Extracellular Vesicles in Renal Disease

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Autoimmune diseases are rare conditions with high mortality and morbidity, particularly when the kidney is involved. Extracellular vesicles (EV) act as regulators of the inter-cellular signals and modulate the immune system. This review focus on the potential contribute of EV on the pathophysiology of Systemic Lupus Erythematosus (SLE), Antiphospholipid syndrome (APS), Thrombotic Microangiopathy, and ANCA-vasculitis. Of interest, EV were recognized as novel biomarkers of disease activity in APS and ANCA-vasculitis. EV are also involved in the pathogenesis of SLE, and particularly in the renal injury associated with the lupus nephritis. This implies that to explore EV for disease biomarker discovery and to investigate their potential as therapeutic targets in autoimmune diseases should be the future challenge.

Keywords: renal disease ; autoimmune diseases ; HUS ; TTP ; APS ; antiphospholipid syndrome ; vasculitis

1. Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent arterial or venous thrombosis and/or obstetric complications in the presence of antiphospholipid antibodies (aPL). APS is the most common cause of acquired thrombophilia and is associated with decreased survival. A severe form of APS, termed catastrophic antiphospholipid syndrome, occurs in <1% of patients with aPL and is associated with high mortality [1]. Despite the clinical relevance of this syndrome, its pathogenesis is not yet fully understood and recent studies have focused on EV as potential damage mediators.

Various studies have reported an increased level of EV in APS patients. Štok et al. [2] have compared APS patients, patients with idiopathic thrombosis and healthy controls and found that circulating EV were increased in patients with a history of thrombotic events (APS patients and patients with idiopathic thrombosis) compared to healthy subjects, suggesting a chronic cell activation even in the absence of an acute thrombotic event. This study demonstrated the presence of platelet, endothelial cell, lymphocyte, antigen-presenting cell-derived EV in patients with a history of thrombosis as well as in healthy controls. These EV express molecules involved in platelet/endothelial function, immune regulation extracellular matrix regulation and cell-to-cell adhesion. The analysis of EV surface proteins demonstrated an increased expression of CD8, CD44, CD133/1 and CD62P in the aPL patients. The increased expression of CD133/1 and CD62P on the EV surface in APS patients could reflect the increased endothelial and platelet activation, respectively, and their possible contribution to the thrombotic events [2]. Endothelial- and platelet-derived EV were increased in aPL patients, suggesting a chronic activation of endothelial cells and platelets. Interestingly, a correlation between the level of endothelial-derived EV and the level of anti-β2GPI has been demonstrated which closely correlates with thrombosis [3].

Breen et al. [4] have shown an increased level of endothelial- and platelet-derived EV in aPL patients compared with healthy subjects, while no difference between obstetric APS or asymptomatic aPL patients was detected. Moreover, plasma from patients with APS and from patients with SLE aPL+ or SLE aPL- increased the release of EV from cultured endothelial cells compared to the plasma of healthy subjects. Of note, only plasma from APS patients caused the release of EV with significant procoagulant activity [5]. aPL induces tissue factor (TF) synthesis in endothelial cells in vitro, and it has been reported that TF+ EV are elevated in aPL+ patients [3]. In particular, TF expression on endothelial-derived EV is increased in APS patients compared to healthy subjects [6]. Moreover, Willemze et al. [7] have demonstrated that EV from APS patients display a higher TF activity compared to asymptomatic aPL+ patients.

More recently, Mobarrez et al. [8] have compared anti-β2GPI-positive SLE patients, aPL-negative SLE patients and healthy controls. They found that SLE patients are depleted of β2GPI-positive EV when compared to healthy subjects, and their level is particularly low in anti-β2GPI-positive patients. They also found that β2GPI preferentially binds to the phosphatidylserine (PS)-positive EV, thus suggesting that anti-β2GPI antibodies may bind to the β2GPI-PS complexes on EV resulting in the loss of EV β2GPI expression. β2GPI promotes the clearance of PS+ EV, thus the increased number of PS-negative EV may act as a possible source of autoantigens and thus trigger the autoimmune response [8].

