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REVIEW

Extracellular Vesicle-Related Thrombosis in Viral Infection

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Abstract: Although the outcomes of viral infectious diseases are remarkably varied, most infections cause acute diseases after a short period. Novel coronavirus disease 2019, which recently spread worldwide, is no exception. Extracellular vesicles (EVs) are small circulating membrane-enclosed entities shed from the cell surface in response to cell activation or apoptosis. EVs transport various kinds of bioactive molecules between cells, including functional RNAs, such as viral RNAs and proteins. Therefore, when EVs are at high levels, changes in cell activation, inflammation, angioplasty and transportation suggest that EVs are associated with various diseases. Clinical research on EVs includes studies on the coagulatory system. In particular, abnormal enhancement of the coagulatory system through EVs can cause thrombosis. In this review, we address the functions of EVs, thrombosis, and their involvement in viral infection.

Keywords: viral infection, thrombosis, extracellular vesicle, exosome, microvesicle

Introduction

Most viruses are small sized (typically 0.02 to 0.3 μm), unlike large and mega-viruses whose maximum lengths can reach 1 μm in length at the maximum.[1–3] The reproduction of a virus depends on bacterial, plant, and animal cells including those in humans.[4] Viruses are classified according to genomic properties and structures as well as their reproduction method, and not according to the disease that each virus causes.[5] Replication in DNA viruses typically occurs in the nucleus of the host cell, whereas RNA virus replication typically occurs in the cytoplasm.[5,6] There are exceptions, however. For example, H1N1 (an RNA virus) cannot reproduce in the host's cytoplasm, whereas vaccinia (a DNA virus) does not need the nucleus to reproduce. After reproduction of a complete virus particle, the host cell typically perishes and the virus is released to infect other host cells.[4–6] Although the outcomes of viral infectious diseases are remarkably varied, most infections cause acute disease after a short period.[7] Novel coronavirus disease 2019 (COVID-19), which recently spread worldwide, is no exception.[8,9]

Extracellular vesicles (EVs) are small circulating membrane-enclosed entities shed from cell surface in response to cell activation or apoptosis.[10] Although detailed understanding of EVs is lacking, information about EVs has been accumulating.[11–13] EVs measure 0.01−4 μm and are generated by various processes.[11,12] EVs transport various types of molecules between cells, such as viral RNAs and proteins.[14–16] Therefore, when EVs are at high levels, cell activation, inflammation, angioplasty and states involving transportation occur, indicating the association of EVs with

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various diseases.[11,14,17–19] Clinical research of EVs includes studies on the coagulatory system. In particular, abnormal enhancement of the coagulatory system by EVs can cause thrombosis and disseminated intravascular coagulation (DIC). Such an abnormality after a viral infectious disease can become a significant clinical problem. In this review, we address the functions of EVs, thrombosis, and their involvement in viral infection.

Classification of EVs

EVs are classified into three groups by size, namely exosomes, microvesicles (MVs), and apoptotic bodies (ABs) (Table 1).[11] Exosomes are EVs with diameters of 30–200 nm, and these membrane-bound vesicles can be precipitated by ultracentrifugation at 100,000×g.[11,12,15,20] Most exosomes carry specific proteins reflecting the characteristics of the origin cell.[21–23] They form through multi-vesicular bodies (MVBs) that fuse with the cell membrane for release.[15,24,25] Exosomes are released from a cell via a mechanism of endosomal complexes required for transport (Figure 1).[26]

MVs are EVs of 10–1000 nm in size.[11] MVs are also called microparticles (MPs).[10,11,27] The differences between MVs and exosomes other than their size are the processes of formation and secretion.[15,28] MVs are generated by the surface of the cell breaking off, which is controlled by cell activation.[29] The plasma membrane includes several kinds of phospholipids.[11,30] The internal leaflet contains aminophosphatides (eg, phosphatidylserine:PS) for a negative charge.[30] MV biogenesis, which occurs via blebbing, is a fragmentation phenomenon whereby nascent MVs are released into the extracellular space via pinching off from the plasma membrane.[31,32] MVs contain distinct protein and lipid components from the plasma membrane.[32] During cell activation, the charge of the leaflet changes the structure of the normal lipid layer, and PS is exposed to MV (Figure 1).[33] This leads to procoagulant activity in the MVs.[34]

