viral components (8, 9). The effects of EVs on viruses are complex and not well understood, as they have been shown to exhibit antiviral effects too (10, 11). Thus during virus infection, EVs may play either pro- or anti-viral roles. It is currently unclear whether these controversial functions of virus infection-induced EVs can in part be explained by different purity or subpopulations of EVs. Therefore, further studies are necessary to establish certain parameters to determine the net effects of EVs on viral infections. In particular, in the case of retrovirus HIV-1, there are many studies showing an interaction between EVs and viral infection. Here, we provide a summary of the potential roles of EVs in HIV-1 infection, as well as an overview of the potential applications of EV therapy.

CONTENT

The biogenesis of extracellular vesicles (EVs)

EVs are naturally released from most nucleated cells, and the formation of EVs is evolutionarily conserved (1). EVs can be broadly classified into microvesicles or exosomes. Microvesicles were initially observed as subcellular material released by platelets, and were later discovered to be plasma membrane-derived vesicles secreted by activated neutrophils (12). Even though the role of microvesicles have been mainly studied in blood coagulation (13, 14), they were reported as oncosomes that have a role in cellular communication in cancer cells.

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Microvesicles typically range in size from 50 nm to 1 μm, however, in the case of oncosomes, their size can reach up to 10 μm, as reported in a previous study (15). They are primarily generated by budding from the plasma membrane, and the subsequent release of vesicles into the extracellular space (16).

Exosomes were first identified as vesicles of unknown origin that were released by different types of cultured cells. They are intraluminal vesicles (ILVs) ranging 30 to 150 nm formed through a process of inward budding within the endosomal membrane during the maturation of multivesicular bodies (MVB). Upon fusion of the MVB with the plasma membrane, exosomes are released into the extracellular environment (17).

Mechanistic details of the biogenesis of EVs have recently been revealed (Fig. 1). The contents of EVs are directed to the site of their origin either at the plasma membrane (in the case of microvesicles) or at the membrane of MVBs (in the case of exosomes). The enrichment of these cargoes within the vesicles is facilitated through the promotion of MVB and ILV generation (18, 19). Subsequently, SNARE proteins and Rab GTPases, such as Rab7 and Rab27, are recruited to fuse with the plasma membrane for the release of EVs (20, 21). The MVB may fuse with a lysosome instead of the plasma membrane, leading to the degradation of ILVs. The mechanism that determines the fate of MVB fusion has not been fully revealed yet.

While the processes involved in the generation of microvesicles are not yet fully elucidated, in the case of exosomes, the generation of MVBs and ILVs relies on the sequential involvement of the endosomal sorting complex required for transport (ESCRT) machinery. ESCRT-0 binds to the endosomal membrane, leading to the eventual recruitment cascade of ESCRT-I, ESCRT-II, and ESCRT-III (11). Although the ESCRT machinery is essential for clustering of cargoes and membrane budding in many cases, some mechanisms can operate independently of the ESCRT system. One such example is the generation of ceramide by neutral type II sphingomyelinase, which can hydrolyze sphingomyelin to ceramide, leading to the formation of membrane subdomains that promote negative curvature on the membranes and subsequent budding (22). Hence, the biogenesis of exosomes appears to involve the operation of both ESCRT-dependent and ESCRT-independent machineries. The relative contribution of each mechanism may differ depending on the type of cell and the nature of exosomal cargoes. These findings suggest that the process of exosome biogenesis is inherently intricate, and can be influenced by various cellular signals and pathological stimuli that are received by the exosome-producing cell. For example, viral infection influences the generation of exosomes by modulating exosomal cargoes.