Regarding obstetric APS, pregnant women with APS had increased PS+ EV, endoglin+ EV and endothelium-derived EV compared to healthy controls in the first and second trimester of pregnancy. Conversely, in the third trimester, higher levels of TF+ EV and platelet-derived EV can be detected. According to the authors, this finding could reflect the activation of both endothelial cells and platelets during pregnancy. In particular, high-risk APS patients (triple aPL positivity plus vascular thrombosis and/or severe pregnancy complications/placental insufficiency) have higher endoglin+ EV, TF+ EV and platelet derived-EV in all three trimesters, sustaining a major vascular activation. Interestingly, endoglin is expressed by vascular endothelium and by syncytiotrophoblasts and altered levels of soluble endoglin are linked to vascular disorders as pre-eclampsia [9].

In conclusion, patients with aPL have an elevated level of circulating EV, which may reflect a state of systemic vascular activation. EV have been shown to act as procoagulant and proinflammatory mediators, thus their level may correlate with the thrombotic risk. However, at present, a clear relationship between elevated EV levels and thrombotic events is still missing (Table 1).

Table 1. Extracellular vesicles in antiphospholipid syndrome (APS).

Study	EV Biomarkers	Cellular Origin of EV	Study Findings	Reference
Štok, U.; et al.	CD8, CD44, CD133/1, CD62P	Platelets, endothelial cells, lymphocytes, antigen-presenting cells	EV increased in patients with thrombotic events EV reflect endothelial and platelet chronic activation	[2]
Chaturvedi, S.; et al., Breen, K.A.; et al.	CD41, CD61, CD51, CD105	Endothelial cells, platelets	EV increased in aPL+ patients EV reflect endothelial and platelet chronic activation	[3][4]
Chaturvedi, S.; et al., Willemze, R.; et al.	Tissue factor (TF)	Endothelial cells	TF + EV increased in APS TF activity increased in EV from aPL+ patients	[3][7]
Mobarrez, F.; et al.	β2GPI+		EV β2GPI+ reduced in SLE aPL+ Anti-β2GPI may bind to β2GPI expressed by EV	[8]
Campello, E.; et al.	Phosphatidylserine (PS), Endoglin, Tissue factor (TF)	Endothelial cells, platelets	PS+ EV, endoglin+ EV and endothelium-derived EV increased in 1st and 2nd trimester of pregnancy; TF+ EV and platelet-derived EV increased in 3rd trimester of pregnancy Correlation with thrombosis and systemic platelet and endothelial activation in obstetric APS	[9]

2. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of autoantibodies against nuclear antigens and the deposition of immune complex (IC) leading to systemic inflammation and tissue damage. Lupus nephritis (LN) is one of the most severe organ manifestations and a primary cause of morbidity and mortality [10].

Studies on circulating EV in SLE patients revealed divergent results regarding their circulating level and characterization. EV were found increased in SLE [11][12], or decreased compared to healthy controls [13]. Those different results reflect the lack of standardized methods for EV evaluation and characterization.

In SLE, circulating EV expose chromatin on their surface and may represent a source of nuclear antigens which can bound both the IgG and the complement, resulting in the formation of IC, which correlate with the disease activity and the vascular damage [12][14]. Circulating EV can bind both IgG and IgM to form immune complexes (EV-ICs) and EV-IgG+ were positively correlated with the disease activity. Platelet-derived EV (PEV), mainly PEV-IgG+, stimulated monocytes in vitro changing their phenotype and promoting their inflammatory response [12]. Several studies have supported the role of the deoxyribonuclease DNASE1L3 as a genetic determinant of susceptibility [15][16]. Sisirak et al. [17] have found that DNASE1L3 can digest chromatin in apoptotic cell-derived EV and, in the absence of DNASE1L3, EV-associated DNA may gather in an extracellular environment and promote autoantibody production by autoreactive B cells. DNASE1L3 is produced by dendritic cells and macrophages, and its circulating level was inversely correlated with anti-dsDNA level [17].

Platelet activation plays a key role in the pathogenesis of SLE. They promote T and B cell activation, NETosis, type I IFN production, and dendritic cell activation resulting in systemic organ damage. Platelet-derived EV are the most prevalent circulating EV in healthy subjects, while conflicting results have been reported regarding platelet-derived EV in SLE. Burbano et al. [12] have found an increased number of circulating EV (mainly platelet-derived EV) in patients with SLE compared to healthy controls. However, platelet-derived EV level was unrelated to disease activity measured with SLEDAI score. Lopez et al. [18] have observed an increased level of platelet-, monocyte- and T lymphocyte-derived EV. Interestingly, the authors found that EV level is influenced by the disease activity and is related to the activation status of blood parental cells. They also reported that glucocorticoid therapy may influence EV production and T cell activation, as EV from patients treated with glucocorticoids induced the upregulation of CD25 and the accumulation of IL-10 in T cells [18]. Moreover, circulating platelet-derived EV correlated with endothelial-independent vasodilatation in SLE [19].