EVs generated by apoptosis are called apoptotic bodies (ABs).[11,35,36] During its final phase of apoptotic death, the cell divides into several Ab,[32] the size of which are 1000–3000 nm.[37,38] Similar to MVs, ABs are formed by PS moving to the cell surface.[33–35] ABs may contain a wide variety of cellular components, such as micronuclei, chromatin remnants, cytosol portions, degraded proteins, DNA fragments, and even intact organelles.[32] The main difference between ABs and MVs is the existence of materials derived from the nucleus such as histones and DNA fragments (Figure 1).[39,40]

Function of EVs

EVs can carry activated coagulation factors, by expressing phosphatides on their surface.[11] Therefore, it is thought that the existence of EVs is related to several diseases, indicating a coagulatory promotion tendency.[11,27] Because EVs promote intravascular coagulation to support thrombin generation, they may be linked with coagulation abnormalities.[27] The procoagulant activity observed on platelet-derived EV surfaces is 50 to 100-fold higher than that observed on activated platelets.[41] This suggests that the coagulatory promotion by EVs is an important defense mechanism for bleeding risk.[11] EVs also carry tissue factor (TF) that is important to activate the coagulation system.[42]

The main characteristics of atherosclerosis are the adhesion of monocytes to the endothelium and movement of monocytes into the subendothelium.[27] When a monocyte is activated by platelet-derived EVs and adheres to the endothelium, several inflammatory cytokines are generated.[43] Furthermore, stimulation or activation of the endothelium by EVs increases the expression of adhesion molecules on the endothelial surface.[43,44] Atherosclerotic lesions can develop and progress in severity via the apoptosis of endothelial cells,

Table 1 Population and Characteristics of EVs

	Exosome	MV (MP)	AB
Size	30–200 nm	100–1000 nm	1000–3000 nm
Shape	Homogeneous	Variable	Variable
Origine	MBV fusion with the plasma membrane	Budding from the plasma membrane	Budding from the plasma membrane
Markers	Tetraspanins (CD9, CD63, CD81) Alix, TSG101, HSP70	Annexin V, Integrin, Selectin, CD40 ligand, metalloproteinase	Annexin V, DNA fragment Caspase 3, Histones
Isolation	Ultracentrifugation (100,000g)	Ultracentrifugation (10,000–100,000g)	Ultracentrifugation (6000–10,000g)
P-Act	Weak	Powerful	Powerful

Notes: Data from Nomura.[11] All vesicles preparations are heterogeneous with different protocols allowing the enrichment of one type over another.
Abbreviations: MV, microvesicle; MP, microparticle; AB, apoptotic body; MBV, multivesicular body; TSG101, tumor susceptibility gene 101; HSP70, heat shock protein 70; P-Act, procoagulant activity.

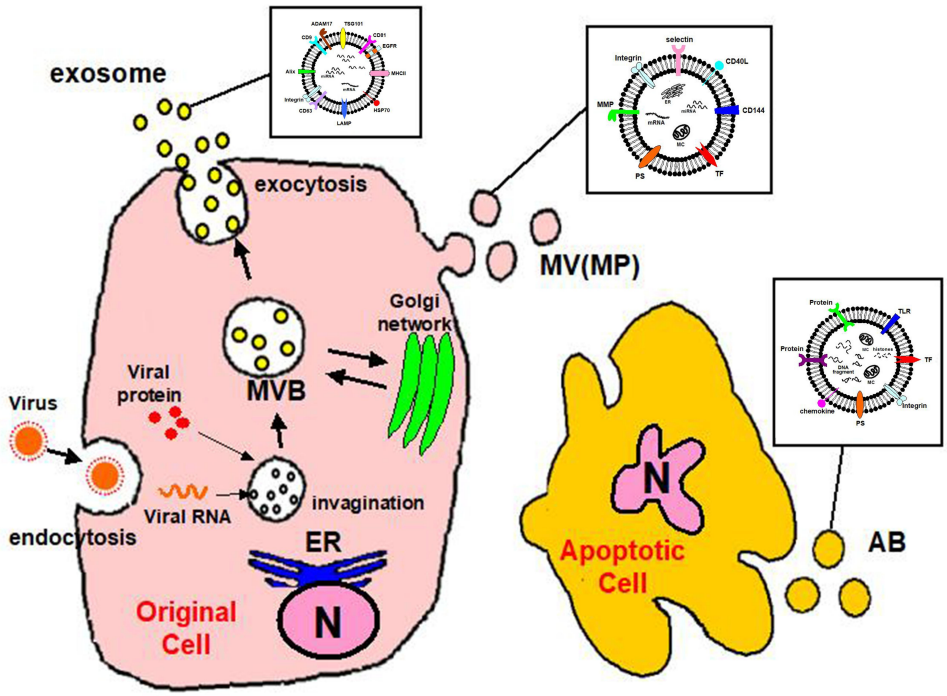

Figure 1 Convergence of EV and virus biogenesis. Original cell owns the endocytic and secretory pathways. Viruses share effectors of EV production for their assembly and release. Exosomes produced in the MVB and shed MV (MP) budding of the plasma membrane. Apoptotic cell finally releases shedding AB.
Abbreviations: MV, microvesicle; MP, microparticle; AB, apoptotic body; N, nucleus; MBV, multivesicular body; ER, endoplasmic reticulum.

