Extracellular Vesicles in Atherothrombosis

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality all over the world. Extracellular vesicles (EVs), small lipid-bilayer membrane vesicles released by most cellular types, exert pivotal and multifaceted roles in physiology and disease. Emerging evidence emphasizes the importance of EVs in intercellular communication processes with key effects on cell survival, endothelial homeostasis, inflammation, neoangiogenesis, and thrombosis. The following content focuses on EVs as effective signaling molecules able to both derail vascular homeostasis and induce vascular dysfunction, inflammation, plaque progression, and thrombus formation as well as drive anti-inflammation, vascular repair, and atheroprotection.

Keywords: atherothrombosis ; atherosclerosis ; extracellular vesicles ; immunoinflammation ; immunothrombosis ; inflammation

1. Introduction

Extracellular vesicles (EVs) are released in healthy physiological steady conditions. Clinical atherosclerotic cardiovascular disease (ASCVD) development is associated with high release of EVs. Assessment of vascular status is crucial for atherosclerosis prevention and to this aim EVs can serve as potential biomarkers in the clinics [1]. Molecular footprints of EVs provide clues about their cellular origin under healthy and diseased states, configuring a precious biomedical tool for liquid biopsy, easily detectable in body fluids. Changes in circulating EVs of different cellular origin have been widely reported for almost all cardiovascular risk factors and pathologies [2] reflecting their pathophysiological severity. Beyond diagnostic use, EVs have been suggested for the prediction of major adverse cardiovascular events (MACE) [3] and mortality [4]. Circulating procoagulant MVs were found at higher levels in patients with acute coronary syndrome (ACS) than healthy subjects [5]. Risk assessment is critical in primary prevention of ASCVD, especially for asymptomatic patients with subclinical atherosclerosis. In this context, EVs emerge as promising biomarkers for cardiovascular risk stratification. It is found that patients with familial hypercholesterolemia (FH) presenting subclinical lipid-rich atherosclerotic plaques have significantly higher amounts of circulating lymphocyte-derived ($CD3^+/CD45^+$) EVs than FH patients with fibrous plaques [6] in agreement with other studies that reported high levels of EVs from T lymphocytes in subjects with essential hypertension [7]. Thus, lymphocyte-derived EVs might help to map atherosclerotic plaque burden. Accordingly, increased circulating levels of leukocyte-derived EVs in patients with unstable atherosclerotic plaques signal for plaque vulnerability [8]. Furthermore, it is also found that asymptomatic high cardiovascular risk FH patients have significantly higher number of circulating prothrombotic platelet EVs [9]. Patients with FH, despite being treated according to guidelines, have ongoing innate immune cell and platelet activation. Indeed, in asymptomatic high cardiovascular risk FH patients from the same cohort, pan-leukocyte-derived and activated neutrophil-derived circulating EVs as well as EVs bearing markers of platelet activation were significantly increased in patients about to suffer an ischemic event [3]. This specific EV signature is a prognostic marker able to improve the prediction of clinical events if included in the risk factor models. Altogether, it is clear that multiple biomarker-based strategies for patient stratification including EVs hold promise in precision medicine.

EVs orchestrate the entire spectrum of atherosclerotic disease phases by means of their intercellular and extracellular communication and adhesion between blood and vessel wall [10]. Human atherosclerotic plaques, from initial lesions to advanced stages, contain EVs expressing markers from vascular and blood cells (leukocytes, red blood cells (RBCs), smooth muscle cells, and endothelial cells (ECs) [11][12][13]. Therefore, it seems plausible that EVs from most cell types of the cardiovascular system participate in the atherosclerotic process. It should be taken into consideration that isolation of EVs from tissues (by homogenization, dissociation, or disruption) preserving their intact biochemical properties is still a challenging procedure that should be further developed. Nevertheless, the landmark study from Leroyer et al. [12] reported that plaque EVs derive mainly from white blood cells (WBCs), demonstrating the existence of an inflammatory milieu. Of interest, plaque EVs favored the balance towards a proinflammatory environment in the culprit lesion [14] and induced T-cell proliferation in a dose-dependent manner, contributing to vascular inflammation and plaque development [13]. A growing body of evidence supports the notion that immuno-inflammation plays a role in the pathogenesis of

atherothrombotic disease either by promoting the disease or lesion resolution and vascular repair. The following sections will unravel the immuno-modulatory effect of EVs in the different stages of atherothrombotic disease.

