

# Antigen-presenting cell-derived extracellular vesicles in accelerating atherosclerosis

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## ABSTRACT

Extracellular vesicles (EVs) are a population of heterogeneous particles that originate from the endosomal system or plasma membrane. Antigen-presenting cells (APCs) produce and release a broad spectrum of EVs involved in the pathogenesis of atherosclerosis. APC-derived EVs contain several bioactive molecules, such as non-coding RNAs, cytokines, chemokines, active proteins, immunomodulatory factors, and growth factors. The review focuses on the role of APC-derived EVs in regulating the transformation of macrophage phenotype, shaping foam cells, driving autophagy and/or inhibiting apoptosis of Th4<sup>+</sup> cells, T regulatory cells, endothelial and smooth muscle cells (SMCs), as well as in facilitating oxidative stress in vasculature. APC-derived EVs act as triggers of angiogenesis, neovascularization and inflammation through their participation in microvascular inflammation, angiogenesis, development of atherosclerotic plaques, and modulation of their instability.

**Key words:** antigen-presenting cells, atherosclerosis, endothelial dysfunction, extracellular vesicles, inflammation, netosis, vascular reparation

## INTRODUCTION

During the last two decades, extracellular vesicles (EVs) have become a subject of scrutiny in various diseases<sup>1-3</sup>. EVs are defined as heterogeneous groups of membrane-enclosed spherical structures with variable sizes and compositions, including microvesicles, exosomes and apoptotic bodies<sup>4</sup>. They are secreted by a wide array of cells, including cardiac myocytes, mature and progenitor endothelial cells, mesenchymal stem cells, immune cells like antigen-presenting cells (APCs), and malignant cells<sup>5,6</sup>. Being involved in the transfer of cellular content (e.g. regulatory proteins, hormones, lipids, growth factors, chromatin materials, and microRNAs), EVs play a multifaceted role in cell-to-cell communication, regulation of immune response, tissue reparation, angiogenesis, inflammation and malignancy, via acting as signal transducers which mediate information by internalization of their contents through fusion with the plasma membrane of target cells or through endocytosis<sup>7-10</sup>.

Atherosclerosis is defined as a chronic progressive disease of the arterial wall having a long asymptomatic phase. The development of the disease is associated with microvascular inflammation and altered immune reaction due to strong infiltration of intima and sub-intima by oxidized lipids, oxidative stress, proliferative responses from cellular components of intima and media, accumulation of extra-

cellular components with the shaping of atherosclerotic plaques, impaired vasomotion ability, endothelial dysfunction, and thrombosis, ultimately resulting in vascular remodeling and artery obstruction<sup>11,12</sup>. Finally, there is a close relationship between a risk of all-cause mortality and incident of fatal and non-fatal cardiovascular (CV) events in the general population and subclinical atherosclerosis<sup>13</sup>.

Numerous animal studies as well as observational and clinical trials have shown that atherosclerosis arises from immune activation, with several cell-type specific pathways involved. These include macrophage and smooth muscle cell (SMC) phenotypic switching and various inflammatory signaling, such as IL-33/suppression of tumorigenesis 2 (ST2), Ras-Raf-MEK-ERK pathways, and JAK-STAT signaling pathways<sup>14-17</sup>. Besides, some chronic infections induced by pathogens such as *Helicobacter pylori* and herpes zoster can increase the risk of atherosclerosis, mediating the presence of HSP60-specific T lymphocytes in peripheral blood<sup>18,19</sup>. However, the innate molecular mechanisms involved in the progression of stable artery lesions to the formation of vulnerable plaques still remain uncertain<sup>20</sup>. There is a wide range of evidence regarding the fact that pro-atherogenic factors (e.g. hypoxia, oxidative stress, oxidized lipids, and inflammation) and aggravating factors (e.g. blood flow turbulence, endothelial dysfunction, and vasoconstriction) influence the production of EVs from

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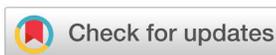
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various cells and promote atherosclerosis<sup>21,22</sup>. It has been defined that EVs derived from APCs regulating key steps of disease pathogenesis, such as microvascular inflammation, immunity, cell survival, apoptosis, angiogenesis, thrombosis and autophagy, exert a role in the development of atherosclerotic lesions<sup>21,23</sup>. The review is to update the current evidence of the role of EVs derived from immune cells and APCs in the development of atherosclerotic plaque and modulation of their instability.