a process induced by a substantial number of EV-dependent coagulatory factors.[11,27,45]

EV appear to constitute a new system of cell-cell communication.[16,46,47] EVs have various important functions such as coagulatory promotion, immunosuppression, and angioplasty.[48,49] EVs may be the most suitable mechanism through which cells communicate with others.[15,48] For example, EVs produced by one kind of cell stimulate another specific cell.[50,51] EVs carry tetraspanin protein and may employ a mechanism that can return in a specific organization.[52,53] Another mechanism involves fusion with the cell membrane, which results in the transfer of mRNA, micro(mi)RNA, proteins, and signaling molecules by EVs.[54,55] The existence of miRNAs has been found in EVs released with biological fluid of patients with various viral infectious diseases.[13,56–58] EVs might play a crucial role in dissemination of pathogens as well as host-derived molecules during infection.[58] Therefore, EVs may be strongly involved in progression of the post-viral condition and the origin of complications.[59]

Viral Infection and Thrombosis

Ebola, H1N1 influenza, cytomegalovirus, chickenpox – herpes zoster, hepatitis C virus, human immunodeficiency virus (HIV), coxsackie virus B3, herpes simplex virus-1, dengue, and Junin virus are accompanied by thrombotic complications and bleeding.[60–71] There are at least two major factors underlying the onset of thrombosis that are associated with these viral infections (Figure 2).[72,73] One factor influencing the blood vessel system is the viruses themselves, because they can influence monocytes, neutrophils and the blood vessel endothelium and also induce the expression of TF.[74] Some viruses can also directly influence platelets and enhance PS expression during their infections.[75–77] Plasma from influenza patients may also contain MVs with TF activity.[78] This leads to strong thrombosis onset, by enhancing the activity of the exogenous coagulatory system. The second mechanism influences the immune system. The viral infection influences the immune system, and inflammation with the cell which immunity decreased spreads, and an imbalance between coagulation and anti-coagulation occurs.[79] This mechanism is related to interactions between the virus and Toll-like receptors (TLRs).[70,79]

Ebola Virus (EBOV)

EBOV is a negative-sense RNA virus that causes a severe disease characterized by high fever, diarrhea, and unexpected

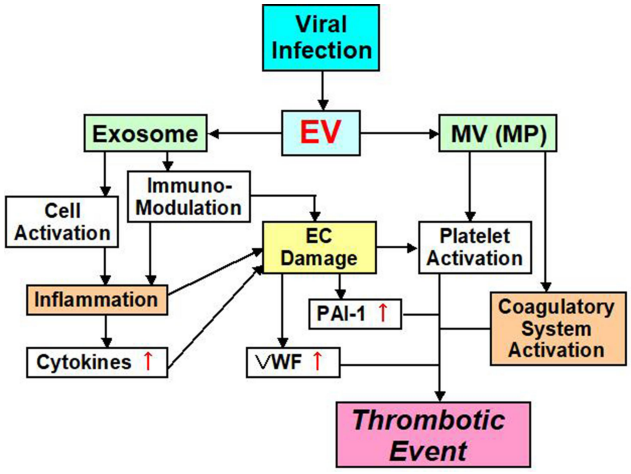

Figure 2 EV mediated thrombotic event pathway.
Abbreviations: EV, extracellular vesicle; MV, microvesicle; MP, microparticle; EC, endothelial cell; PAI-1, plasminogen activator inhibitor-1; VWF, von Willebrand factor.

onset of vomiting.[80] Additionally, this virus causes a serious procoagulatory abnormality with liver damage.[80] EBOV infection induces TF expression in infected cells and serum D-dimer rises, finally causing DIC.[81] EBOV disrupts the functions of dendritic cells coordinating a T cell increase.[82,83] Therefore, it is thought that EBOV infectious disease develops a thrombotic tendency by failure of the immune system and enhancement of coagulation.[70,84]

Influenza A Virus (IAV)

Influenza A virus (IAV) is a negative-sense RNA virus that commonly causes death.[85] Cardiovascular system disorders, such as acute myocardial infarction, deep vein thrombosis, and pulmonary embolism, are observed.[86–90] Disorder of the blood vessel wall barrier by IAV may contribute to the development of pulmonary damage in patients with influenza.[91,92] H5N1-infected chickens show microthrombosis and thrombocytopenia.[93] IAV infectious disease causes a high level of plasma von Willebrand factor (vWF) and a decrease of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13), which may result in clot-related microangiopathy.[94,95] Therefore, IAV infectious disease is thought to cause immunity and aggravation of the wall system, which results in inflammatory induction and coagulatory enhancement.