2. Atherogenesis

Endothelial dysfunction (ED) characterized by a proatherogenic environment is an early sign of atherosclerosis development [1]. Under pathological conditions, such as risk factors or injury, circulating EVs contribute towards a dysfunctional endothelium [15][16][17][18][19][20][21][22][23][24][25][6]. Beyond the well-studied traditional cardiovascular risk factors, atherothrombosis is spearheaded by multiple risk factors such as clonal hematopoiesis and air pollution [26]. It has recently become apparent that particulate matter (PM) could induce an inflammatory response and EC damage favoring the initial formation of atherosclerotic lesion. EVs derived from PM-exposed alveolar epithelial cells fueled inflammatory signaling via inhibitor of the nuclear factor kappa alpha (IκBα)–nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)–vascular cell adhesion protein 1 (VCAM1) axis [27]. Nevertheless, EVs shed after PM exposure could also mediate crosstalk between EC-immune cells to cope with the inflammatory assault [28], a response impaired in overweight subjects at increased cardiovascular risk [29].

EVs of several cellular origins (mainly derived from ECs) upon distinct inflammatory stimuli (oxidized low-density lipoprotein (LDL), angiotensin II, hypertension, visceral adipose tissue, and infection) or isolated from diseased patients (circulating EVs) directly cause harmful effects on physiological EC function and vasorelaxation by impairing nitric oxide (NO) bioavailability via regulation of NO, nitric oxide synthase, nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase, and prostacyclin as well as reactive oxygen species (ROS) and endoplasmic reticulum stress [30][31][32][33][34][35][36][37]. RBCs play key roles in vascular homeostasis. Not only altered RBC function but also RBC-derived EVs could reduce NO bioactivity and induce ED [38][39]. Likewise, excessive erythrocytosis exhibited by Andean highlanders also induce ED by means of dysfunctional circulating EVs [40]. Extracellular signal-regulated kinase (ERK) 1 embedded in platelet EVs from a mouse model of diabetes induce ED via intracellular adhesion molecule 1 (ICAM-1) [41]. Senescent EC-derived MVs (eMVs) from ACS patients induce premature ED and thrombogenicity through the angiotensin II–induced NADPH oxidase system [42]. On top of this detrimental vascular effect, EVs are also responsible for endothelial permeability [43][44]. Several works suggest that the disturbance of EC barrier function could also be mediated through apoptosis by EVs [45][46][47][48], whereas other studies ascribe to them a protective role as a way of reducing intracellular levels of caspase-3 [49]. Along the same line, Jansen et al. showed that eMV uptake in ECs via annexin I/PS receptor-p38 signaling protects against apoptosis [50]. Li et al. have demonstrated that endothelial progenitor cell (EPC)-derived EVs inhibit ferroptosis and alleviate atherosclerosis vascular injury via the miR-199a-3p/specificity protein 1 axis [51]. Of interest, EVs in basal conditions or from healthy subjects do not show deleterious effects to the vascular wall [52][53], highlighting that the impact of EVs in vivo is cell source- and context-dependent [54][55][56][57][58].

3. Atheroinflammation

An additional key feature of early atherosclerosis is the activation of the endothelium and, subsequently, the adhesion and recruitment of immune cells to the vasculature [59]. Importantly, EVs contribute in a multifaceted fashion to instigate vascular inflammation by increasing levels of adhesion molecules, ROS, and proinflammatory cytokines (e.g., interleukin (IL)-6 and -8) [60][61][62][63]. Specifically, platelet-derived EVs (pEVs) have shown in vitro to enhance the expression of adhesion molecules including E-selectin, ICAM-1, and VCAM-1 [64][65]; thus, favoring the adhesion of monocytes to the inflamed endothelium. Of note, P-selectin-enriched pEVs were found to promote leukocyte–leukocyte interactions leading to monocyte diapedesis through the endothelium even when flow conditions were not favorable [66]. Such chemo-attraction can be regulated by multiple mechanisms such as the transfer of Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) protein to ECs [67] and might contribute to long-term leukocyte differentiation [68]. In this regard, apoptotic-platelet-derived EVs can mediate the polarization towards M2 monocyte and resident macrophages. pEVs not only facilitate leukocyte adherence to the arterial wall but also to the atherosclerotic plaque [69]. In contrast, pEVs can also reshape the secretome of angiogenic early outgrowth cells (EOC) magnifying EOC-driven endothelial regeneration and promoting vascular protection [70]. Latter findings emphasize the importance of the environment in the final EV-directed effect.

