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Chapter 4

Exosomes and Their Role in Viral Infections

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Abstract

Exosomes are excretory nano-vesicles that are formed by the cell’s endocytic system and shed from the surface of almost all types of cells. These tiny extracellular vesicles, once thought to be “garbage bags for cells,” carry a wide variety of molecules of cellular origin, including proteins, lipids, and RNAs, that are selectively incorporated during the formation of exosomes. Exosomes are now known to play a central role in several important biological processes such as cellular communication, intercellular transfer of bioactive molecules, and immune modulation. Recent advances in the field have shown that a number of animal viruses can exploit the exosomal pathway by incorporating specific cellular or viral factors within exosomes, in order to modulate the cellular microenvironment and influence downstream processes such as host immunity and virus spread. In this chapter, we provide an overview of our current understanding of exosome biogenesis and how this normal physiological process is hijacked by some pathogenic viruses. Viral components that appear to be selectively incorporated into exosomes and the potential role of these exosomes in viral pathogenesis are discussed. Identifying viral signatures in exosomes and their mode of action is fundamental for any future diagnostic and therapeutic strategies for viral infections.

Keywords: exosomes, viruses, immune modulation, pathogenesis, biomarkers

1. Introduction

Exosomes are nano-secretory vesicles ranging in size from 30 to 100 nm and having a density between 1.13 and 1.19 g/ml [1]. Exosomes are derived from the cell’s endosomal pathway, and their membranes are rich in lipids such as sphingolipids, ceramide, and cholesterol [2]. These tiny vesicles are released by virtually all cell types, but at varying degree, upon fusion of multivesicular bodies (MVBs) with the plasma membrane [3–5]. It is now well established that
Exosomes are not the cell’s trash bags, as initially thought, but rather they serve as important nano-vehicles for the transport of specific cargo in and out of the cells [6]. Depending on their cargo, exosomes can mediate certain intercellular communication processes [7, 8]. Although the mechanism of how this cargo is selected for packaging into these vesicles destined for excretion remains poorly understood, it is believed that the endosomal membranes play a central role in this process [9, 10].

A number of molecular mechanisms are involved in the formation of intraluminal vesicles (ILVs) and multivesicular bodies (MVBs) in a cell. One of the best studied and well-characterized group of proteins involved in this process belong to the ESCRT (endosomal sorting complex required for transport) family of proteins [11–13]. These proteins are believed to play a role in the inward budding and scission of ILVs. One of the mechanism by which viruses hijack the exosome pathway is by directly interfering with the machinery involved in exosome biogenesis, such as the ESCRT proteins [14]. Others such as the oligomerization of the tetraspanin complexes [15], the sphingomyelinase pathways [16], phospholipase D2, and ADP ribosylation factor-6–mediated pathways have also been reported to be involved in the ILV budding process [17]. Another family of proteins that are essential for vesicular formation, trafficking, and fusion in eukaryotic cells belongs to a large family of highly conserved proteins known as Rab GTPases [18]. A number of Rab proteins such as Rab5 and Rab7 have been shown to be important in endosome maturation and sorting of material in the ILVs [19, 20]. Rab27 a/b are involved in the fusion of the ILVs with the plasma membrane and release of exosomes [50]. A number of other Rab GTPases are also found to play an instrumental role in exosome release. Depending on the cell type, Rab5, Rab7, Rab11, Rab27, and Rab35 have all been implicated in the release of vesicles. Altering the levels of any of these Rabs may lead to interference with progression of exosomal cargo at specific endocytic locations [20]. The fact that the exosomal pathway has some similarities with certain phases of viral life cycle has led to the observations that a number of viruses can indeed hijack the exosome pathway during their replication and pathogenesis [21, 22].

