

## Extracellular vesicles as mediators of vascular inflammation in kidney disease

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### Abstract

Vascular inflammation is a common cause of renal impairment and a major cause of morbidity and mortality of patients with kidney disease. Current studies consistently show an increase of extracellular vesicles (EVs) in acute vasculitis and in patients with atherosclerosis. Recent

research has elucidated mechanisms that mediate vascular wall leukocyte accumulation and differentiation. This review addresses the role of EVs in this process. Part one of this review addresses functional roles of EVs in renal vasculitis. Most published data address anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and indicate that the number of EVs, mostly of platelet origin, is increased in active disease. EVs generated from neutrophils by activation by ANCA can contribute to vessel damage. While EVs are also elevated in other types of autoimmune vasculitis with renal involvement such as systemic lupus erythematoses, functional consequences beyond intravascular thrombosis remain to be established. In typical hemolytic uremic syndrome secondary to infection with shiga toxin producing *Escherichia coli*, EV numbers are elevated and contribute to toxin distribution into the vascular wall. Part two addresses mechanisms how EVs modulate vascular inflammation in atherosclerosis, a process that is aggravated in uremia. Elevated numbers of circulating endothelial EVs were associated with atherosclerotic complications in a number of studies in patients with and without kidney disease. Uremic endothelial EVs are defective in induction of vascular relaxation. Neutrophil adhesion and transmigration and intravascular thrombus formation are critically modulated by EVs, a process that is amenable to therapeutic interventions. EVs can enhance monocyte adhesion to the endothelium and modulate macrophage differentiation and cytokine production with major influence on the local inflammatory milieu in the plaque. They significantly influence lipid phagocytosis and antigen presentation by mononuclear phagocytes. Finally, platelet, erythrocyte and monocyte EVs cooperate in shaping adaptive T cell immunity. Future research is needed to define changes in uremic EVs and their differential effects on inflammatory leukocytes in the vessel wall.

**Key words:** Extracellular vesicle; Atherosclerosis; Kidney disease; Glomerulonephritis; Macrophage

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**Core tip:** This review addresses the role of extracellular vesicles (EVs) in vascular inflammation that can cause renal damage and is also shaped by uremic mediators. Vasculitides are common causes of renal damage. Functionally, neutrophil EVs induced by anti-neutrophil cytoplasmic antibody contribute to endothelial damage. EVs are main distributors of shiga toxin in the circulation and into tissues in typical hemolytic uremic syndrome. In atherosclerosis in patients with and without kidney disease, endothelial EVs are elevated. Uremic EVs are deficient in mediating vascular relaxation. EVs modulate mononuclear phagocyte differentiation, cytokine production, lipid phagocytosis and antigen presentation, atherosclerotic inflammatory processes significantly altered in uremia.

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## INTRODUCTION

Subcellular membrane vesicles collectively termed extracellular vesicles (EVs) are a third pathway of intercellular communication between direct cell-to-cell contact and secretion of soluble signaling molecules<sup>[1]</sup>. EVs can be secreted by virtually all cell types and contain a variety of components<sup>[2,3]</sup>. They are already present under physiologic conditions in a variety of bodily fluids<sup>[4]</sup>. EVs critically modulate local and systemic inflammatory and immune processes<sup>[4-7]</sup>. How EVs affect leukocytes and their function in the arterial wall in patients with kidney disease will be discussed for both acute vasculitis and chronic vascular inflammation in atherosclerosis.