A similar effect of chemo-attraction and transmigration of leukocytes to ECs towards the plaque is induced by EVs from other cellular sources [71]. Of note, neutrophil-derived EVs (nEVs) cause myeloperoxidase-mediated damage of vascular ECs [72]. nEVs shuttle Cox-1 substrate arachidonic acid (AA) from neutrophils to platelets, thereby fostering thromboxane A2, EC activation, and neutrophil recruitment in an experimental model of pulmonary hypertension [73]. Thus, nEVs are involved in platelet–neutrophil crosstalk. Leukocyte-derived EVs released upon proinflammatory triggers can adhere to ECs and promote further leukocyte adhesion in a positive feedback loop [74][75][76]. One of the mechanisms by which EVs

exert their proinflammatory activity is by harboring mitochondria or mitochondria-derived proteins, the so-called mitovesicles [77][78]. Extracellular mitochondria cause inflammatory responses to injury because they bear damage-associated molecular patterns [79][80], mitochondrial DNA [81], and oxidized proteins [82]. For instance, monocyte-derived mitovesicles can induce type I interferon and tumor necrosis factor (TNF)α response in ECs [83]. It has also been described that coronary artery disease (CAD) patients with low levels of mitochondrial oxidase subunit I in monocyte-derived EVs are at higher risk for new cardiovascular events [84]. pEVs released from thrombin-stimulated platelets also have embedded mitochondria that act as a substrate for phospholipase A2 IIA [85]. Altogether, EVs selectively enriched with mitochondrial material promote the expression of inflammatory mediators and drive leukocyte recruitment in the vasculature. Another mechanism involved in the vascular pro-inflammatory milieu is the exporting and transferring of miRNAs to target cells. Endothelial-derived EVs (eEVs) have shown to transport miRNA-155 and reprogram monocytes into an M1 proinflammatory phenotype [86] and miRNA-92a to macrophages promoting an atheroprone phenotype [87]. Not only miRNAs but also post-translational modifications can influence EV-driven inflammatory signals to ECs. Recently, Yang et al. have shown that monocyte–EC interactions responsible for EC inflammatory phenotype depend on EV-associated glucose transporter 1 and glycosylation [88].

Conversely, EVs can also act as inflammatory repressors. Endothelial-derived EVs bearing the endothelial protein C receptor-activated protein C complex induce protease-activated receptor (PAR) 1-dependent survivable, cytoprotective, and anti-inflammatory effects on ECs [89]. MVs derived from lipid-loaded macrophages ($CD16^+$) and containing LRP5 induce anti-inflammatory phenotypes in macrophages in an autocrine and paracrine fashion [90]. The EC-derived miRNA-143/-145 cluster is delivered to adjacent smooth muscle cells, through a MVs-mediated mechanism, to induce a vasculoprotective phenotype [91]. Neutrophil-derived EVs induce the release of transforming growth factor (TGF) β1 from macrophages with anti-inflammatory effects [92] that could be reinforced by the expression of annexin I on the surface of nEVs [93]. Moreover, ICAM-1 is downregulated by miRNA-222 embedded in eEVs [94]. Another example of a favorable vesicle-mediated miRNA transfer is the anti-inflammatory miRNA-10 targeting monocyte NF-κB pathway [95]. When EVs are taken up by B cells and monocytes, they are able to reprogram target cells towards an anti-inflammatory profile dependent on distinct factors [96]. Continuing with this dichotomy of pro- and anti-inflammatory properties of EVs and in an attempt to untangle the particular contribution of each vesicle subtype to the early phase of atherosclerotic disease, Hosseinkhani et al. provided evidence of a differential immunomodulatory content (inflammatory signals, chemokines, and cytokines) between small and large EVs released from activated ECs [97][98]. Specifically, sEV stimulate monocyte migration while lEVs are prompt to induce ICAM-1 expression and inflammation profile in target cells.

Even though most of the data regarding EVs as pro- and anti-inflammatory mediators in atherosclerosis derives from in vitro models, several studies with EVs from pathological conditions have been conducted [99][100][101][102][103]. Deepening to the mechanism, monocyte-derived EVs carrying IL-1β are involved in EC activatio [76] and, consistently, IL-1β-rich eEVs in inflammation in the setting of ACS [104]. Remarkably, MVs within atherosclerotic plaques are able to recruit pro-inflammatory cells through transfer of ICAM-1 to ECs [105].