## DEFINITION AND NOMENCLATURE OF EXTRACELLULAR VESICLES

The recently updated guideline of the International Society for Extracellular Vesicles (ISEV) on minimal information for studies of extracellular vesicles (MISEV) has defined EVs as "particles naturally released from the cell that is delimited by a lipid bilayer and cannot replicate"<sup>24</sup>. The nomenclature, main characteristics, and biological function of several subpopulations of EVs are reported in **Table 1**. Exosomes, microvesicles, and apoptotic bodies are validated to describe several types of particles. Although different subpopulations of EVs have a particular and unique morphological structure, which is a result of their origin, EVs can be substantially distinguished from each other in terms of their components, such as cell organelles (endoplasmic reticulum, Golgi, mitochondrial and nuclear components), cytosolic and cytoskeleton proteins (heat shock proteins, tubulins, moesin, cofilins, actin, myosin, protocadherin, apolipoproteins), lipids (cholesterol, sphingomyelin, ceramide, phosphatidylcholine, ethanolamine, and inositol), eicosanoids, enzymes (phospholipases, matrix metalloproteinases), adhesion molecules (CD44, EPCAM, ICAMs, integrins), genetic materials (chromatin debris, DNA, non-coding and coding RNAs), and growth factors (vascular endothelial growth factor [VEGF], epidermal growth factor [EGF], fibroblast growth factor [FGF] and their receptors [EGF and FGF receptors], interleukins, and other biomolecules)<sup>25,26</sup>. Some components (cytosolic and cytoskeleton proteins, growth factors and their receptors, MHC molecules, and adhesive molecules) are constitutively present in various subtypes of EVs. Other components, such as prions and  $\beta$ -amyloid peptides, occur in pathological condition. Moreover, there is no strong correlation between the components, the size, and the number of these particles in circulation<sup>27</sup>. Despite protein/lipid profiles, as well as nucleic acid species, which could serve as markers for quantitative and compositional

characterizations of several subtypes of EVs, there is a need to use other criteria including size, immune phenotype, bilayer morphology, labeling with fluorescent lipids, proteins, or antibodies- to discriminate EVs from each other.

## EVS DERIVED FROM IMMUNE AND ANTIGEN-PRESENTING CELLS: BIOLOGICAL ROLE AND FUNCTION

EVs are produced by immune cells and APCs (macrophages, B cells, dendritic cells) facilitate cell-to-cell communication processes, such as forming immune synapses between APCs and T cells, promoting the delivery of peptide complexes of class II major histocompatibility complex (pMHC-II) molecules, and assisting in the differentiation of T cells into CD4<sup>+</sup> or CD8<sup>+</sup> T cells. Besides, they can act as antigen-presenting EVs, thereby mediating the initiation, expansion, maintenance, or silencing of adaptive immune responses, while also promoting differentiation of regulatory T lymphocytes, inflammation, and apoptosis<sup>27,28</sup>. Therefore, EVs- especially exosomes, which are secreted by naïve human monocytes/macrophages are involved in regulating the phagocytic activity of activated macrophages as a result of the transfer of interleukin (IL)-10 and transforming growth factor (TGF)-beta. It has been found that numerous microRNAs (-27a, -29b, -125a, -146a, -155, and -222), which are transmitted from naïve human monocytes to macrophages, were powerful triggers for the polarization of macrophages into M2 phenotype<sup>29-31</sup>. Nevertheless, proliferation and differentiation of progenitor endothelial precursors, which are crucial for angiogenesis and neovascularization, are under regulation by APC-derived EVs<sup>32</sup>. Well-known inducers of cell differentiation, such as circulating oxidase low-density protein and cell-free microRNAs cannot strongly support epigenetic-related regulation of proliferative activity of resident cells in the vasculature. Several microRNAs (such as microRNA-128, microRNA-128-1, microRNA-148a, microRNA-130b and microRNA-301b) are cargoes for EVs and act as specifically-designed core post-transcriptional regulators of target genes involved in cellular lipid homeostasis, microvascular inflammation, and energy metabolism. These target genes include LDL receptor, ATP-binding cassette transporter A1, sirtuin 1, and insulin receptor substrate 1<sup>33-35</sup>. Thus, specific proteomic, transcriptomic, and lipidomic profiles of EVs secreted by immune cells and APCs are engaged in control of migration, proliferation and differentiation of recipient cells.

