The Pathophysiological Role of Platelet-Derived Extracellular Vesicles

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Abstract

Platelets are very abundant in the blood, where they play a role in hemostasis, inflammation, and immunity. When activated, platelets undergo a conformational change that allows the release of numerous effector molecules as well as the production of extracellular vesicles, which are circulating submicron vesicles (10 to 1,000 nm in diameter) released into the extracellular space. Extracellular vesicles are formed by the budding of platelet and they carry some of its contents, including nucleic acids, surface proteins, and organelles. While platelets cannot cross tissue barriers, platelet-derived extracellular vesicles can enter the lymph, bone marrow, and synovial fluid. This allows the transfer of diverse contents carried by these platelet-derived vesicles to cell recipients and organs inaccessible to platelets where they can perform many functions. This review highlights the importance of these platelet-derived extracellular vesicles under different physiological and pathophysiological conditions.

Keywords
- extracellular vesicles
- platelets
- coagulation
- platelet-derived extracellular vesicles

Recent developments in extracellular vesicles (EVs) have led to a reimagining of the idea of a secreted signal.[1] Our understanding of communication between cells, tissues, and organs is radically changing due to the possibility of membrane-bound packages delivering RNA, proteins, lipids, and organelles.[1,2] A more traditional view of cell–cell communication being upheld by chemical signals or contact between cells has been extended to include an option of bundled messaging that come from vesicle-mediated signals.[3,4]

EVs have been of increasing interest to researchers for over 50 years. The story of their discovery goes back to 1946 when Erwin Chargaff and Randolph West demonstrated that platelet-free plasma (PFP) was still capable of coagulation.[5] A study by Sinauridze and collaborators showed that platelet-derived extracellular vesicles (PEVs) are 50 to 100 times more potent than thrombin-activated platelets at promoting coagulation.[6] Coagulation parameters of PFP were characterized by standard clotting assays: activated partial thromboplastin time, prothrombin time and kaolin time, and by determination of spatial clot growth rate.[6]

Workers were even able to isolate the fraction of plasma that gave it this procoagulant activity by centrifugation, without identifying what was responsible.[5] In 1967, Peter Wolf completed this discovery by characterizing the content of this fraction.[7] He showed by electron microscopy that this fraction is made up of particles derived from activated platelets rich in phospholipids, which he named "platelet dust."[7] Over time this term has been replaced by microparticles (MPs) and then by EVs. The use of the generic term

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Table 1 Release modes and characteristics of EV types[14,15]

Subtypes of EVs	Origin	Size (mm)
Microparticles	Budding of the plasma membrane	100–1,000
Exosomes	Are first formed inside the cells, in structures called multivesicular bodies (MVBs), and are then released into the extracellular environment following the fusion of these MVBs with the plasma membrane	40–1,000
Apoptotic bodies	Plasma membrane budding in apoptotic cells	1,000–5,000

Abbreviation: EV, extracellular vesicles.

"extracellular vesicles" is now recommended by the International Society for Extracellular Vesicles (ISEV) to refer to any particle released from the cell that is characterized by a lipid bilayer and the absence of a nucleus.[8]

EVs are submicron vesicles (size between 10 nm and 1 µm) released into the extracellular medium by most cell types.[9] EVs have a circular shape and are bounded by a lipid bilayer and have varying sizes depending on their type.[10] These EVs can be isolated from different biological fluids (plasma, urine, saliva, cerebrospinal fluid, cell culture supernatant...).[11] For a long time, they were considered to be simple cellular debris, but are now considered to be true biological information vectors that can modulate the metabolism of numerous target cells by transferring information and/or modulating cell signaling. These vesicles carry different nucleic acids (messenger ribonucleic acid [mRNA], microribonucleic acid [miRNA], transfer ribonucleic acid [tRNA]...), proteins (enzymes, transporters, and extracellular matrix proteins...) as well as lipids (oleic acid, arachidonic acid...) derived from their cell of origin, which can induce modifications in the functioning of the target tissues.[12]

Three types of EVs can be distinguished: MPs also called microvesicles, exosomes also called exovesicles, and apoptotic bodies[13] (►**Table 1**). In blood, the majority of circulating EVs originate from platelets.

This review focuses on the classical role PEVs play in hemostasis, as well as recent studies that demonstrate broader potential therapeutic applications.