In addition to chronic vascular inflammation, atherosclerosis is also characterized by an impaired resolution response leading to non-resolving inflammation persistence. EVs circulating in plasma could also exert such immunomodulatory potential in atherosclerosis. For instance, deregulated anti-inflammatory and pro-resolving molecules (CD5L and Resolvin E1 bioactive lipid mediator) in circulating EVs contribute to the systemic hyperinflammation in the context of chronic liver disease [106]. In atherosclerotic inflammation, miR-155 was found decreased in a model of atherosclerosis regression and increased in urinary EVs (uEVs) from unstable CAD patients. Interestingly, CAD progression was associated to increased $CD45^+$ and $CD11b^+$ uEVs, and decreased in $CD16^+$ uEVs, pointing at miR-155 and uEVs as a potential prognostic marker of disease progression and severity and a therapeutic target [107].

4. Lesion Progression

4.1. Atherogenic Foam Cell Formation

The adaptive immune system appears at the center of human ASCVD development. Oxidized (ox-LDL) and aggregated LDL particles are taken up by the macrophages that, by removing the excess of lipids, become foam cells. As a consequence, macrophage lipid accumulation via shedding of EVs (1) inhibits their clearance [108], (2) leads to the formation of oxidation-specific epitopes in a subset of cholesterol-induced EVs [109], and (3) amplifies the inflammatory response. For instance, monocyte-derived EVs promote T-cell infiltration in atherosclerotic plaques [110]. More specifically, macrophages have shown to promote proinflammatory and proatherogenic phenotypes in recipient cells through secretion of EVs conveying miRNAs. Upon lipid uptake, atherogenic (cholesterol-loaded) macrophages secrete EVs and deliver miRNA-146a to naïve macrophages where it represses the expression of specific promigratory target genes (insulin-like

growth factor 2 mRNA-binding protein 1 and human antigen R), leading to decreased macrophage migration and potential entrapment in the atherosclerotic plaque [108]. Finally, MV-mediated miR-223 transfer reinforces the macrophage activation loop [111]. Ox-LDL also induces EV release from ECs containing miR-155 which promotes M1 macrophage polarization [86]. Indeed, beyond macrophages and foam cells, ECs and platelets also secrete EVs that regulate macrophage polarization and contribute to atherosclerotic plaque progression. TNFα or low shear stress-induced EC-derived EVs also target macrophages [112]. Activated pEVs stimulate ox-LDL phagocytosis and inflammatory cytokine release by macrophages [113]. Thereafter, macrophages and foam cells undergo apoptosis, either by their phagocytosis of ceramide and AA-rich EVs [45][114] or by the EV-driven transfer of programmed-cell-death-related caspases [115] even in SMCs [48]. Lymphocyte accumulation in inflamed arteries can also display a regulatory and atheroprotective function. B-cell-derived natural IgM recognizes EVs bearing oxidation-specific epitopes and represses their inflammatory signaling and pathological endeavors [116]. Moreover, natural IgM antibodies inhibit MV-driven coagulation and thrombosis [117].

4.2. Vascular Smooth Muscle Cell Proliferation, Migration, and Phenotype Switching

During lesion growth, vascular smooth muscle cells (VSMC) located in the media change from a contractile to a proliferative phenotype and migrate into the intima layer. VSMC cell proliferation and migration, another key step in the development of atherosclerosis, is also influenced by EVs either from platelets [118] or foam cells [119]. Platelet-released EVs induce a pro-inflammatory phenotype in VSMC affecting vascular remodeling [118]. In addition, platelet-derived MVs have shown to promote VSMC proliferation and migration via a platelet-derived growth-factor-independent mechanism [120][121] and calcium oscillations and transient receptor potential vanilloid 4 [122], respectively. Macrophages release EVs rich in cholesterol that can be taken up by VSMC [123]. The contribution of macrophage foam cell-derived EVs to enhance VSMC adhesion and migration was shown by the transfer of integrins and subsequent downstream activation of ERK and Ak strain transforming (AKT) [119] and the transport of miR-19b-3p and targeting juxtaposed with another zinc finger gene 1 [124]. Those EVs rich in tissue factor (TF) have the capacity to modulate VSMC migration though PAR interaction [125]. Another study found that VSMC-derived EVs intervene in autocrine VSMC proliferation by upregulation of mitogen-associated protein kinase [126]. Interestingly, other studies address this question with a translational perspective. EVs bearing Ras-related protein 1 from patients with metabolic syndrome favored VSMC migration and proliferation [127]. Plasma EV containing miRNA-501-5p promotes VSMC phenotypic modulation through targeting Suppressor of mothers against decapentaplegic homolog (Smad) 3 in patients with in-stent restenosis one year after coronary stent implantation [128]. Conversely, several studies emphasize the fact that EVs and their miRNA content present an atheroprotective effect on VSMCs. In this regard, miRNA-223-EVs inhibited VSMC migration and proliferation, thereby decreasing plaque size [129]. Similarly, both high shear stress and Krüppel-like factor 2-expressing ECs-derived EVs enriched in the miR-143/145 cluster prevented VSMC dedifferentiation [91]. Moreover, macrophage-derived EVs also transmit miR-503-5p into VSMCs and inhibit their proliferation and migration via the Smad7-Transforming growth factor-β axis [130]. Finally, MVs reduced VSMC proliferation, migration and subsequent neointima formation by delivering functional miR-126 into recipient VSMCs [130]. Even EVs from adipose mesenchymal stem cells were involved in the regulation of VSMC phenotype to limit intimal hyperplasia [131].