2. Viruses and the exosomal pathway

The endocytic pathway and the budding of viruses, especially enveloped viruses, share many common features. Both processes require generation of membrane curving, packaging of specific cargo, and membrane budding for release from the cell [22]. What is most surprising is that different viruses with very different evolutionary paths appear to converge in their use of the host endocytic pathway in the entry and exit from their host cells [23]. The receptor or clathrin-mediated endocytosis to enter the cell is found to be utilized by a number of viruses of the Flaviviridae family, which includes medically important pathogens such as hepatitis C (HCV), West Nile (WNV), Dengue, and Zika viruses [24–27]. These viruses can enter the late endosomes and then fuse with the ILVs within the endosome compartments [28]. Recently, it was shown that HCV can incorporate its full-length RNA genome into the ILVs and be excreted out via exosomes, and retain infectivity [29, 30]. Since HCV is fairly small, it is possible that HCV infectious particles could be released directly within exosomes and account for infection. However, the observation that exosomes isolated from...
HCV sub-genomic replicon cell lines lacking HCV structural proteins remained infectious argues against the notion that mature viral particles are released in exosomes [30]. Currently, HCV and hepatitis A virus (HAV) are the only viruses that have been shown to incorporate their full-length genomic RNA within exosomes [31]. Another virus that can utilize the endosomal/exosomal system to deliver viral cargo to uninfected cells is the human immunodeficiency virus (HIV-1). Based on the similarities between HIV-1 assembly and egress, and exosome biogenesis, Gould et al. proposed the “Trojan exosome hypothesis,” in which they suggested that HIV has evolved to exploit the exosome system to infect cells in the absence of the receptor-mediated interaction [32, 33]. This hypothesis is supported by the observation that HIV virions are released together with exosomes, but the infectivity is reduced in the absence of exosomes, implying that the process of exosome release from HIV-infected cells probably also contributes to the release of HIV virions. This mechanism was demonstrated using HIV-infected dendritic cells, which were able to transfer the virus to closely associated uninfected T cells via exosomes [34, 35]. Unlike HCV, direct packaging of HIV genomic RNA into exosomes has not been observed, probably reflecting the findings that HIV predominately buds from the plasma membrane and not from the endosomal pathway [36–38].

2.1. Viruses hijack the ESCRT and Rab GTPases involved in exosome biogenesis

Viruses are obligate intracellular parasites that hijack cellular pathways to complete their life cycle. In recent years, an accumulating body of data has emerged suggesting that some viruses can also manipulate with the vesicular trafficking machinery for their assembly, egress, and transmission [39, 40]. For example, HIV has been shown to exploit the ESCRT, lipid raft domains, and Rab GTPases components, all of which are involved in exosome biogenesis [23, 41, 42]. Specifically, HIV Gag has been shown to interact with exosomal tetraspanins, especially CD63 and CD81, to aid in virion egress [42]. Using electron microscopy, human herpesvirus 6 (HHV-6) virions have been shown to be present in MVBs and egress together with exosomes through the same pathway [43]. HHV-6 infection dramatically increases MVB formation, suggesting that the endosomal pathway is likely to be important for HHV-6 infection and assembly [43]. Furthermore, HHV-6 glycoprotein gB was found to co-localize with CD63 [43], but the importance of this association for virus egress remains to be demonstrated. Besides interfering with the ESCRT pathway, some viruses can also utilize the Rab GTPase complexes to assist in their replication and egress processes. Several negative strand RNA viruses, such as influenza A virus (IAV), hantavirus, and respiratory syncytial virus (RSV), have all been reported to utilize the Rab pathway for their transport to the plasma membrane for exit [44–47]. It is known that interfering with Rab11 levels can inhibit or promote the release of exosome-containing contents such as transferrin, HSP-70, flotillin, and anthrax toxin [44, 48, 49]. In the case of hantavirus-infected cells, depletion of Rab11 results in a tenfold reduction in virion production [46]. Similarly, IAV and RSV also appear to hijack the Rab11 pathway to their benefit [45, 47]. Rab27a, another member of the Rab GTPase family, has also been shown to be essential for exosome biogenesis, particularly in the steps involving the fusion of MVBs with plasma membrane for the final release of exosomes [50, 51]. For example, in cytomegalovirus (CMV)-infected cells, the levels of Rab27a are increased and co-localized with the viral envelope components at assembly sites in the cytoplasm [52], but the molecular mechanisms and ultimate changes to exosome production remain to be
elucidated. HIV proteins are also found to interact with Rab27a resulting in increased levels of exosome formation [41, 53]. Herpes simplex virus 1 (HSV-1) is another virus that appears to use Rab27a for its intracellular transport and exocytosis [54, 55]. Depletion or down-regulation of Rab27a leads to decrease in HSV-1 viral production [54, 55].