**Table 1: The main characteristics of EVs' subpopulations**

Characteristics	Exosomes	Microvesicles	Apoptotic bodies
Size (nm)	40 - 120	50 - 1000	500 - 5000
Mechanisms of formation	Multiple exocytosis from the endosomal system with shaping intraluminal budding of endosomal compartments and intraluminal vesicles prior to the release, which is under control Rab11/35 and Rab27 GTPases, the tetraspanin, ceramide, and the SNARE complex	Blebbing of the plasma membrane due to multiple complex Ca <sup>2+</sup> -depending regulatory pathways, which include myosin light chain and depend on Rho-associated kinase I and II, NF-κB, TNF-related apoptosis-inducing ligand, p38 MAPK	Budding from plasma membrane due to caspase-mediated cleavage and activation of Rho-associated kinase I
Morphology	Cup-shaped	Predominantly heterogeneous	Heterogeneous
Composition	Proteins, lipids, non-coding and coding RNAs, DNAs, growth factors, MHC molecules, receptors, heparan sulfate proteoglycans including syndecans, complement-binding proteins CD55 and CD59, cystatin C, TNF-α and INF-γ, CD47; heterotrimeric G proteins, transferrin receptor, ADAM10; GPI-anchored 5' nucleotidase CD73, interleukins, FGF-1/2, PDGF	Proteins, lipids, non-coding and coding RNAs, DNAs, growth factors, hormones, and cell organelles, HSC70 (HSPA8), and HSP84, APOA1/2, APOB; APOB100, TGFβ1/2; INF-γ; VEGF-A, FGF-1/2, PDGF; EGF; interleukins	Proteins, cell organelles, membrane and cytosolic components, chromatin fragments, histones, non-coding and coding RNAs
Main biological function	Cell-to-cell communication	Cell-to-cell communication	Facilitate phagocytosis, autophagy, immune response
Markers	ESCRT components, MFGE8, PDCD6IP, TSG101, flotillin, tetraspanins (CD8, CD63, CD81), SNARE proteins (syntaxin 6 and syntaxin 13).	Integrins, selectins, and CD40 ligand	Annexin V, phosphatidylserine

TNF: tumor necrosis factor; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; SNARE: soluble N-ethylmaleimide-sensitive attachment protein receptor; ESCRT: endosomal sorting complex required for transport; MFGES: milk fat globule-EGF factor 8 protein; PDCD6IP: programmed cell death 6 interacting protein; TSG101: tumor susceptibility gene 101 protein; MHC: major histocompatibility complex; TNF: tumor necrosis factor; INF: interferon; HSP: heat shock proteins; VEGF-A: vascular endothelial growth factor-A; FGF: fibroblast growth factor; PDGF: platelet-derived growth factor; EGF: epidermal growth factor.