Historical Findings on the Role of PEVs

PEVs account for approximately 80% of circulating EVs in blood.[16,17] They are formed upon activation of platelets by various agonists such as thrombin, collagen, and complement.[18]

Detailed electron microscopic analysis of activated platelets linked data from various publications and described the release of two different populations of EVs called microvesicles and exosomes.[19] These vesicles play several roles in the regulation of physiological and pathological functions[20] by accelerating the generation of thrombin.[21–23] Also, they have procoagulant activity, the procoagulant properties of these vesicles are associated with microvesicles but not with exosomes.[19,24]

The procoagulant activity of PEVs arises primarily from the exposure of negatively charged phospholipids, primarily phosphatidylserine, and tissue factor that provide a site for the assembly of coagulation factors.[19] One early study showed that PEVs have a procoagulant activity that is 50 to 100 times higher than that of activated platelets.[6]

Another later study provided the first evidence that PEVs can exert both pro- and anticoagulant effects. This study showed that PEVs could promote prothrombin activation but also inactivation of factor Va,[25] through binding of protein S to the coagulation inhibitor protein C.[26] This shows a possible role of PEVs in maintaining the balance between pro- and anti-thrombotic states.

The expression of platelet markers by PEVs varies according to the state of the original cell at the time of release.[27,28] Indeed, all PEVs express the constitutive markers of this cell type (CD41, CD42b, CD61, or CLEC-2), but only those secreted by activated platelets carry platelet activation markers (CD62p and CD63) on their surface.[27,28]

PEVs also have other proteins on their surface such as von Willebrand factor and CD31. However, these proteins are not exclusive to platelets.[29] PEVs also have a role in the regulation of immunity (stimulation and suppression), where they can interact with T cells and regulate their differentiation and regulatory activity.[30,31] In addition, they can promote the formation of germinal centers and IgG production by B cells depending on their CD40L content.[32,33] As PEVs can circulate in lymph, they have the potential to transport molecules of adaptive immunity to lymphoid organs.[34,35]

The cargo carried by PEVs (growth factors, proteins, nucleic acids, organelles, etc.) also allows them to play a role in intracellular communication.[36,37] Through the exchange of nucleic acids (mRNA, miRNA, and other types of rubonucleic acid [RNA]), they can regulate cells at post-transcriptional levels.[38]

Therapeutic Potential of PEVs

EVs can be used for cardiac regenerative therapies.[39] In a 2005 study, it was shown that PEVs stimulate vascular endothelial growth factor (VEGF)-dependent revascularization after chronic ischemia, pointing to the potential regenerative effect of EVs on cardiac regeneration.[40] Additionally, a study published in 2015 demonstrated that plasma-derived EVs activate the toll-like receptor 4 on cardiomyocytes to induce cardioprotective signals following ischemia–reperfusion.[41]

On the other hand, several studies report a significant increase in tissue factor activity associated with PEVs from coronavirus disease (COVID-19) patients. Indeed, COVID-19 patients have been shown to have a higher PEV-associated tissue factor activity associated with thromboembolic events.[42–45]

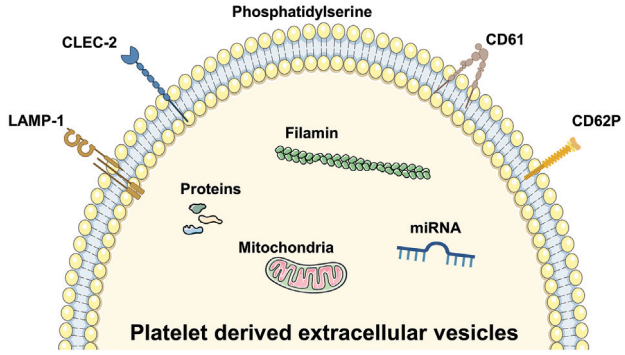

Fig. 1 The content of platelet-derived extracellular vesicles (PEVs). Different molecules have been identified at the surface of these extracellular vesicles. CD61, CLEC-2, and LAMP-1 are constitutively expressed on PEVs surface. Phosphatidylserine as well as P-selectin are also observed on PEVs. Several studies have shown that PEVs contain nucleic acids, proteins, and filamin. Moreover, mitochondria can be found in a proportion of the PEVs.