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a positive-sense single-stranded enveloped RNA virus of the Retroviridae family.[96] One cause of death in HIV-infected patients is cardiovascular disease (CVD), and functional disorder in the blood walls caused by HIV reproduction is a considerable determinant of it.[96–98] Additionally, the immune reaction and inflammation caused by HIV infection may be cardiovascular risks.[99,100] The death rate is strongly related to interleukin (IL)-6, high sensitivity C-reactive protein (hsCRP), and D-dimer. In particular, IL-6 and hsCRP are related to the development of acquired immunodeficiency syndrome.[101,102] Funderburg et al[103,104] reported that TF expression on the surface of monocytes increases in HIV patients. Additionally, Harley et al[105] reported that T-cell kinetics and activity of the thrombin-PAR1 signaling axis are increased by proinflammatory cytokines during HIV infection and contribute to adaptive immunoreactions. Furthermore, young patients with HIV infection have a high level of vWF and a low level of ADAMTS13, which are related to stroke.[106] Therefore, HIV infection has a thrombotic risk through various mechanisms.[107,108]

Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is a positive-sense, single-stranded RNA virus of the Flaviviridae family. HCV infection carry the risk of thrombosis, which increases with expression of TF, fibrinolysis interference, and increased platelet aggregation and activation.[109] HCV viral RNA activates TLR-3 in endothelial cells (ECs), leading to inflammation and expression of tumor necrosis factor (TNF)-α.[110] Damaged ECs can affect immune cells through CXCL12 chemokine expression.[111] Through these mechanisms, increased TNF-α induces expression of TF and downregulation of thrombomodulin (TM).[112] Hodowanec et al[113] confirmed that elevation of TF expression and enhancement of coagulatory activity increase in some chronic HCV patients. Similarly, during chronic HCV infectious disease, wall functional disorder caused by plasma vWF levels increases.[114]

Coxsackievirus (CoxV)

Coxsackievirus (CoxV) is negative-sense RNA virus of the Picornaviridae family.[70] It is accompanied by a considerable risk of thromboembolism caused by myocarditis.[115] Additionally, myocarditis coagulopathy and hepatic necrosis occur, and ventricular clot formation increases significantly because of platelet activation.[116]

Herpes Simplex Virus (HSV)

Herpes simplex virus (HSV) is double-stranded, linear DNA genome virus of the herpesvirus family.[70] Infection of blood vessel ECs by HSV increases TF activity and reduces TM

expression.[69,117] Sutherland et al[118] reported that HSV type 1 (HSV-1) is a cofactor for PAR-1 that induces TF and glycoprotein C, causing thrombin production. HSV-1 and HSV-2 move FX to the cell surface via internal mechanism phosphatides.[117–119] It is thought that these viruses drive thrombin generation on the cell surface via this mechanism.[117]

Epstein-Barr Virus (EBV)

Epstein-Barr virus (EBV) belongs to the herpesvirus family and has double-stranded DNA. Its name was changed to human herpesvirus type 4 (HHV-4), but the former name is still widely used.[70] EBV triggers autoantibody-producing autoimmunity in response to various autoimmune diseases.[120] Patients with EBV experience portal vein thrombosis caused by hypercoagulable syndrome.[121]

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) has double-stranded DNA with the generic name of herpesvirus characterized by forming a characteristic inclusion body of the observable "eyes of the owl" state in the nucleus of the host cell under an optical microscope. CMV transforms monocytes and induces production of inflammatory cytokines. Therefore, the incidence of thrombosis in patients with acute CMV infection is common.[121,122]

Corona Virus (CoV)