The regulatory functions of the Rab GTPase mentioned above are still not fully understood. However, it is widely accepted that cells react to stimuli to adjust the distribution and levels of intracellular proteins as well as their degradation, secretion, and recycling [56]. Manipulation of specific steps in the endocytic pathway by viruses highlights the need for further research to unravel the complex interplay between regulators of the endocytic process and exosome release. Such studies may shed light to potential targets for anti-virals.

### 2.2. Viral signatures in exosomes

The discovery that certain features in the life cycle of viruses and the cellular endosomal/exosomal pathway are common, and that some viruses can exploit the exosomal pathway to their benefit, triggered a search to identify viral signatures in exosomes. This line of research has obvious downstream benefits, not only in terms of viral diagnosis, but also for understanding the mechanisms of viral-mediated pathogenesis. We now have a growing list of viral-specific components that have been identified in exosomes (Table 1). Moreover, functional analysis of excreted exosomes carrying viral components is beginning to shed light on how some viruses can modulate cellular processes as diverse as immune evasion, apoptosis, proliferation, and even viral infectivity (Table 1). In this context, one family of viruses that has been widely studied is the human herpesviruses. This family of viruses contains two members, namely Epstein-Barr virus (EBV) and Kaposi’s sarcoma virus (KSV), that are oncogenic and implicated in the pathogenesis of a number of human malignancies [57]. Both of these viruses have now been shown to exploit the exosome pathway to secrete various components ranging from proteins to various species of RNAs, including messenger RNAs (mRNA), microRNAs (miRNA), and small non-protein coding RNAs [58–61]. In fact, viral miRNAs (vmiRNA) were first identified in EBV-infected cells [62] and subsequently shown to be excreted out of cells via exosomes [63]. It is now known that exosomes shed from EBV-infected cells contain a large number of viral miRNAs, most of which appear to be smaller products of larger BamH1 EBV transcripts [64, 65]. It is believed that these viral miRNAs, together with cellular miRNAs, play a role in modulating the expression of target genes in recipient cells (Figure 1) [59, 65–67]. Recently, it was shown that the two non-protein coding EBV small RNAs, EBER-1 and EBER-2, are also consistently excreted from infected cells within exosomes [68]. EBERs are highly abundant EBV RNA polymerase II/III transcripts expressed in all EBV latently infected cells. The significance of their high abundance within infected cells, or the reasons for their release in exosomes, remains intriguing. One study showed that EBERs released from infected cells could induce innate immune responses via activation of Toll-like receptor 3-mediated signaling [69]. In addition to RNAs, a number of studies have shown that EBV-infected cells can also excrete viral-specific proteins, including the latent membrane protein 1 and 2A (LMP-1, LMP-2A) and the viral envelop glycoprotein 350 (gp350) [70–73]. Export of these proteins via exosomes indicates another dimension to how EBV can modulate cellular processes, not only within the cells it infects, but also in the surrounding cells.
Another virus which has attracted considerable attention is HIV. There are over 38 million people living with HIV, and there is still no cure [74]. Analysis of exosomes released from HIV-1-infected and non-infected cells shows that they differ in their densities [75]. This implies that the contents of the exosomes from infected and non-infected cells are clearly different [60, 61]. Although retroviruses are much smaller than herpesviruses, they are nevertheless