The role of EVs during HIV-1 infection

Human immunodeficiency virus 1 (HIV-1): Despite advances in treatment and prevention, HIV-1 remains a significant public health concern globally, having claimed over 36 million lives as of 2021. As of now, an estimated 37 million individuals are living with HIV-1, with 1.5 million new cases reported in 2020 alone. HIV-1 infects immune cells and causes a depletion of helper $CD4^+$ T cells that are critical for effective adaptive immune responses, ultimately almost invariably leading to AIDS in the absence of treatment (23). Combined antiretroviral therapy (cART) prevents viral replication, reducing the risk of transmission, and preventing or delaying disease progression (23, 24). However, cART does not cure the infection; upon treatment interruption, the virus usually rebounds within weeks. Further-

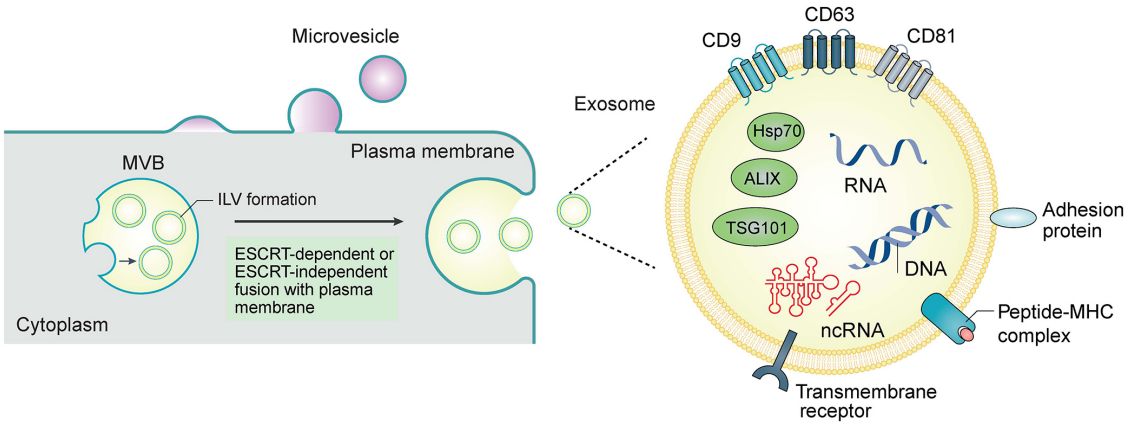

Fig. 1. The biogenesis of Extracellular Vesicles (EVs). Extracellular vesicles are membrane vesicles from various origins. Recently, EVs are classified into two distinct groups-exosomes and microvesicles. Microvesicles are formed by budding of plasma membrane and exosomes are generated from intraluminal vesicles within the lumen of multivesicular body (MVB) that are sequentially fused with the plasma membrane. Several proteins are implicated in exosome biogenesis such as Rab GTPases, ESCRT proteins, and other proteins that are also used as markers for exosomes (e.g. tetraspanins, TSG101, Alix). Exosomes include tetraspanins (e.g. CD63, CD81, CD9), MHC complex, transmembrane receptor, and adhesion proteins in their surface. It has been reported that exosomes contain different types of intracellular proteins, DNA, and RNA including non-coding RNAs (ncRNA).

more, HIV-1 evolves rapidly, and may develop resistance (25). Although HIV-1 infection triggers innate and adaptive immune responses, the virus can replicate continuously and efficiently in the infected host, causing chronic inflammatory responses, and accelerating aging processes. Notably, accumulating evidence has shown the interplay between HIV-1 infection and EVs. The potential roles of EVs during HIV-1 infection are covered here.