4.3. Intravascular Calcification

Under pathological stimuli, EVs released by VSMCs and macrophages aggregate between collagen fibers and serve as a platform for ectopic mineralization eliciting micro- and macrocalcifications in the vessel wall. Vascular calcification in atherosclerosis shows a bimodal behavior in terms of risk and impact; while it has been shown that microcalcifications have a burdening effect on plaque rupture due to the low number of inflammatory cells and being more prone to rupture, higher amounts of calcification within stable plaques at various phases of atherosclerosis progression have also been found. Cellular-derived EVs from VSMCs, ECs, and platelets indisputably regulate the loss of the VSMC contractile phenotype and impact vascular calcification [132][133][134] favoring plaque calcification and atherogenesis [135][136][137][138]. EVs from dysfunctional endothelium [139] and senescent ECs [133][140] promote vascular calcification. VSMCs also release calcifying EVs themselves [141][142]. One described mechanism driving the VSMCs towards calcification involves the regulation of calcifying EVs by sortilin [141]. Oxidative stress also intervenes in this process. VSMC phenotype switching caused an increased Nox5 expression that was responsible for the subsequent extracellular calcium entry, ROS production, reduced contractile phenotype, and enhanced EV release fostering VSMC calcification [143].

4.4. Necrotic Core

EV-mediated cell death [48][114] triggers necrotic core formation and, in turn, lipid-rich necrotic core contains high amounts of thrombogenic EVs as well [12][13][144], conferring a procoagulant potential and instability to the atherosclerotic lesion and shifting towards a vulnerable plaque.

5. Advanced Lesion and Plaque Rupture

Atherosclerotic plaque erosion or rupture and the subsequent thrombosis leads to, eventually, acute ischemic syndromes. The interdependence between innate immune cells and platelets is essential for plaque destabilization and thrombotic occlusion [145][146].

5.1. Arterial Neoangiogenesis and Intraplaque Hemorrhage

During the last steps of atherosclerosis development, an increased number of vasa vasorum brings about intraplaque hemorrhage, a highly inflammatory environment, and a rapid activation of the coagulation cascade and platelet aggregation forming a fibrin mesh [147][148]. Several studies support the notion that EVs exert regulatory roles in these events [149][150]. EPC-EVs activate ECs and stimulate angiogenesis [151]. Inflammation-induced EC-derived EVs enhanced vascular endothelial growth factor B expression in pericytes, which in turn might mediate pathological neovascularization and vascular leakage in response to an inflamed endothelium [152]. Atherosclerotic EC-released EVs promoted angiogenic responses in ECs by a thrombospondin-1-depedent mechanism [87]. Communication between ECs and immune cells plays key roles in disease development. Spleen EC-derived $VCAM1^+$- EVs mobilize splenic monocytes in myocardial infarction (MI) [153]. It has been reported that hypoxic ECs release endothelial-cell-derived MVs rich in TF and transport miRNA-126 that induces monocyte recruitment into the ischemic zone, reprogramming of monocytes and their differentiation into EC-like cells, and angiogenic response, which altogether improve tissue reperfusion [154],[155]. Of note, TF-containing eMVs could interact via paracrine signaling with other microvascular ECs and trigger angiogenesis ex vivo and postischemic collateral vessel growth in vivo [156]. MVs from human atherosclerotic plaques promoted in vivo angiogenesis [157]. Of interest, in vitro studies showed that the mechanism was mediated by MVs expressing the CD40 ligand [157]. Similarly, MVs from ischemic muscle induced postnatal vasculogenesis [158]. Fibrinolytic activity of EC and WBC-derived EVs could also favor angiogenesis and hamper thrombus dissolution [159]. Furthermore, Loyer et al. found that small and large cardiomyocyte-derived EVs are locally released from the heart to regulate the inflammatory process in a mouse model of myocardial ischemia [160]. Indeed, ischemia-induced cardiosomes stimulate cardiac angiogenesis both in vitro and in vivo [161]. Besides intraplaque neovascularization and bleeding, plaque, EC, and immune-cell-derived EVs influence endothelium denudation and fibrous cap integrity. EVs exert structural extracellular matrix degradation and fibrous cap weakening via metalloprotease activities [14][162][163][164][165][166][167][168]).