Patients with SLE have increased cardiovascular risk due to platelet activation and systemic endothelial activation. EV may be involved in this process, as EV and EV-ICs from SLE patients can activate endothelial cells by increasing the expression of adhesion molecules (CD54, CD102), the production of chemokine (CCL2, CCL5, IL-6) and the adherence of monocytes. EV may also mediate endothelial injury by increasing endothelial permeability through the alteration of cytoskeletal proteins leading to adhesion and migration of monocyte to the inflamed organs [20].

Polymorphonuclear leukocytes (PMNs) are greatly involved in SLE pathogenesis, as PMNs showed generalized hyperactivity, with enhanced apoptosis and increased production of neutrophil extracellular traps (NETs) [21]. Moreover, increased oxidative stress has been observed in SLE, which may contribute to immune dysregulation [22]. Winberg et al. [23] have found that EV from SLE patients induced ROS production in the patient's own PMNs re-suspended in autologous serum, particularly in patients with low circulating C3 level, which reflects disease activity. The ROS production partly depends on EV properties, serum components (including autoantibodies) and PMN hyper-responsiveness [23].

In vitro studies have shown the proinflammatory effect of EV on blood-derived plasmacytoid dendritic cells and myeloid dendritic cells by increasing the expression of costimulatory molecules (CD40, CD80, CD83, CD86) and the release of proinflammatory cytokines (IL-6, TNF, IFNα). Moreover, EV enhanced the formation of neutrophil extracellular traps (NETs) which may represent a source of nuclear autoantigens thus contributing to the pathogenesis of SLE and renal inflammation [24]. EV from patients with active LN contain a higher level of acetylated chromatin compared to patients with remissive LN, without LN, or healthy controls. Rother et al. [25] have found that the degree of EV acetylated chromatin determines their strength to stimulate neutrophils to form NETs.

According to proteomic and flow cytometry analysis, circulating EV in SLE patients have an increased content of IgG and galectin-3 binding protein (G3BP), a glycoprotein that may contribute to the pathogenesis of SLE. G3BP is induced by type I IFN and exhibits a high binding capacity toward components of the glomerular basement membrane (GBM) [26], including collagen IV, fibronectin and galectin-3. Interestingly, patients suffering from lupus nephritis show a glomerular G3BP/IgG co-localization pattern specifically in the GBM, suggesting the presence of G3BP in the IC delivered either by EV from the circulation or locally formed [27]. In SLE patients, in vitro stimulation of peripheral blood mononuclear cells (PBMCs) with TLR-9 agonist increases the release of EV expressing both G3BP and dsDNA. This was particularly relevant in patients with active LN, compared to healthy donors [28].

Urinary EV may reflect structural damage and renal dysfunction, and they have been investigated as potential LN diagnostic and prognostic biomarkers. Urinary podocyte-derived EV reflecting the glomerular podocyte damage are increased in LN and SLE patients compared to healthy controls. Interestingly, urinary EV level is correlated to the SLE disease activity index (SLEDAI) score, anti-dsDNA antibodies titer, proteinuria and histopathological lesions [29]. A recent study demonstrated that urinary EV expressing the high-mobility group box 1 molecule (HMGB1) are higher in SLE patients with active LN than in those without renal involvement, and correlate with proteinuria. HMGB1 is involved in the pathogenesis of several autoimmune diseases and it may be an important mediator in LN. Indeed, its expression is increased in glomerular endothelium and mesangium, and its blood and urinary level is increased in LN [30].

Several studies have identified EV-derived miRNA as markers of renal damage which can also discriminate active LN [31]; miR-21, miR-150, and miR-29c were correlated to renal fibrosis and could predict the progression to the end-stage renal disease [32][33]. A unique circulating miRNA expression profile was detected in class IV LN [34] and urinary EV-derived miRNA have been proposed as peculiar biomarkers of class IV LN [35].