Corona virus (CoV) causes disease in mammals and birds, and has a single strand plus chain RNA genome.[123] In 2003, a CoV epidemic caused by severe acute respiratory syndrome CoV (SARS-CoV-1) emerged in China.[124] SARS-CoV-1 was associated with severe thrombotic complications.[124] Several SARS-CoV-1 cases exhibited pulmonary embolism and deep vein thrombosis.[125] The characteristics of SARS-CoV-1 are a prolonged prothrombin time, prolonged activated partial thromboplastin time, elevated D-dimer, and worsening thrombocytopenia.[126] These findings are consistent with DIC. Furthermore, interestingly, thrombopoietin levels increase in SARS-CoV-1 patients at the convalescent phase compared with normal controls.[127] These findings have also been reported in patients with septic DIC.[128]

Another CoV infection was reported in 2012.[129] This CoV was responsible for "Middle East respiratory syndrome" (MERS-CoV).[129] MARS-CoV is similar to SARS-CoV-1 and associated with thrombotic complications. Specifically, DIC is one of the major complications reported in fatal MERS-CoV cases.[130]

In 2019, another CoV caused a global pandemic. CoV disease 2019 (COVID-19) is a novel CoV strain disease.[8,9] COVID-19 patients suffer from severe respiratory or systemic manifestations. Therefore, COVID-19 is also called SARS-CoV-2.[131] Thrombotic complications also emerge in patients with COVID-19.[132–135] COVID-19 patients have elevated D-dimer levels, prolonged prothrombin times, and thrombocytopenia similar to DIC.[132,136–138] Both elevated D-dimer levels and thrombocytopenia can be explained by excessive activation of platelets and the coagulation cascade. In contrast, phagocytosis or direct viral targeting by the immune system can also cause these abnormal clinical findings. Thus, viral infections elicit systemic inflammatory immune responses resulting in imbalanced coagulation.[70]

EVs and Coagulatory Abnormalities During Viral Infection

EVs from a virally infected cell include not only the virus, but also information on the host.[139] Therefore, EVs are involved in interactions between a virus and various cells of the host. As we have mentioned, the function and role of EVs are varied.[15,27,46,47] Most importantly, EVs that participate in post-viral coagulatory abnormalities may be MVs (or MPs), because it appears that most characteristic functions of MVs promote coagulation depending on TF (Figure 2). In addition, MVs can substantially increase procoagulant activity on platelet surfaces, thereby contributing to coagulant abnormality during viral infection.[11,41] In contrast, exosomes contain many functional features, one of which concerns the immune system (Figure 2).[56,139–142] For example, lymphatic exosomes promote dendritic cell migration along guidance cues, thereby regulating the immune system.[142] Therefore, it is possible that exosomes do not influence the coagulatory system.

EVs are involved in some aspects of viral infectious disease.[143] After infection, for example, EBOV packages the protein moiety characteristic of this virus in EVs. Apoptosis of immune cells in the host is guided by inflammatory cytokines.[144] This drives failure of the homeostasis mechanism in blood vessels, leading to coagulatory abnormalities such as vein clots and DIC. Airway epithelial cells release EVs that neutralize human influenza virus.[145] This mechanism of EVs might play an important role in defense against respiratory viruses.[146] EVs after HIV infection have a significant influence on the immune system.[147–149] CMV-related EVs are useful to reinforce infectivity of CMV.[143,150] Human CMV infection is controlled by T cell-mediated immunity and CMV infects ECs.[151,152] One of the functions

of EC-derived EVs after CMV infection might be contributing to innate surveillance.[151]

One role played by post-viral EVs exosomes is their participation in maintaining the pathological state and promoting the spread of viral infection. The main roles of MVs and MPs appear to be in coagulation abnormality.[59,153–161] Regarding COVID-19, reports involving EVs are still rare.[162–165] However, a similar role of exosomes and MVs is assumed in COVID-19 as other virus infectious diseases.[166–170] In particular, concerning thrombosis, there is no doubt that COVID-19 causes more symptoms in comparison with the past virus infectious disease.[171] Accumulation of important reports of EVs in conjunction with COVID-19 is expected in the future.

Conclusions

We have addressed the functions of EVs in thrombosis, and their involvement in viral infections. Clinical research on EVs should include studies on the coagulatory system. In particular, abnormal enhancement of the coagulatory system by EVs can cause thrombosis and DIC (Figure 2). There are reports about EVs in some virus infectious diseases. Apoptosis of immune cells in the host is guided by inflammatory cytokines. As a role of post-viral EVs, exosomes participate in pathological maintenance and infection spreading. The main roles of MVs appear to be in coagulation abnormalities. Although many viral infections involve EVs, the role of EVs in COVID-19 is unclear. Nevertheless, thrombosis is a major problem that affects the prognosis of COVID-19 patients. Accumulation of important reports of EVs in conjunction with COVID-19 is expected in the future.

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Disclosure

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

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