## LEUKOCYTES IN THE VASCULAR WALL

Leukocytes are an integral part of the healthy vessel<sup>[8,9]</sup> and differentially increase in vascular inflammation<sup>[10]</sup>. The arterial wall is invaded by blood leukocytes in inflammation both directly across the main vascular endothelium and through vasa vasorum of larger vessels. This process is a tightly regulated cascade of leukocyte activation, rolling, adhesion and transmigration, to date studied mostly in neutrophilic granulocytes<sup>[11-13]</sup>. Vascular inflammation is mostly found in the arterial tree and microvessels including glomerular capillaries. Inflammation of the much thinner venous wall is rarely a clinical problem beyond reaction to intravascular thrombosis<sup>[10]</sup>. This is remarkable as most endothelial leukocyte adhesion and transendothelial migration is observed in venules<sup>[14]</sup>. Vascular inflammation is central in allo-immune processes such as transplant rejection. These have recently been reviewed (among others<sup>[15,16]</sup>). This review focuses on native arteries and

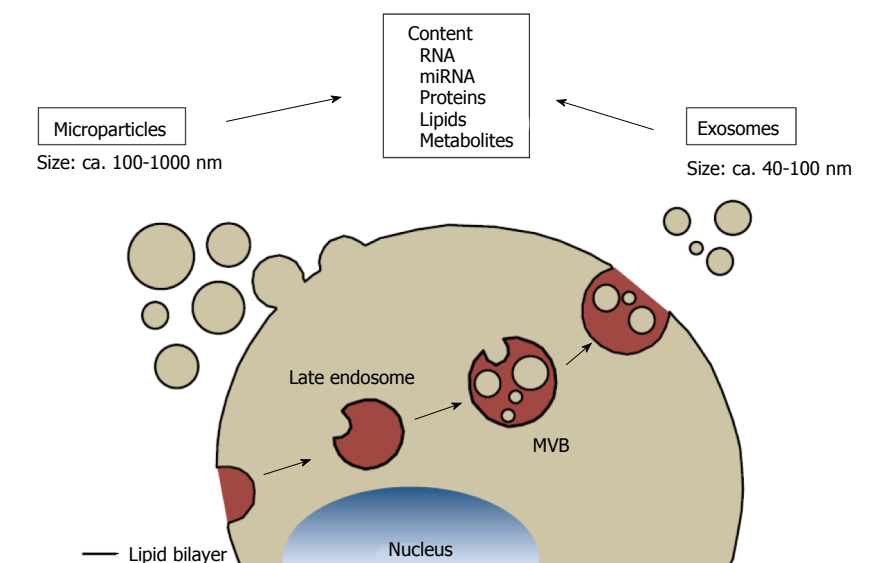
glomerular capillaries.

Impaired renal function during both acute kidney injury and chronic kidney disease significantly influences the structure of the arterial wall, affecting arterial endothelial cells and smooth muscle cells<sup>[17,18]</sup>. Structural changes are most obvious in enhanced atherosclerosis development<sup>[19-21]</sup>. A prominent feature in humans and mouse models with end stage kidney disease is extraosseous calcification of the arterial media<sup>[19,22]</sup>. Chronic inflammation in atherosclerosis occurs in normal and reduced kidney function, however, both innate and adaptive leukocytes are specifically altered by renal impairment<sup>[23-25]</sup>.

## CHARACTERIZATION OF EVS

Since the first description of "platelet-dust" in 1967<sup>[26]</sup>, EVs were found in diverse biological fluids<sup>[27]</sup>. Important factors of EV characterization are size and surface markers indicating their cellular origin<sup>[5,28-30]</sup>. EVs are a very heterogeneous population as both characteristics additionally vary with mode of EV generation<sup>[31]</sup>. In addition, most of the currently used flow cytometry instruments are not optimal for detection of particles of submicrometer size<sup>[32,33]</sup>. Organizations such as the Society for Extracellular Vesicles, formed in 2011, and databases such as EVpedia (<http://evpedia.org>) are instrumental in establishing reliable standards, including specification of preanalytical procedures and basic clinical information<sup>[4,27,34]</sup>.