<table>
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Viral-infected cells have been shown to shed exosomes containing cellular and viral-specific components. Table lists viral components that have been detected in exosomes. These include viral mRNAs, microRNAs (vmiRNA), non-protein coding RNAs (vRNA), full-length genomic RNA (gRNA), as well as virus-specific proteins. Depending on the exosomal cargo and type of recipient cells, different biological changes may be induced. **Abbreviations:** EBV, Epstein-Barr virus; HSV, herpes simplex virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; HPV, human papillomavirus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RVFV, Rift Valley fever virus.

Table 1. Exosomes, their viral cargo, and their potential role in virus-mediated pathogenesis.
still slightly larger than exosomes and as such it is unlikely that mature infectious HIV-1 particles could be packaged and excreted within exosomes. However, there is mounting evidence that HIV-1 egress is partly mediated by the endosomal pathway, and both exosomes and HIV-1 are released together in the same fraction [76]. HIV-1 Gag protein has been shown to interact with the exosomal membrane tetraspanins, CD63 and CD81, aiding in the assembly and exit of HIV-1 from infected cells [77–80]. Moreover, several functionally active HIV-1 components have also been shown to be excreted out of infected cells using the exosomal “bus” (Figure 1). Once released, exosomes can bind to neighboring cells, travel passively through the blood stream to distant sites, and induce biological changes depending on the nature of the cargo they carry (Figure 1) [42]. Nef is one HIV-1 protein that has been shown to be released within exosomes [81]. Studies indicate that Nef plays an important role in activating resting bystander CD4+ T cells making them susceptible to HIV
infection and viral replication [81–83]. Reports have indicated that HIV-1 may also facilitate its spread to other cells by secreting viral co-receptors, CCR5 and CXCR4, in exosomes [84, 85]. In addition to functional proteins, exosomes from HIV-1-infected cells have been shown to carry several viral miRNAs, including vmiRTAR transcripts, vmiR88 and vmiR99 [23]. Similarly, another human retrovirus, the human T-lymphotropic virus 1 (HTLV-1), also appears to export viral components via the exosomal transport systems. Exosomes released from HTLV-1-infected cells contain not only viral mRNA transcripts, such as those for Tax, HBZ, and Env, but also the biologically active trans-activator protein, Tax [86, 87]. Moreover, HTLV-1 Tax protein has been demonstrated in exosomes isolated from cerebrospinal fluid of patients with HTLV-1-associated myelopathy/tropical spastic paraparesis, suggesting that HTLV-1 may modulate its microenvironment by selective secretion of specific viral cargo [88].

The list of components of cellular and microbial origin detected in exosomes is constantly expanding. This has led to the establishment of several online databases to catalogue the contents of exosomes. There is now substantial evidence indicating that many different types of pathogens, including bacteria, viruses, parasites, and even prions, can exploit the exosomal pathway [89, 90]. Of the viruses, members belonging to families as diverse as Bunyaviridae (enveloped RNA viruses) and Papillomaviridae (non-enveloped DNA viruses) have been shown to export their products in exosomes (Table 1). Moreover, studies are beginning to address the functional impact of exosomes carrying viral cargo in the pathogenesis of viral infections. One major challenge is to understand the mechanisms that regulate the selection of cargo to be packaged into exosomes and how we can use exosomes as biomarkers for viral infections and disease progression [89, 91].