Researchers are creating new ways to optimize drug efficacy and prevent off-target effects by developing a better understanding of various diseases and their pathologies.[46] Nanoparticles and liposomes, including nanoparticle-based drug delivery technologies, are gaining considerable attention for delivery of anti-inflammatory drugs or chemotherapy. Therapeutic EVs may prove to be valuable since they provide efficient cargo delivery systems for long-distance communication between cells and organs. As a result of rheumatoid arthritis, which is a chronic inflammatory disease characterized by platelet activation, the blood is more abundant in PEVs.[47] Otherwise, the absence of PEVs has been associated with bleeding and coagulation disorders, according to several clinical studies. In Scott syndrome, characterized by mild to moderate bleeding, circulating PEVs are decreased, possibly due to reduced PS exposure capacity.[48]

PEVs are currently being explored as therapeutic tools,[49] due to the nature of their molecular cargo, which contains bioactive molecules such as growth factors, proteins, coagulation factors and non-coding RNAs (►**Fig. 1**).[50,51]

Microvesicles have been identified as cardio protectors through their association with Sonic hedgehog factor, known for its muscle tissue repair properties.[52] One study showed that procoagulant PEVs were significantly increased in subjects following cardiac stress induced by dobutamine, a cardiac adrenergic receptor stimulator, and then decreased after 1 hour.[53] This increase was less significant in patients with a history of vascular disease (coronary heart disease, ischemia, etc.).[53] This suggests that the increase in circulating levels of these procoagulant microvesicles, in the face of this cardiac stress, would be a physiological response which would nevertheless be diminished in individuals with cardiac pathologies. Therefore, the possible use of PEVs in the treatment of cardiovascular diseases has been explored.[54]

PEVs also participate in the inflammatory process through their influence on cell–cell interaction and their role in inducing the expression of adhesion molecules and the release of cytokines by different cell types, also, contain pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor α.[55]

A recent study has also suggested that PEVs could infiltrate the bone marrow during an inflammatory state and promote hematopoiesis.[56] Other studies have shown that PEVs also possess anti-inflammatory activities and may suppress inflammation mainly by inhibiting cytokine release.[57,58]

Some populations of PEVs may be particularly suitable for therapy to restore hemostasis and inhibit vascular permeability.[59] The surface of circulating PEVs is 50 to 100 times more pro-coagulant than that of an activated platelet.[6] They express negatively charged phospholipids exposed on their surface, and have binding sites for coagulation factors such as activated factor V and factor VIII and thrombin.[6]

Results from other studies have shown that PEVs can help treat neurological disorders, with administration of these vesicles in an animal model of cerebrovascular accident showing increased neural cell growth at the site of injury, resulting in improved behavioral outcomes.[60] Treatment with PEVs increased the potential for neural stem cells to differentiate into glia and neurons.[61] In addition, growth factors such as platelet-derived growth factor, VEGF, fibroblast growth factor, and brain-derived neurotrophic factor, which are known to be present in platelets and their vesicles, may promote neurotrophic effects and neurogenesis.[62,63] PEVs can be used as targeted drug carriers, due to their interaction with other cells as they express various platelet membrane glycoproteins, such as GPIIbIIIa (CD41/CD61 or integrin αIIb/β3), GPIaIIa (CD49b/CD29), GPIba (CD42b), P-selectin (CD62P), PECAM-1 (CD31), and GP53 (CD63).[64]

The ability of cancer cells to internalize PEVs and the known interactions between tumor and platelets, may make PEVs a suitable cancer treatment.[65–67] Proof of concept that PEVs can be used as vehicles for anti-cancer drugs has been demonstrated.[68] Indeed, PEVs express higher levels of surface proteins like P-selectin and CD41, as well as lipids such as phosphatidylserine, which contributes to cancer-associated thrombosis.[6] Some native platelet vesicles inhibit tumor growth by transferring miRNA-24.[69]

Conclusion

EVs have been shown to have alternative and non-redundant functions. In the past two decades, a rapidly increasing number of studies and scientific papers have discussed the functional role of PEVs in many physiological and pathological processes. A wide range of physiological and pathological processes are regulated by PEVs, including inflammation, cell communication, coagulation, and metastasis. A further understanding of PEVs use and manipulation will lead to improved disease diagnosis and associated morbidity and mortality.

Authors' Contributions
M.M., F.G., A.N., and Y.Z. contributed to literature search and writing of this review. Y.M. and Y.Z. designed the structure and content of this review. Y.Z. provided the figure. All authors approved the submitted version of the manuscript.

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Conflict of Interest
None declared.

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