Currently, two main groups of EVs are distinguished by both size and mode of generation: Exosomes and microparticles<sup>[1,3,28,29]</sup> (Figure 1). Exosomes are small EVs, ranging from 30-100 nm. They originate from endosome-derived multivesicular bodies and are released to the extracellular space when the multivesicular bodies fuse with the plasma membrane<sup>[35,36]</sup>. Microparticles (also referred to as ectosomes, membrane vesicles, nanovesicles and shedding vesicles) measure 100-1000 nm<sup>[3,30,35,37]</sup>. They directly bud off from the plasma membrane<sup>[35,36]</sup>. Both types of vesicles are enclosed by a lipid bilayer, but due to the fact that microparticles directly bud from the plasma membrane, they have a more similar membrane composition to their parent cell than exosomes<sup>[28,35]</sup>. For example, leukocyte surface proteins such as CD14, CD36 and CD11c are found on leukocyte microparticles<sup>[38]</sup>. Phosphatidylserine was initially thought to be enriched on microparticles only, but was later also found on exosomes<sup>[3]</sup>. Exosomes display endosome-associated proteins like annexins, flotillins or CD63 on their surface<sup>[28]</sup>. However, the expression of these proteins on microparticles cannot be completely excluded<sup>[3]</sup>. In addition to a possible biological overlap, this also reflects the technical challenge of multicolor fluorescence analysis of small particles<sup>[32,33]</sup>. Principal intravesicular contents such as cytoplasmic proteins, metabolites, RNAs, microRNAs and lipids can be found in both, exosomes and microparticles, however, in different abundance<sup>[2,3,35]</sup>. In addition to exosomes and microparticles, apoptotic bodies have been described as a separate entity by some authors<sup>[35,36,39]</sup>. These have been defined as large (1-5 µm) vesicles



**Figure 1 Classification of extracellular vesicles.**

Types of extracellular vesicles are distinguished by their mode of generation. Microparticles directly bud off the plasma membrane and measure approximately 100-1000 nm. Exosomes are released by fusion of multivesicular bodies with the plasma membrane and their sizes range between 40-100 nm. Both types of extracellular vesicles can contain RNA, microRNA, proteins, lipids and metabolites. MVBs: Multivesicular bodies.

generated during apoptosis. However, other EVs also express the inner membrane marker Annexin V on their surface.

Following current recommendations<sup>[29]</sup>, the overarching term EV will be used for all secreted vesicles in this review and further characterization will be provided by naming specific surface markers.

## EVS IN CHRONIC KIDNEY DISEASE

In end stage renal disease, both the uremic milieu and hemodynamic changes during the dialysis procedure can contribute to EV generation<sup>[40]</sup>. Uremic toxins such as p-cresol and enoxylsulfate induced EV shedding from HUVECs<sup>[41]</sup>. Hemoconcentration by dialysis increased blood viscosity, thereby decreasing shear stress and EV generation<sup>[42]</sup>. In addition, morphologically similar EVs may serve different functions is generated in an uremic milieu - for example, EVs from healthy controls, but not patients with end stage renal disease conferred endothelium mediated arterial relaxation *in vitro*<sup>[43]</sup>.

Counts and provenience of circulating EVs have been characterized in patients with chronic renal impairment with and without renal replacement therapy. Some studies found elevated serum concentrations of total and CD42<sup>+</sup> platelet EV<sup>[44-46]</sup>, total, endothelial (CD31<sup>+</sup>, CD114<sup>+</sup>)<sup>[43,46]</sup>, platelet (CD41<sup>+</sup>), and erythrocyte (CD235<sup>+</sup>) EVs<sup>[43]</sup> in patients with end stage renal disease, while in others, total plasma EV concentrations were unaltered<sup>[47,48]</sup> or only endothelial EVs were increased<sup>[41]</sup>. Also, the effect of the hemodialysis procedure is controversial with an increase in some<sup>[47]</sup> but not other studies<sup>[44,45]</sup>. The currently available studies included relatively small patient numbers and discrepancies that are at least partly explained by pre-analytical variables such as different modes of blood draw, storage and anticoagulation, flow cytometry equipment and surface markers used. However, addressing a possible pathophysiologic cause, a recent study further stratified patients with moderate kidney disease (mean GFR 39 mL/