### 3. Role of exosomes in viral pathogenesis

Exosomes released by viral-infected cells contain not only viral components, but also those of cellular origin [23, 67, 89]. It appears that viruses are able not only to export their own products in exosomes, but also to somehow influence which cellular products are packaged within the excretory vesicles. This is evident by the findings that exosomal cargo of cellular origin is clearly different from non-infected cells of the same type [60, 61, 92]. Thus, any pathophysiological impact of viral exosomes on recipient cells is by no means due to viral components only. An accumulating body of data indicates that exosomes from viral-infected cells can induce processes as diverse as immune evasion, apoptosis, proliferation, transcellular spread, and cytokine modulation (Table 1). The molecular details of how these processes are triggered are poorly understood and most probably dependent on multiple factors, including the type of cells releasing/receiving exosomes, nature of the exosomal cargo, mode of delivery, and stage of infection [1, 90]. This probably explains why apparently contradicting results have been reported in different studies [93, 94]. For EBV, it has been shown that uninfected epithelial cells exposed to exosomes derived from infected B cells are internalized via caveolar-dependent endocytosis and induce physiological changes in these cells [95]. Studies reported that exosomes derived from nasopharyngeal carcinoma (NPC) and from EBV-immortalized lymphoblastoid cell lines (LCLs) either inhibit
proliferation of EBV-reactive CD4+ cells or induce apoptosis [70, 93, 96]. Similar results were observed with exosomes isolated from EBV-associated NPC patients and mice xenografted with NPC [97]. These pathophysiological changes were suggested to be due to viral and cellular components such as LMP-1, LMP-2A, viral miRNAs, and cellular galectin 9, excreted in exosomes from EBV-infected cells [72, 93, 97, 98]. The finding of EBV LMP-1 in exosomes is noteworthy [70, 93]. This is a well-known oncoprotein that plays a key role in the immortalization of EBV-infected cells [99]. Not surprisingly, LMP-1 has been extensively studied and shown to function as a constitutively activated receptor, signaling through the TRAF pathway leading to the activation of the master transcription factor, NFκB [100, 101]. LMP-2A is also an EBV latent protein expressed on the plasma membrane of latently infected cells [102]. Like LMP-1, LMP-2A also appears to be a constitutively activated receptor; while LMP-1 mimics CD40 receptor, LMP-2A mimics activated B-cell receptor (BCR), allowing infected cells to develop and survive, even in the absence of BCR signaling [103, 104]. Although it is not known how these membrane proteins are selected for export in exosomes, or what their functional impact is on recipient cells, it is tempting to postulate that the cell survival signals provided by LMP-2A and cell proliferation signals provided by LMP-1, if transferable to recipient cells, would be important in EBV pathogenesis.

Recently, we reported that exosomes from both EBV-infected and non-infected B cells are taken up by recipient cells, but only the exosomes from EBV-infected cells induced apoptosis in recipient cells in a dose-dependent manner [92]. We further showed that apoptosis was induced via the activation of the extrinsic pathway involving Fas-ligand (Fas-L) present in EBV exosomes. Moreover, the process could be blocked by using anti-Fas-L antibodies [92]. Another study reported that LCL-derived exosomes contain Fas-L and MHCII molecules and induce apoptosis in autologous CD4+ T cells [96]. Taken together, these studies indicate that one mechanism by which EBV could evade the body’s immune system may be by shedding exosomes containing signals that inhibit proliferation and/or promote apoptosis of anti-EBV-infiltrating lymphocytes. The fact that similar effects on bystander cells, albeit through different mechanisms, have also been reported for exosomes released from rotavirus and HIV-1–infected cells [105, 106] supports this hypothesis.