## IMMUNE AND APC-DERIVED EVS IN ATHEROSCLEROSIS

Previous preclinical and clinical studies have revealed that EVs are associated with the presence, progressiveness, and severity of atherosclerosis<sup>36-38</sup>. Indeed, circulating levels of EVs have been found to be increased in atherosclerosis, and EVs were involved in key stages of atherosclerosis progression, such as accumulation of lipid, thickness of intima, proliferative response from SMCs, promotion of vascular media and calcification, plaque shaping and progression, and thrombus formation after plaque rupture<sup>36</sup>. The proliferation and migration of macrophages, epithelial cells and vascular SMCs, as well as the transformation of macrophages into foam cells, are all essential elements for the formation of atherosclerotic plaques and acceleration of atherosclerosis<sup>37</sup>. Activated macrophages can interact with vascular SMCs through exosomes and stimulate them to migrate and adhere to the intima. EVs derived from foam cells have been demonstrated to stimulate vascular SMC migration and activate extracellular signal-regulated kinase (ERK) pathways, enabling the progression of aggravated lesions<sup>38</sup>. Oxidized low-density lipoproteins, from internalization into EVs, can be transferred from foam cells to vascular SMCs and endothelial cells. The resident precursors act as destructive stimuli, inducing oxidative stress and disintegration of the endothelial barrier. It has been established that several transcriptional factors, such as Krüppel-like factor-5 (KLF5), JunD (a member of the activated protein-1 family of transcription factors), and nuclear factor erythroid 2-related factor 2 (Nrf2), were found to be incorporated into EVs derived from macrophages. Consequently, EVs mediating the proliferation and migration of vascular SMCs via supply of transcription factors- play a pivotal role in adverse vascular remodeling and atherosclerotic plaque shaping while suppressing oxidative homeostasis in target cells of the vasculature; however, they can attenuate angiopoietin capacity<sup>38,39</sup>.

There is convincing evidence that a large number of non-coding RNAs, including microRNA-146a, microRNA-128, microRNA-185, microRNA-199a-5p, microRNA-365 and microRNA-503, are transmitted between immune cells and target somatic cells (such as epithelial cells, progenitor endothelial cells and SMCs), promoting specific signals for suppression of aerobic glycolysis, promoting macrophage polarization, and decreasing cell migration<sup>39,40</sup>. Interestingly, delivery of microRNA-146a from macrophage-released EVs repressed the

expression of target genes of insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) and human antigen R or ELAV-like RNA-binding protein 1 (HuR) in naïve macrophages<sup>40</sup>. These genes activate downstream cascades, including that of NLRP3 inflammasome, and support Toll-like receptor (TLR) signaling and endoplasmic reticulum stress responses, thereby hampering recruitment of circulating monocytes and macrophages into the vascular intima<sup>41</sup>. Nonetheless, microRNA-223 contained in macrophage-released EVs was found to be a powerful trigger for macrophage turn-over into foam cells in atherosclerotic plaques<sup>41</sup>. Moreover, microRNA-199a-5p can exert its effect by targeting Klotho, which induces polarization of M2 macrophages through the TLR-4 pathway<sup>42</sup>.

There is a large body of evidence that shows macrophages can secrete so-called atherogenic exosomes containing microRNAs (-21-3p, -133a, -141-3p) to mediate cell-to-cell crosstalk and encourage pro-atherogenic phenotypes of vascular SMCs<sup>43-45</sup>. Indeed, EVs enriched by microRNA-21-3p and derived from plaque-resident macrophages increase vascular SMC migration and proliferation via their phosphatase and tension homology<sup>43</sup>. The package of microRNA-133a in macrophage secretome is associated with a negative regulation of cell proliferation, inflammatory factor secretion, and apoptosis in vascular wall and plaque by modulating FGF-1<sup>44</sup>. Animal studies have revealed that microRNA-141-3p deletion reverses the positive effects on vascular SMCs via long non-coding RNA-taurine-upregulated gene 1<sup>45</sup>. Thus, macrophages modulate pro-inflammatory and pro-atherogenic phenotypes in recipient cells via the secretion of EVs containing microRNAs.