min) according to the presence of cardiovascular disease defined by significant stenosis on coronary angiography<sup>[49]</sup>. EVs of both platelet (CD42<sup>+</sup>) and endothelial (CD31<sup>+</sup>) origin were significantly higher in patients with coronary artery disease, irrespective of renal impairment. Indeed, a large number of observational studies report increased concentrations of circulating EVs in atherosclerosis<sup>[50-53]</sup>. Especially endothelial EV concentrations appear to be predictive for cardiovascular prognosis<sup>[54]</sup>. This was confirmed in a recent observation in a large group of 844 individuals from the Framingham offspring cohort. Endothelial EV counts (CD31<sup>+</sup> or CD114<sup>+</sup>) correlated with hypertension, elevated triglycerides the metabolic syndrome and an overall higher Framingham in patients inversely correlated with brachial artery flow-induced dilatation and positively correlated with indices of arterial stiffening<sup>[43]</sup>. Endothelial (CD31<sup>+</sup>) EV concentration was associated with severe hypertension in a number of cohorts<sup>[55,56]</sup>. Concentrations significantly correlated with renal damage manifesting as micro- or macro-albuminuria in this condition<sup>[57]</sup>.

The currently available data is also limited by a mostly cross-sectional study design that precludes detection of temporal changes in single patients<sup>[52]</sup>. Measurement of EV concentration is evaluated as a predictive factor in a number of ongoing prospective trials<sup>[58]</sup>. However, there are some longitudinal data for patients with end stage kidney disease. A follow up study of 81 hemodialysis patients for a mean of 50 mo revealed that endothelial (CD31<sup>+</sup>) EV concentration in serum obtained after the long interval was a significant predictor of all cause and cardiovascular mortality, an association that was not observed for CD41<sup>+</sup> platelet, CD11b<sup>+</sup> leukocyte or CD235<sup>+</sup> erythrocyte EVs<sup>[59]</sup>. Another prospective study investigated endothelial EV counts (CD31<sup>+</sup>) in a cohort of 227 patients with end stage renal disease who were scheduled for kidney transplantation<sup>[48]</sup>. Endothelial EVs significantly decreased during 60 d of longitudinal follow up after kidney transplantation. However, they did not differ from

healthy controls at start of the trial<sup>[48]</sup> which may reflect that these patients represent a subgroup with relatively few co-morbidities.

In summary, chronic elevation of endothelial EVs currently appears to be significantly associated with vascular dysfunction and atherosclerosis in renal disease.

## THE ROLE OF EV IN RENAL VASCULITIS

Systemic inflammation is frequently associated with elevated EV concentrations. Pathophysiologically, monocytic and endothelial EVs can directly induce MCP1, interleukin (IL)-6 and VEGF production in human podocytes<sup>[60]</sup> thus enhancing glomerular injury. Investigations of EVs in systemic lupus erythematoses (SLE), ANCA vasculitis and typical hemolytic uremic syndrome (HUS) will be reviewed. It is also of note that our literature review revealed no information on EVs in either the pathogenesis or regarding the circulating EV counts in other common forms of renal vasculitis, including postinfectious glomerulonephritis, a historically common cause of renal vascular inflammation, and IgA nephropathy as the currently most common entity in the Western world.

## RHEUMATIC DISEASE WITH RENAL INVOLVEMENT

EVs function has been studied in systemic rheumatic disease<sup>[61,62]</sup>. In SLE, a common rheumatic cause of glomerulonephritis, elevated levels of EVs, particularly of platelet origin, have consistently been detected in patients with active antiphospholipid syndrome<sup>[63-66]</sup>, and also in Sjögrens syndrome<sup>[64]</sup> and closely been associated to intravascular thrombosis. Mechanisms of modification of inflammation of the vascular wall by EVs in SLE have not been reported to date. However, EVs in SLE display increased amounts of immunoglobulin and complement<sup>[67]</sup> and it is conceivable that they may contribute to deposition of these in the renal glomerulum. Furthermore, the proteome of these EVs in SLE appears to differ from healthy controls<sup>[68]</sup> and EVs constituents in SLE such as Galectin 3 binding protein have also been detected in glomerular deposits in individual patients with lupus-associated glomerulonephritis<sup>[69]</sup>.