Antiviral effects of EVs: EVs have the ability to transport host-derived restriction factors to nearby cells, thereby triggering antiviral responses. In a recent study, it was demonstrated that EVs derived from CD4 T cells contain the cellular cytidine deaminase APOBEC3G (A3G) (26). A3G is a cytidine deaminase produced by cells, which functions as an inhibitor of HIV-1 replication by impeding the process of reverse transcription in HIV-1 (27). Thus, A3G-containing EVs help to restrict HIV-1 replication in recipient cells. However, the physiological significance of A3G-EV on HIV-1 restriction is limited due to the minimal binding of A3G to extracellular vesicles (EVs), resulting in negligible suppression of HIV-1 *in vivo* (28). Exosomes with CD4 on the surface can be released from CD4 T cells. The CD4-containing EVs potentially lead to the restriction of HIV-1 by acting as a decoy for CD4 T cells and neutralizing HIV-1 virions, thereby inhibiting HIV-1 spread (29). The EVs released by CD8 T cells carry proteins that have anti-HIV properties, which can inhibit the replication of HIV-1 (30). In addition, it has been reported that EVs trigger innate immunity to restrict HIV-1. When Toll-like receptor 3 (TLR-3) is activated in human brain microvascular endothelial cells (HBMEC), they release EVs that carry antiviral factors and interferon-stimulated genes (ISGs) which can prevent HIV-1 infection in the central nervous system (31). In line with this, intestinal epithelial cells that have been activated by TLR-3 can release EVs containing miRNAs that inhibit HIV-1 infection. These EVs are able to protect CD4 T cells and macrophages in the gastrointestinal system from becoming infected by HIV-1 (32). Moreover, EVs obtained from breast milk have the ability to attach to DC-SIGN receptors, which prevents the binding of HIV-1 to dendritic cells generated from monocytes and restricts the viral transmission to CD4 T cells (33). EVs originating from uninfected semen or vaginal fluid can impede the sexual transmission of HIV-1 by regulating the process of reverse transcription of the virus (34). Thus, EVs contribute to restrict HIV-1 transmission and replication by delivering various antiviral factors.

Proviral effects of EVs: Recent studies have demonstrated that EVs can also contribute to the exacerbation of HIV-1 infection and the progression of the disease. PBMCs release CCR5-containing EVs to transfer CCR5 to neighboring cells, enhancing