Additionally, EVs are a powerful messenger for signals from infected cells to naïve cells. EVs released from virus-infected cells deliver viral RNA to dendritic cells and macrophages, thereby activating pattern recognition receptors (PRRs) on recipient cells, resulting in the expression of type I interferons and pro-inflammatory cytokines<sup>46,47</sup>. On the other hand, exosome-mediated secretion of a multitude of immunoregulatory proteins from APCs has been demonstrated; moreover, EVs can promote inflammasome creation and release as an alternative to caspase-1<sup>48,49</sup>. Consequently, EVs can indirectly modulate the non-canonical secretion of pro-inflammatory cytokines IL-1 $\beta$  and IL-18 as a package of the inflammasome. Moreover, TLR-9 activated macrophages can secrete EVs that ensure transport of various nucleic acids and CpG

oligodeoxynucleotides to naïve macrophages and induce them to release chemokines and TNF- $\alpha$ <sup>50,51</sup>. Besides, one of the largest stress-induced proteins and molecular chaperones- glucose-regulated protein 170 (Grp170)- is highly responsible for the internalization of CpG oligodeoxynucleotide package and facilitates synergistic activation through GTP-binding protein Ras and MyD88-dependent signaling (MyD88/IRAK/TRAF6 kinases cascade, ERK/JNK/NF-kappaB), which ensures a subsequent enhancement in production of pro-inflammatory cytokines and nitric oxide<sup>52-54</sup>. These molecules were previously defined as triggers for proliferative responses from vascular SMCs, epithelial and endothelial cells, and resident macrophages<sup>55</sup>.

Apoptotic APC-derived EVs have been found to be core players in contributing to macrophage-mediated production of TGF-beta *in vitro* and *in vivo*<sup>56</sup>. In extracellular immune surveillance, APC-derived EVs also interacted with secreted phospholipases to generate eicosanoids, regulating the transfer of cargo into a cellular recipient<sup>57</sup>. Eicosanoids are involved in various biological functions, including modulation or modification of phenotype of the recipient cells, such as SMCs, macrophages, and endothelial progenitor cells; distal immune responses and proliferative responses from SMCs can also be modulated<sup>58,59</sup>.

Since EVs contain a wide spectrum of lipids, the final metabolic effect on target cells depends on lipids that enrich EVs and the immune phenotype of EVs. For instance, di-saturated phospholipids that are embarked by exosomes enhance their membrane rigidity and facilitate binding with circulating IgM-type immunoglobulins<sup>60</sup>. There are additional specific eliminating proteins that may favor the clearance of circulating immune complexes, IgM antibodies, and apoptotic cells by exosomes. Indeed, the phospholipase iPLA2, which is specifically associated with the endosomal and exosomal membranes, can be activated by reactive oxygen species and mediates lysophosphatidylcholine synthesis. It is recognized by IgM antibodies on the surface of EVs and specifically binds with apoptotic cells, leading to their removal from circulation<sup>61,62</sup>. Because apoptotic cells derived from macrophages and other APCs can suppress pro-inflammatory and pro-immunogenic reactions through their cargo contents, altered elimination of these EVs from peripheral blood with exosomes is considered as an impaired endogenous tissue-protective mechanism<sup>63,64</sup>. In fact, apoptotic cells can induce 15-lipoxygenase and 15-hydroxyeicosatetraenoic acid production, which potentiate the anti-inflammatory pathway through peroxisome proliferator-activated receptor-gamma and

lipoxin A4 production, leading to maintenance of vascular integrity and prevention against atherosclerosis<sup>65</sup>.