Recently, Garcia-Vives et al. investigated the miRNA expression profile of urinary EV in proliferative LN as a new potential prognostic biomarker. Patients with clinical responses to therapy are characterized by an increased level of miR-31, miR-107, and miR-135b-5p in urine and in renal tissue (mostly localized in epithelial tubular cells), compared to non-responder patients. In vitro stimulation of tubular epithelial cells with proinflammatory cytokines increases the release of these miRNA, which can be taken up by endothelial cells and mesangial cells in responder patients [36].

Recent studies have evaluated the role of mitochondria in autoimmune diseases. Activated cells can release EV containing mitochondria or free mitochondria which may stimulate immunity. Mobarretz et al. [37] have demonstrated the presence of circulating particles (approximately 3 µm), and among them, a population of large EV carrying mitochondrial molecules (mitoEV) were found that both increased and associated with the disease activity in SLE patients. Furthermore, patients suffering from active LN have higher levels of mitoEV and IgG-coated mitoEV, suggesting that they may contribute to the formation of IC and thus be involved in renal damage [37].

In conclusion, EV may play a crucial role in the pathogenesis of SLE, and particularly in LN-associated renal injury. For these reasons, EV have been proposed as potential biomarkers of disease in SLE patients as well as early biomarkers of renal damage in LN (Table 2).

Table 2. Extracellular vesicles in systemic lupus erythematosus.

Study	EV Concentration	Cellular Origin of EV	EV Pathological Significance	Reference
Burbano, C.; et al.	Increased in SLE compared to healthy controls	platelet	Formation of immune complexes, source of nuclear antigens, correlation with disease activity	[12]
López, P.; et al.	Increased in SLE compared to healthy controls	platelet, monocyte, T lymphocyte	EV level correlated with: disease activity, glucocorticoid therapy, endothelial vasodilatation	[18]
Atehortúa, L.; et al.			Endothelial cell activation, endothelial injury,	[20]
Winberg, L.-K.; et al., Dieker, J.J.; et al., Rother, N.; et al.			In vitro stimulation of polymorphonuclear leukocytes with EV from SLE patients increased ROS production EV promote neutrophil activation and NETs production	[23][24][25]
Nielsen, C.T.; et al., Rasmussen, N.S.; et al.			IgG/galectin-3 binding protein (G3BP)+ EV are involved in the pathogenesis of lupus nephritis	[27][28]
Lu, J.; et al., Vanegas-García, A.; et al.	Urinary podocyte-derived EV increased in SLE	Urinary EV	Urinary podocyte-derived EV level correlated with systemic disease activity and renal injury Urinary EV high-mobility group box 1 molecule (HMGB1)+ were found to be higher in lupus nephritis	[29][30]
Felip, M.L.; et al., Solé, C.; et al., Navarro-Quiroz, E.; et al., Li, Y.; et al., Garcia-Vives, E.; et al.	EV derived miRNA		miR-21, miR-150, and miR-29c, miR-31, miR-107, and miR-135b-5p correlated with renal injury in lupus nephritis	[32][33][34][35][36]
Mobarrez, F.; et al.	EV containing mitochondrial molecules (mitoEV)		mitoEV were associated with disease activity, immune complex formation and renal damage	[37]

3. Thrombotic Microangiopathies

Thrombotic microangiopathies include different diseases characterized by microangiopathic hemolytic anemia and thrombocytopenia also potentially involving the kidney. Thrombotic microangiopathies include Shiga toxin-producing *Escherichia coli* (STEC-HUS) and thrombotic thrombocytopenic purpura (TTP).

Haemolytic uremic syndrome (HUS) is characterized by nonimmune microangiopathic haemolytic anemia, thrombocytopenia and acute kidney injury. Typical HUS is subordinate to Shiga toxin-producing *Escherichia coli* (STEC-HUS) infection, which first colonizes the intestine and produces the toxin which enters the bloodstream and causes renal injury.

In STEC-HUS, EV mainly derive from platelets, monocytes, neutrophils and red blood cells. Ståhl et al. have found EV expressing TF and phosphatidylserine potentially involved in the formation of microthrombi. Moreover, in the acute phase of the disease, circulating EV derived from platelets, monocytes, and neutrophils show deposition of C3 and C9 on their surface. Interestingly, EV also express phosphatidylserine, which activates the coagulation factor V and X, thus enhancing and promoting thrombosis [38]. Those findings may reflect the systemic complement activation and the role of EV in the inflammatory and thrombogenic events in HUS [39].