## ANCA ASSOCIATED VASCULITIS

In anti-neutrophil-cytoplasmic antibody (ANCA) associated vasculitis, a number of studies have shown elevated serum EV concentrations during active disease<sup>[47,70-72]</sup>. Counts reverted normal during remission. In addition, counts were significantly higher than in patients with other glomerulonephritides such as IgA nephropathy, minimal change disease, diabetic nephropathy but also lupus nephropathy<sup>[47,71]</sup>. Most EVs in ANCA disease were of platelet origin, but leukocyte and endothelial derived EVs were also found<sup>[47,70-73]</sup>. Histologically, ANCA vasculitis presents as acute necrotizing vasculitis not only of the

glomeruli, but arteries of all sizes with predilection of small vessels<sup>[74]</sup>. The most prominent infiltrating cell types are neutrophilic granulocytes and even more abundantly, monocytes<sup>[75]</sup>. However, most research on leukocyte function within the vascular wall has concentrated on neutrophils. ANCA can induce generation of EVs from pre-activated, *e.g.*, tumor necrosis factor (TNF) $\alpha$  primed neutrophils<sup>[72,76,77]</sup>. These particles increased CD54 surface expression and IL-6 and IL-8 production from human vein endothelial cells (HUVECs) *in vitro*, suggesting that they can promote inflammation of the vessel wall<sup>[72]</sup>. ANCA induced EVs also contained tissue factor and may thus promote hypercoagulability and the increased rates of thrombosis observed in patients with ANCA disease<sup>[76,77]</sup>.

## TYPICAL HUS

Typical HUS is a complication of enteral infection with shiga toxin producing strains of *Escherichia coli* (STEC). EVs are highly elevated in patients with active systemic disease and platelet EV attach to leukocytes, most abundantly monocytes in peripheral blood<sup>[78-80]</sup>. Recent research shows that EVs are also generated from erythrocytes in this condition<sup>[81]</sup>, a type of EV that can activate monocytes to produce pro-inflammatory cytokines<sup>[82]</sup>. Platelet monocyte complexes and EV generation from both can be induced by shiga toxin. These EVs contain tissue factor and can thereby contribute to the microthromboses characteristic of the disease<sup>[80]</sup>. They also bore activated complement constituents, namely C3 and C9<sup>[78]</sup>. Neutrophils phagocytosed them, a process that may further contribute to their activation, adhesion and vascular inflammation<sup>[78]</sup>. Both leukocyte and platelet EVs contain shiga toxin and significantly contribute to its spreading into tissues including podocytes and tubular epithelium in the kidney<sup>[83]</sup> thus contributing to toxicity. Whether or not shiga toxin increases or diminishes leukocyte lifespan appears to depend on experimental conditions *in vitro*<sup>[84]</sup>. *In vivo*, increased rates of both monocyte and neutrophil cell death were observed during STEC-HUS<sup>[79]</sup>. It is conceivable that shiga toxin transferred into the vascular wall by EVs will also influence vascular resident leukocytes<sup>[83]</sup>.

## THE ROLE OF EVS IN VASCULAR INFLAMMATION IN ATHEROSCLEROSIS

EVs are abundant within the atherosclerotic wall which may enhance their biologic functions<sup>[6]</sup>. EVs from human endarterectomy specimens have been isolated by serial centrifugation and analyzed by flow cytometry in comparison to material from macroscopically unaffected arteries<sup>[85,86]</sup>. A detailed analysis determined that most plaque EVs are of leukocyte origin, including 29% macrophage (CD14<sup>+</sup>), 15% lymphocyte (CD4<sup>+</sup>), 8% granulocyte (CD66b<sup>+</sup>) provenience<sup>[86]</sup>. No platelet, but erythrocyte and smooth muscle cell markers were detected in EVs from the plaque lysate, recent *in vitro* data providing first evidence of EV generation from smooth muscle cells in

contact with pro-atherogenic lipids<sup>[87]</sup>. The analysis of plaque EV provenience was confirmed by subsequent studies including proteome analysis<sup>[38,88]</sup>.