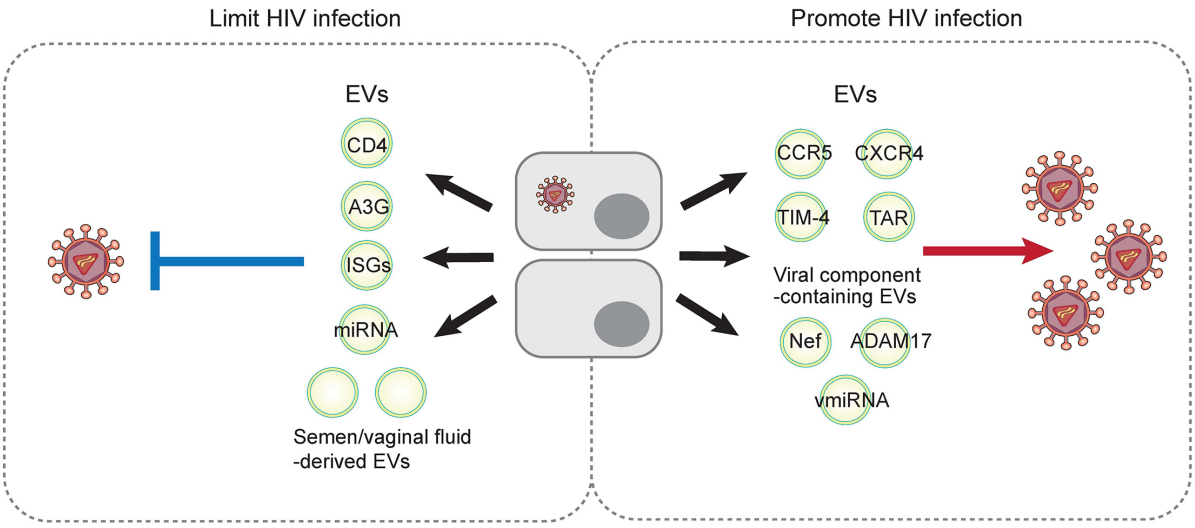

Fig. 2. The dual roles of EVs during HIV-1 infection. The EVs released upon HIV-1 infection have shown to have antiviral and proviral functions. EVs contribute to suppress HIV infection by limiting viral replication or enhancing antiviral immunity. CD4-containing EV may serve as a decoy for CD4 T cells and neutralize HIV-1 virions. Exosomal cargo such as APOBEC3G (A3G) inhibit HIV-1 replication. EVs can transport ISGs such as ISG15, ISG56, and MX2 trigger antiviral immunity and EVs derived from bodily fluids such as breast milk, semen, and vaginal fluids can hider HIV-1 infection. However, EVs also can promote HIV-1 infection and pathogenesis. Co-receptors such as CCR5 or CXCR4 can be delivered to neighboring cells via EVs, enhancing susceptibility to HIV-1 infection. TIM-4-containing EVs assit trafficking of HIV-1 to immune cells. EVs can carry TAR element RNA to enhance susceptibility to HIV-1 infection in undifferentiated immune cells. Transport viral component by EVs may enhance viral entry and infectivity. EV-mediated transport of HIV-1 Nef protein may lead viral-mediated apoptosis of immune cells. Well-known TNFα converting enzyme ADAM17 can be loaded into EVs. These EVs can contribute to chronic inflammation by secretion of mature TNFα. Host-derived miRNAs or viral miRNAs can be transported by EVs, resulting in enhancement of HIV-1 infection and chronic immune activation, leading to HIV-1 pathogenesis.

susceptibility to HIV-1 infection (35). Similarly, EVs derived from megakaryocytes containing CXCR4 deliver this co-receptor of HIV-1 to CXCR4-lacking nearby tissues, facilitating viral spread (36). Furthermore, recent research has suggested that EVs may contribute to the progression of HIV-1 infection and disease. One mechanism is through the presence of T-cell immunoglobulin and mucin domain-containing 4 (TIM-4) in EVs, which can facilitate the entry of HIV-1 into host cells. When HIV-1 binds to TIM-4 on EVs, it can increase the trafficking of HIV-1 to immune cells, leading to increased infection and potential disease progression (37). Additionally, HIV-1-infected cells release transactivating response (TAR) element RNA-abundant EVs, enhancing naïve cell susceptibility to HIV-1 (38). However, the EV-mediated effects on the spread of HIV-1 are yet unknown as to whether such a phenomenon plays an important role *in vivo*.

EVs can facilitate HIV-1 infection by transferring viral components to surrounding cells, thereby amplifying viral replication. HIV-1-infected EVs have been shown to contain the gp120 envelope protein, which enhances viral infectivity in lymphoid tissues. Additionally, EVs can act as carriers for the transfer of HIV-1 particles to uninfected cells, thereby promoting viral spread (39). EVs containing Nef, a viral accessory protein, can be released from HIV-1 infected cells and have been found in high levels in the blood plasma of individuals with HIV-1 (40, 41). Nef-EVs have the potential to cause a decline in CD4 T cells, promote apoptosis through CXCR4, and increase the vulnerability of CD4 T cells to HIV-1 (42, 43). Active ADAM17-containing EVs are released from HIV-1-infected cells, contributing to chronic inflammation by the secretion of mature TNFα via protease activity (41, 44, 45). The cargoes of EVs that facilitate HIV-1 infection are not limited to viral proteins. Recent studies have reported that host-derived miRNAs or viral miRNAs are uploaded into EVs, resulting in the enhancement of HIV-1 infection. HIV-1-infected macrophages release miRNA-containing EVs to suppress host RNA interference (46). Furthermore, it has been shown that these EVs contain HIV-1 miRNAs, such as vmiRNA88 and vmiRNA99, supporting chronic immune activation by promoting the release of TNFα from macrophage via TLR8 activation (47). Taken together, EVs have pro-viral roles to increase HIV-1 infectivity and pathogenesis.