5.2. Thrombus Formation after Rupture

Fibrous cap disruption within the atherosclerotic plaque results in the exposure of subendothelial extracellular matrix (collagen and von Willebrand factor) and thrombogenic substances and, thus, a huge release of tissue factor triggering platelet activation, aggregation, and thrombus formation in the damaged area [169]. EVs from platelet/monocyte aggregates are capable of modulating human atherosclerotic plaque reactivity [170]. Under in vitro simulated conditions of coagulopathy, EV from different cellular origins (EC and platelet) and at distinct concentrations showed a divergent but procoagulant effect within the coagulation process [171]. Numerous studies have dissected in vitro and in vivo the procoagulant effect of EVs, mainly MVs, leading to thrombosis [117][172][173][174][175][176][177][178][179][180][181][182]. Procoagulant EVs within the necrotic core of atherosclerotic plaques provoke the burst of the coagulation cascade upon plaque rupture [144] being TF^+-MVs the main initiators [183][184][185]. TF is functionally transferred to monocytes through MVs [186] in a PAR2-filamin A-mediated process [187]. The fact that the proinflammatory cytokine IL-33 [188] and EC-derived EVs [189] trigger the release of procoagulant TF^+-MVs underscores the synergy between inflammation and thrombosis. TF^+-MVs are also engulfed by platelets and trigger platelet aggregation [190][191]. In addition, TF-rich monocyte-derived EVs are recruited at the thrombus site [192]. TF shares the limelight of plaque thrombogenicity with phosphatidylserine. Negatively charged PS exposure in EV surface confers procoagulant activity [193], enables the concentration of factors VII/VIIa in the EV membrane [194], enhances platelet adhesion to the endothelium, and it is important for TF function, thrombin generation, and clot formation [195]. Beyond these two key factors (TF and PS), EVs were shown to directly modulate the clotting. A seminal study on leukocyte-derived EVs expressing P-selectin glycoprotein ligand-1 (PSGL-1) on their surface deconvolutes the crosstalk between platelets and TF-rich immune cells at the lesion site. Interactions between platelet adhesion molecule P-selectin and $PSGL\text{-}1^+$-EVs allowed higher recruitment and activity of TF perpetuating thrombus formation [196]. Not only WBC-derived EVs participate in this dynamic process, circulating and platelet-derived MVs also enhance thrombus formation and growth on thromboactive substrates [180]. It has also been found that pEVs bearing surface epitopes of platelet adhesion and activation in perfused blood tend to bind more to adhered platelets and prothrombotic surfaces stimulating further platelet deposition and thrombus growth [182]. Interaction of platelets with subendothelial matrix, immobilized platelet surfaces [197], or fibrin [198] depends on pEV-associated αIIbβ3a integrin [199].

Several other platelet biological components contribute to this phenomenon such as protein disulphide isomerase [200], factors VIII and Va [201][202], and bioactive lipids [203]. Platelet-derived EVs also modulate EC–monocyte interactions [64] likely inducing enhanced expression of cell adhesion molecules under high shear stress conditions [65]. Interestingly, pEVs support megakaryocyte differentiation and platelet production that is relevant to keep a physiological level of circulating platelets after their consumption during thrombosis [204]. Recently, researchers have investigated the proteostatic characteristics of EVs shed from platelets upon thrombin activation by an untargeted proteomic approach [205]. Proteins involved in cell–cell interaction and signaling events underlying thrombus formation have been identified such as CUB domain-containing protein-1 or membrane glycoprotein gp140, fermitin family homolog 3 or kindlin-3, and the novel pEV-associated protein protocadherin-α4, among others. Deciphering platelet and cell signaling and biology by proteomics technique [205][206] will help to unveil paracrine regulation of EVs and provide new therapeutic targets involved in occlusive thrombus formation and atherothrombosis.

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