Mechanistic roles of EV action in atherosclerotic inflammation have mostly been ascribed to their protein content<sup>[50,51]</sup> including large cytoplasmic protein structures such as proteasomes and inflammasomes<sup>[89,90]</sup>. In addition, other constituents such as nucleic acids, notably microRNA<sup>[91,92]</sup>, glycosylation pattern<sup>[93]</sup> and lipids<sup>[94]</sup> critically contribute to EV function in atherosclerosis<sup>[6,90,91]</sup>. Elevated systemic lipid levels and local deposition in the plaque makes EV lipids likely candidates for modulation of plaque development<sup>[95]</sup>. High levels of free cholesterol induce generation of phosphatidylserine and tissue factor rich EVs from human monocyte-derived macrophages, partly induced by caspase-3 mediated apoptosis. Systemically, circulating EV concentrations, mostly of platelet origin (CD41<sup>+</sup>) were significantly decreased after lipid apheresis in humans<sup>[96]</sup>. In renal impairment, lipoprotein function is markedly changed and protective functions are lost<sup>[97,98]</sup> making it a possible mediator of the observed functional shift in uremic EVs.

Patients with chronic kidney disease from any cause are at a markedly elevated risk of cardiovascular morbidity and mortality<sup>[97,99-101]</sup>. Medial calcification is characteristic of end-stage kidney disease<sup>[99,100]</sup>. Atherosclerotic plaques in moderate renal impairment are mostly found in the arterial intima and are histologically similar to lesions in normal renal function<sup>[102]</sup>, a phenotype that has been replicated in animal models of atherosclerosis<sup>[103,104]</sup>. Given the high prevalence of cardiovascular disease already in the general population, the role of inflammatory leukocytes in atherosclerotic plaque development has been explored in human samples and atherosclerotic animal models with a variety of methods including histology, flow cytometry and live cell imaging<sup>[105-107]</sup>. Numbers of both adaptive and innate leukocytes in the vessel wall markedly increase during atherogenesis. With specific regards to renal impairment, current data on EV effects on innate and adaptive leukocyte populations prominent in atherosclerotic lesion formation will be reviewed.