In vitro experiments showed that whole blood incubated with Shiga-toxin and/or STEC-lipopolysaccharide increased the release of TF-positive EV, C3- and C9-positive EV derived from platelets, monocytes and red blood cells [39][40]. It has been speculated that activated complement factors carried by EV can be transferred to recipient cells, driving cell damage [41].

Since STEC are non-invasive bacteria, a small amount of Shiga toxin is present in the circulation; however, EV may transfer the toxin to the kidneys via peritubular capillaries. EV containing Shiga toxin were found within the kidney into renal cells, and in vivo experiments showed that EV enriched in Shiga toxin can reach renal cells through the glomerular and tubular basement membranes. In vitro studies also demonstrated that EV undergo endocytosis in glomerular endothelial cells, leading to cell damage [42].

Shiga toxin interaction with circulating cells is mediated by two different receptors: the globotriaosylceramide (Gb3) toxin receptor and TLR4. Shiga toxin can be taken up by cells after binding to Gb3 or by cellular uptake of EV carrying the toxin derived from different host cells. EV expressing Shiga toxin are taken up by both Gb3-positive and Gb3-negative recipient cells. However, only Gb3-positive host cells are susceptible to toxin-induced cellular damage, reduced cellular metabolism and protein synthesis [43]. Of note, renal endothelial cells express both Gb3 and TLR4. In vitro experiments using soluble Shiga toxin have shown that TLR4 acts as a Gb3 coreceptor, thus facilitating renal cell injury [41].

TTP is a rare microangiopathic hemolytic anemia in which mutations of vWF protease (ADAMTS13) or autoantibodies against ADAMTS13 lead to the deposition of von Willebrand factor (vWF) multimers within capillaries. Systemic endothelial cell injury and platelet aggregation activate systemic microthrombosis mainly involving the brain and the kidney.

A comparison of circulating EV in TTP patients and healthy subjects has shown that platelet-derived EV are the most represented EV subtype in both groups. Moreover, in TTP patients the platelet-derived EV level is significantly higher, as are EV express markers of platelet activation such as CD62p. Interestingly, platelet-derived EV have a procoagulant activity greater than platelets due to phospholipid expression on their surface which triggers the coagulation cascade [44].

Other studies have found higher levels of platelet-derived and endothelial-derived EV in TTP. Endothelial-derived EV have shown procoagulant and proadhesive roles as they express CD62E (E-selectin), VWF, intercellular adhesion molecule 1 (ICAM-1), platelet endothelial cell adhesion molecules (PECAM-1; CD31) and endoglin (CD105) [45]. Tati et al. [46] have shown that circulating endothelial-derived EV are coated with C3 and C9 and complement activated on platelets and glomerular endothelium. Complement activation may represent an ancillary phenomenon to platelet activation and endothelial injury, and thus may drive the microangiopathic process [46].

Unfortunately, only a few studies have investigated the role of EV in TTP, and future research is needed to better understand the pathogenesis of TTP (Table 3).

Table 3. Extracellular vesicles in thrombotic microangiopathies.

Disease	Study	Cellular Origin of EV	EV Biomarkers	EV Pathological Significance	Reference
STEC-HUS	**Ståhl, A.-L.; et al., Arvidsson, I.; et al.**	**platelets, monocytes, neutrophils**	**Tissue factor, phosphatidylserine (PS), C3, C9**	**Promotion of thrombosis EV reflect complement activation**	**[40][38]**
STEC-HUS	**Varrone, E.; et al., Ståhl, A.-L.; et al., Johansson, K.; et al.**		**EV carrying Shiga toxin**	**Delivery system of Shiga toxin to the kidney involvement in renal cell injury**	**[41][42][43]**

Disease	Study	Cellular Origin of EV	EV Biomarkers	EV Pathological Significance	Reference
TTP	Tahmasbi, L.; et al., Jimenez, J.J.; et al.	platelets, endothelial cells	CD62E (E-selectin), VWF, intercellular adhesion molecule 1 (ICAM-1), platelet endothelial cell adhesion molecule (PECAM-1; CD31) and endoglin (CD105)	Pro-coagulant and pro-adhesive roles	[44][45]
TTP	Tati, R.; et al.	Endothelial cells	C3, C9	EV reflect complement activation	[46]