Another well-known mechanism by which some viruses can evade the immune responses is by down-regulating the expression of viral lytic genes and persisting in the infected cells in a latent state [107]. It’s a simple strategy; no viral antigens expressed in infected cells means no immune system can be triggered [108]. In this context, herpesviruses are among the most extensively studied [109, 110]. For example, herpes simplex type 1 (HSV-1) replicates in mucosal epithelial cells during primary infection and then enters sensory neurons where it establishes life-long latency [111]. During the latent state, although no viral proteins are expressed, numerous vmiRNAs have been detected, and some of these vmiRNAs appear to be central in suppressing viral gene expression and maintaining latency [112–114]. The complexity of this process has been further exposed by recent findings indicating that HSV-1 can excrete vmiRNAs in exosomes, which on transfer to recipient cells, can suppress viral gene expression and viral spread to uninfected cells [115]. Furthermore, HSV-1 can also transfer antiviral factors, such as STING (stimulator of IFN genes), to suppress its cell-to-cell spread in circumstances that may be unfavorable [116]. Thus, inhibiting viral replication and spread in the face of a competent immune threat could be an important strategy for viruses to escape immune elimination and persist.
In some viral infections, such as with hepatitis B (HBV), non-infectious subviral particles are released into the serum, often at levels 1000s of fold higher compared to mature infectious particles [117, 118]. In evolutionary terms, it does not make sense why a virus would opt to shed enormous amounts of non-infectious subviral particles if it was not beneficial for the virus. One plausible hypothesis is that such subviral particles act as a decoy to divert the immune responses away from the bonafide infectious virions [118, 119]. HSV-1-infected cells can also release subviral particles, referred to as the L-particles. These particles have neither viral capsid nor viral DNA, and they are not infectious, but they do contain several HSV proteins [120, 121]. Recent studies suggest that the transfer of L particles to bystander cells can modulate the microenvironment to facilitate immune evasion and viral infection [122]. Similarly, there is evidence that some viruses can manipulate their microenvironment by secreting exosomes containing cargo that interferes with the host inflammatory and antiviral factors [119, 123].

In addition to immune modulation, exosomes released from some viral-infected cells can promote infection and enhance viral spread. A good example of this is HIV-1. Exosome-mediated transfer of HIV-1 co-receptors CCR5 and CXCR4 to recipient cells that do not normally express these receptors can facilitate HIV-1 infection in these cells [84, 85]. In the case of hepatitis C virus, it has been reported that infected cells release exosomes containing full-length viral genomic RNA as well as viral-specific proteins [29, 30, 124]. Importantly, HCV RNA carrying exosomes could transmit the infection to non-infected cells and establish a productive infection [29, 30, 124]. This receptor-independent mechanism of HCV transmission would prevent the virus from being exposed to antibodies that would normally be effective in neutralizing cell-free virus [125, 126]. Some viruses can also manipulate with the endocytic pathway, not for export of their cargo, but for virion assembly and egress from the infected cells during replication. For example, HSV-1 can interact with Rab27a via its tegument protein and its glycoproteins gH and gD [55]. Depletion of Rab27a results in significant reduction in both viral production and viral egress, highlighting the importance of the Rab27a in the egress of HSV-1 [55]. A similar phenomenon has been reported for several other members of the herpesviridae family, including cytomegalovirus (CMV) and human herpesvirus 6 (HHV-6) [23].

Although we have focused on how viruses exploit the exosome system to aid their infection and pathogenesis, it should be borne in mind that the shedding of exosomes is a normal physiological process and it also plays a role in defending against infections [90, 127]. For example, a recent study reported that exosomes isolated from semen, but not from blood of healthy individuals, were able to inhibit the replication of HIV-1 in in vitro culture [42]. Remarkably, this anti-viral activity of semen exosomes appeared to be restricted to retroviruses and had no effect on HSV-1 or HSV-2 replication [5]. Ironically, some viruses are able to not only overcome these defense mechanisms but also exploit them to their benefit.

4. Conclusions

Our current understanding of microvesicle biology and function, especially in regard to virus infections, is still in its early stages. The study of viral exosomes has shown that the transfer of viral and cellular factors in exosomes enables the manipulation of the neighboring unaffected
cells. Microvesicle-mediated communication allows the virus to respond and control the cellular microenvironment. A number of reports suggest that viruses utilize the cellular vesiculation pathway for virus budding/assembly, immune evasion, and intercellular communication. Understanding the role of exosomes in the host-viral interactions can open new avenues of understanding the disease mechanisms and future diagnostic and therapeutic interventions.

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