## THE ROLE OF EVS IN LEUKOCYTE INTERACTION WITH THE ENDOTHELIUM

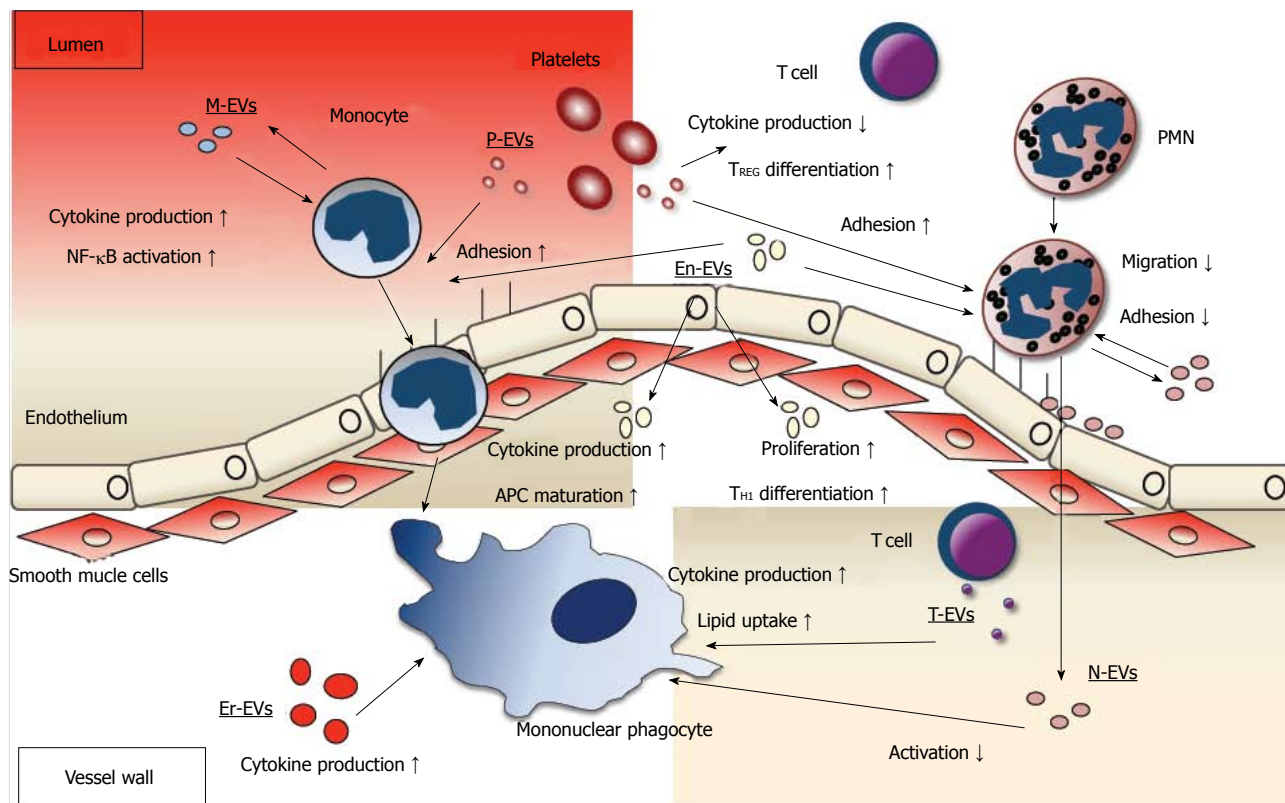
When entering the vascular wall and again with growing intimal plaques, leukocytes come into close contact with endothelial cells. As a possible mechanism of proatherogenic EV effects on endothelial cells, CD40 ligand on human carotid plaque EVs is required for endothelial cell activation and neoangiogenesis by promotion of endothelial cell proliferation<sup>[88]</sup>. EVs isolated from human atherosclerotic plaques can transfer ICAM-1 to endothelial cells, thus facilitating leukocyte, mainly monocyte adhesion and transmigration<sup>[108]</sup>. They also expressed TNF $\alpha$  converting enzyme and plaque EVs that increase shedding of both TNF $\alpha$  and activated protein C from activated HUVECs<sup>[109]</sup>. The fact that monocyte and T cell EVs

induced matrix metalloproteinase in synovial fibrocytes in rheumatoid arthritis suggests that this is a general EV property<sup>[110]</sup>. Neutrophil EVs increased endothelial cell IL-6 release *in vitro*<sup>[111]</sup>. T cell EVs generated both in *in vitro* and *in vivo* and EVs from patients with myocardial infarction decreased flow induced endothelial relaxation and downregulate eNOS expression<sup>[112,113]</sup>. As a potential positive feedback loop, NOS inhibition induces L-selectin and PSGL-1 expressing EVs from neutrophilic granulocytes seeded to HUVECs *in vitro*, that in turn increasing neutrophil transmigration<sup>[114]</sup>. Given NO inhibition by a range of uremic toxins<sup>[115]</sup>, it is conceivable that these processes cooperate in renal impairment to impair vascular function.

Circulating EV counts are highly elevated during acute arterial thrombosis in a large number of studies. These have recently been reviewed and will therefore only be referred to in relation to vascular leukocytes in this manuscript<sup>[116-119]</sup>. However, it is of note that EV phosphatidylserine surface expression as a pro-thrombotic mediator was significantly increased in patients with the nephrotic syndrome of different etiologies<sup>[120]</sup> and the *in vitro* pro-coagulant effect of EVs from both hemodialysis and peritoneal dialysis patients was enhanced<sup>[46]</sup>.