Another pathophysiological mechanism by which exosomes released from oxidized low-density lipoprotein-stimulated macrophages influence atherosclerosis development and progression is via induction of neutrophil extracellular traps (NETs)<sup>66</sup>. Overall, NETosis is a unique cell death mechanism that is a crucial component of the adaptive immune response, linking microvascular inflammation with atherosclerosis<sup>67,68</sup>. Exosomal microRNA-146a secreted by activated macrophages promote the generation of intracellular reactive oxygen species and NET release via targeting superoxide dismutase 2<sup>66</sup>. Therefore, activation of endothelial cells with APC-derived EVs can promote them to secrete exosomes embarked with microRNA-505, oxidized low-density lipoprotein, and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). Furthermore, MALAT1 and microRNA-505 containing various endothelial cell-derived EVs (mainly exosomes) are able to initiate the formation of NETs and plaque resident dendritic cell maturation, which in turn deteriorate atherosclerosis<sup>68-70</sup>. Indeed, transcripts of long non-coding RNAs found in EVs related to atherosclerosis have included many molecules, such as ANRIL, SENCN, CoroMarker, LIPCAR, HIF1 $\alpha$ -AS1, LncRNA H19, APPAT, KCNQ1OT1, LncPPAR $\delta$ , LincRNA-p21, MALAT1, MIAT, and UCA1<sup>71</sup>. Some of them, such as CoroMarker, have predictive value for coronary artery disease<sup>72,73</sup>. On the other hand, animal studies have revealed that exosomal MALAT1 enhances autophagy and survival in oxidized low-density lipoprotein-treated human umbilical vein endothelial cells through suppression of microRNA-216a-5p, and that regulation of Beclin-1 expression can lead to vascular protection<sup>74</sup>. Consequently, the secretome of APC-derived EVs can play a dual role in atherosclerosis development and progression, depending on the compounds incorporated in the EVs<sup>75</sup>.

## FUTURE INVESTIGATIONS

Since circulating EVs are enriched with various subtypes of biologically active molecules and can be derived from individual APCs, single EV analysis might have practical utility to identify patients at high-risk for atherosclerosis by evaluating EV numbers and the cargo composition. Perhaps, extensive clinical studies are required to evaluate whether EVs derived from cells, including APCs, could serve as potential biomarkers of subclinical atherosclerosis. Finally, an

exosome-based therapeutic strategy can also be used to attenuate atherosclerotic heart disease and promote cardiovascular regeneration.

## CONCLUSION

EVs derived from APCs play a central role in accelerating atherosclerosis through their participation in microvascular inflammation, angiogenesis, coagulation, and NETosis. While limited, there is strong evidence in the literature for APC-derived EVs as potential diagnostic and predictive markers but this requires further investigations. Large clinical trials can help deepen our understanding of APC-derived EVs as potential surrogate biomarkers of atherosclerosis-associated diseases.

## ABBREVIATIONS

**Apo:** apo-lipoproteins  
**CD:** cluster of differentiation  
**CV:** cardiovascular  
**CVD:** cardiovascular disease  
**EGF:** Epidermal Growth Factor  
**ESCRT:** endosomal sorting complex required for transport  
**FGF:** fibroblast growth factor  
**HSP:** heat shock proteins  
**INF:** interferon  
**MAPK:** mitogen-activated protein kinase  
**MFGE8:** milk fat globule-EGF factor 8 protein  
**NF- $\kappa$ B:** nuclear factor- $\kappa$ B  
**PDCD6IP:** programmed cell death 6 interacting protein  
**PDGF:** platelet-derived growth factor  
**SNARE:** soluble N-ethylmaleimide-sensitive attachment protein receptor  
**TNF:** tumor necrosis factor  
**TSG101:** tumor susceptibility gene 101 protein  
**VEGF-A:** vascular endothelial growth factor-A

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## AUTHOR'S CONTRIBUTIONS

Berezin AE and Berezin AA have equal responsible for the paper. All authors read and approved the final manuscript.

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## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

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