4. ANCA-Associated Vasculitis

Systemic vasculitis consists of different syndromes characterized by blood vessel inflammation and multiple organ involvement. Small vessel vasculitis is often associated with anti-neutrophil cytoplasmic antibodies (ANCA), predominantly IgG autoantibodies directed against neutrophil cytoplasmatic constituents such as proteinase 3 (PR3, named cANCA) and myeloperoxidase (MPO, named pANCA). ANCA-associated vasculitis (AAV) comprises microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's) (GPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA). AAV can affect small vessels in different organs resulting in pauci-immune glomerulonephritis, vasculitis involving the respiratory tract, and is associated with an increased risk of systemic thrombosis [47]. Despite new treatment options that have recently improved AAV prognosis, early diagnostic and prognostic biomarkers are still an unmet need.

Patients with AAV have an increased risk of thromboembolic events due to the hypercoagulable state [48]. ANCA can induce neutrophil activation, neutrophil degranulation and release of neutrophil extracellular traps (NETs), which are involved in the development of vasculitis lesions [49]. Moreover, complement activation via the alternative pathway is crucial for the development of the disease [50]. In vitro experiments have found that both pANCA IgG and cANCA IgG can stimulate C5a-primed neutrophils to produce TF-expressing EV and TF-expressing NETs which, in turn, promote thrombin generation and the activation of the coagulation cascade [51]. Notably, Mendoza et al. [52] have measured the TF activity of EV and found higher TF activity in patients with AAV and associated venous thromboembolism, compared to patients without thrombotic events [52].

Recent studies have demonstrated a potential role of platelet- and neutrophil-derived EV in the pathogenesis of vasculitis. Polyclonal ANCAs isolated from patients and chimeric PR3–ANCA induces the release of EV from primed neutrophils in vitro. Moreover, these EV are enriched in PR3 and MPO, exhibit thrombin-generating capacity, can bind the endothelium and induce its activation, induce ROS production and the release of proinflammatory cytokines (IL-6, IL-8) [53].

An increased level of circulating platelet-, neutrophil- and endothelial-derived EV in patients with vasculitis has also been found [54]. In particular, a high level of neutrophil-EV during the acute phase of the disease which decreased after steroid treatment has been reported, reflecting the key role of neutrophil activation. Of note, endothelial-EV level correlated with the Birmingham Activity Vasculitis Score (BVAS) and acute phase reactants, suggesting their potential application as disease biomarkers [54].

The kinin system contributes to the inflammatory response and the development of vasculitis. The kinins regulate local blood pressure, promote inflammation, and capillary leakage. The kinins achieve their effect through B2 and B1 receptors. The B2 receptor is constitutively expressed and involved in inflammation and hyperalgesia, while the B1 is upregulated during chronic inflammation (such as vasculitis), and controls neutrophil migration. Kahn et al. [55] have found increased circulating leukocyte-derived EV bearing the B1-kinin receptor during vasculitis. In particular, neutrophil-derived EV bearing the B1 receptor were found docking to glomerular endothelial cells in kidney biopsies of patients with AAV. In vitro experiments showed that neutrophil-derived EV transfer functional B1-receptors to wild-type human embryonic kidney cells, which suggests a similar mechanism in vivo and could potentially promote kinin-associated inflammation. The observation that the main inhibitor of the kinin system, named the C1-inhibitor, is also involved in the inhibition of the release of EV enriched in B1-receptor has suggested a novel therapeutic target in vasculitis [55].

Prikryl et al. [56] recently performed proteomic profiling of urinary EV isolated from patients with AAV and renal involvement and in healthy controls. The study showed different levels of proteins potentially involved in AAV pathogenesis. As an example, they found a significantly decreased level of Golgi mannosidases, such as MAN1A1, both in urinary EV and in the whole urine in active AAV. Interestingly, MAN1A1 is involved in protein glycosylation, which is considered to be involved in autoimmune disease and T cell activation, supporting its role in the pathogenesis of AAV. Moreover, they showed different levels of proteins related to neutrophil activation and degranulation, platelet regulation and podocyte-associated proteins, to name a few [56].