Collectively, EVs formed during HIV-1 infection participate in the interplay between virus and host. EVs may play an either pro or counter viral role in various ways (Fig. 2). It is still unclear whether the diverse functions of HIV-1-induced EVs may be partially explained by differences of EVs purity and/or subpopulations of EVs or cellular origin. Therefore, further studies on the fundamental regulatory mechanisms of EVs during HIV-1 infection, as well as technical advances on EVs separation, are necessary.

Therapeutic potential of EVs

The studies on EVs in disease are still emerging, and the utility of EVs have been suggested in the diagnosis and treatment of various pathologies. The altered content of EVs in pathological condition leads to the great potential of EVs as a diagnostic window (48). EVs are detected in all biological fluids, and the composition of the complex cargoes of EV is accessible by liquid biopsies (49). Thus, EVs are attractive as a minimally invasive disease detector and/or monitoring tool. The EV can pass cellular barriers without immunogenic reactions, and the contents of EVs can be manipulated, leading to their unique potential for therapeutic applications (50-52). They have the potential to act as vehicles for the transport of a range of substances, including pharmaceuticals, proteins, enzymes, and antibodies (53, 54). Furthermore, EVs can transport both hydrophobic and hydrophilic molecules by embedding within the lipid membrane, and storing in the interior, respectively. The EV can be engineered to deliver short RNAs, such miRNA or siRNA, to suppress gene expression in recipient cells (52, 55). In contrast to liposomes, EVs efficiently enter other cells, and transfer functional cargoes with minimal immune clearance *in vivo* (56, 57). However, most animal models and preclinical studies for the diagnostic and therapeutic potential of EVs are extensively focused on cancers or neurological disease. The potential of EVs for clinical applications to viral diseases remain to be determined. Furthermore, the fundamental targeting/uptake mechanisms of EVs need to be revealed to improve the precise delivery of EVs to specific target cell for antiviral therapeutic approaches.

CONCLUDING REMARKS

EVs have critical roles in viral infection and pathology. In the case of HIV-1, numerous studies have highlighted the pivotal roles of EVs in viral infection. EVs released from HIV-1 infected cells may play a significant role in facilitating the transmission of HIV-1 perpetuating inflammation by transferring viral components. On the other hand, EV derived from uninfected various cell types including endothelial cells, CD4 T cells, and CD8 T cells can contribute to the restriction of HIV-1 infection.

Much technological and experimental progress has been made in recent years to yield valuable information regarding the role(s) of EV, as well as its diagnostic and therapeutic potential (1, 3, 17). However, further investigations are needed to completely understand the functional abilities of these tiny sacs. For example, new technological attempts are needed to separate EVs and virions efficiently, to study the respective functions of EVs. In the case of retroviruses, including HIV-1, this separation is more difficult, because both EVs and retroviruses are comparable in size and buoyant density (58). Novel approaches, such as an EV specific antigen-mediated immunoaffinity method, may facilitate the discrimination of EVs and virus particles. High-throughput methods to analyze nanosize particles, such as flow cytometry-based techniques, have already opened up the possibility of identifying and characterizing EVs (59).

A growing body of evidence indicates that particular cellular and/or viral component-containing EV are released upon viral

infections (60). Therefore, EVs hold great potential for therapeutics intervention aimed at combating viral infectious diseases. For example, the utilization of EVs as carriers for the targeted delivery of specific compounds has emerged. Achieving precise targeting of EVs to recipient cells will be crucial for their use as high-precision vehicles. Thus, future research needs to be performed to unravel the detailed regulatory mechanisms of EVs. Despite the great clinical potential, the field of EVs still requires novel *in vivo* models integrated with advanced imaging techniques to comprehensively monitor the release, trafficking routes and ultimate destinations of EVs within the complex organism. Unraveling the fundamental roles and mechanisms of EVs may lead to better assessment of the risk of future viral infections, and be translated into novel therapeutic strategies for infectious diseases.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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