Several studies have also shown that EV may contain enzymes linked to lipid metabolism. Indeed, a comparison between EV in active GPA and healthy controls showed an increased content of leukotriene (LT)B_4 and 5-oxo-eicosatetraenoic acid (5-oxo-ETE) in EV from GPA patients. Moreover, neutrophils primed with GM-CSF, and stimulated with EV recovered from GPA patients, generate ROS and release dsDNA. Interestingly, in vitro-primed neutrophils were stimulated by LTB_4 and 5-oxo-ETE, thus EV carrying lipid enzymes may contribute to AAV pathogenesis [57]. In a recent study, Surmiak et al. [58] stimulated human umbilical endothelial cells (HUVEC) with EV from anti-PR3-activated neutrophils and analyzed their miRNA and mRNA content. They found a miRNA/mRNA profile consistent with the release of proinflammatory cytokines, which may be involved in endothelial injury in vasculitis. The most increased cytokines were IL-8, IL-33, Dickkopf-related protein 1 (DKK-1), soluble interleukin (IL)-1 like receptor-1 (ST2) and angiopoietin-2. Interestingly this cytokine profile is similar to the circulating cytokine profile in GPA patients [58].

Recent studies have investigated the role of EV in mediating endothelial injury in MPA. EV can be taken up by glomerular endothelial cells in vitro and can increase the release of soluble cellular adhesion molecules (sICAM-1 and sVCAM-1) leading to the injury of the glomerular endothelial barrier. A sequencing analysis of EV miRNA cargo in MPA patients revealed a different miRNA profile in MPA patients. In particular, a correlation between miR-185-3p, miR-125a-3p and clinical parameters, such as BVAS and 24-h urine proteins, was reported. Thus, the EV-miRNA content has been proposed as a biomarker of renal involvement in MPA [59].

Circulating EV expressing MPO are elevated in AAV patients compared with healthy subjects. Interestingly, MPO+ EV expressing inflammatory biomarkers such as PTX3 and HMGB1 are associated with disease activity. Of interest, PTX3 is released by neutrophils during the inflammatory process, while HMGB1 may be associated with renal injury in AAV [60]. HMGB1 enhanced neutrophil activation and migration towards glomerular endothelial cells in the presence of ANCA, leading to glomerular cell injury and the release of TF-positive EV and endothelin-1, which is involved in the fibrogenesis [61].

The comparison of circulating EV expressing MPO in AAV patients and healthy controls reveals an increased expression of the complement components C3a and C5a on EV from AAV patients. Moreover, among AAV patients, C3a and C5a expression is higher in patients with active renal involvement compared to non-renal disease. Interestingly, the level of C3a and C5a expression on EV correlated with disease activity evaluated by BVAS [62].

Platelet-derived EV were also found to be increased in AAV patients, particularly in MPO-positive patients with active disease in whom EV also expressed higher levels of chemokines, adhesion molecules, growth and apoptotic factors. Moreover, EV level correlated with the disease activity and the renal involvement, with serum creatinine and glomerular histologic lesions [63].

Taken together, these results may provide insight into the role of EV in the pathogenesis of renal injury in AAV (Table 4).

Table 3. Extracellular vesicles in thrombotic microangiopathies.

Disease	Study	Cellular Origin of EV	EV Biomarkers	EV Pathological Significance	Reference
STEC-HUS	Ståhl, A.-L.; et al., Arvidsson, I.; et al.	platelets, monocytes, neutrophils	Tissue factor, phosphatidylserine (PS), C3, C9	Promotion of thrombosis EV reflect complement activation	[40][38]
STEC-HUS	Varrone, E.; et al., Ståhl, A.-L.; et al., Johansson, K.; et al.		EV carrying Shiga toxin	Delivery system of Shiga toxin to the kidney involvement in renal cell injury	[41][42][43]
TTP	Tahmasbi, L.; et al., Jimenez, J.J.; et al.	platelets, endothelial cells	CD62E (E-selectin), VWF, intercellular adhesion molecule 1 (ICAM-1), platelet endothelial cell adhesion molecule (PECAM-1; CD31) and endoglin (CD105)	Pro-coagulant and pro-adhesive roles	[44][45]
TTP	Tati, R.; et al.	Endothelial cells	C3, C9	EV reflect complement activation	[46]

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