## GRANULOCYTES

Neutrophilic granulocyte concentrations in peripheral blood and even more so, the neutrophil/lymphocyte ratio, are well-documented predictors of cardiovascular mortality<sup>[121,122]</sup>. This relationship is also highly significant in patients with end stage renal disease<sup>[123]</sup>. Recent animal data suggest that neutrophils mechanistically promote hypertension associated vascular damage and endothelial dysfunction<sup>[124]</sup>. Neutrophils are essential in early atherosclerotic plaque development, probably by NET formation<sup>[125]</sup>. They also generate a variety of EVs with pro- and anti-inflammatory functions<sup>[111,126-128]</sup>. Acting directly on the parental cell type, Annexin A1 present in neutrophil EVs inhibits neutrophil rolling, adhesion and migration in mice<sup>[126]</sup>. Neutrophil extravasation is promoted by close neutrophil contact with platelets and platelet EVs<sup>[12,13]</sup> (Figure 2). Both platelets and neutrophils generate long tethers during adhesion, some of which remain as free vesicles in the environment<sup>[129,130]</sup>. The essential role of platelet particles for directed neutrophil migration through the vessel wall is under active *in vivo* investigation by advancing imaging techniques<sup>[11-13,131,132]</sup>. Thrombus formation after plaque rupture directly activates neutrophils<sup>[133]</sup>, a process that continues to be mechanistically explored in experimental arterial lesions<sup>[134]</sup>. Antagonizing either glycoprotein I b or II b III A on platelet EV inhibited neutrophil activation<sup>[135,136]</sup>. This may be relevant beyond acute thrombosis, as enhanced platelet activation by junctional adhesion molecule A deficiency<sup>[137]</sup> increased while deletion of glycoprotein Ib decreased myeloid cell activation and atherosclerotic lesion size<sup>[138]</sup>. These data suggest that platelet and platelet EV interactions with granulocytes promote also chronic



**Figure 2** Roles of extracellular vesicles in leukocyte function in the atherosclerotic plaque. Data on interaction of EVs with neutrophilic granulocytes, monocytes and mononuclear phagocytes and T lymphocytes is summarized. Regarding neutrophilic granulocytes (PMN), platelet EVs (P-EV) promote neutrophil (PMN) adhesion to the endothelium, neutrophil EVs (N-EV) mostly decrease adhesion and migration through the endothelium. Regarding monocytic cells, endothelial (En-EV) and P-EVs promote adhesion to the endothelium. Inside the plaque, En-EVs promote antigen presenting cell (APC) maturation and cytokine production and erythrocyte EVs (Er-EVs), monocyte EVs (M-EVs) and T cell EVs (T-EVs) increase cytokine production. T-EVs also increase lipid uptake. N-EVs suppress activation. Regarding T cells, P-EVs decrease cytokine production, En-EVs promote T cell proliferation and TH1 differentiation. EVs: Extracellular vesicles.

atherosclerosis, in the absence of plaque rupture or thrombosis.

## MONOCYTES AND MONONUCLEAR PHAGOCYTES

Myeloid phagocytes are central in atherosclerotic plaque development. They have a dual role with lipid uptake on the one hand, resulting in foam cell formation that can lead to cell death and thereby necrotic plaque cores and antigen presentation to cells of the adaptive system on the other hand<sup>[139-143]</sup>. In atherosclerosis enhanced by renal impairment, lesional macrophage content increased<sup>[104,144]</sup>. Angiotensin receptor I on myeloid cells<sup>[144-146]</sup> and IL-17<sup>[104]</sup> are instrumental in mediating this phenotype. Myeloid derived phagocytes in the atherosclerotic plaques differentiate from immigrating monocytes, but also proliferate locally, especially in mature plaques in which they are subject to the local milieu<sup>[147]</sup>. Both processes are influenced by EVs (Figure 2).

Monocyte adhesion to the endothelium *in vitro* was enhanced platelet EVs, induced by storage, thrombin or shear stress<sup>[148-150]</sup>. Platelet EVs also increased monocyte surface expression of adhesion molecules such as CD11a, CD11b integrins, platelet adhesion molecule 1 (CD31),

CD33 lectin, and receptors such as CD14 and CD32 Fc receptor<sup>[148-150]</sup>. Endothelial EVs elicited by oxidized LDL or homocysteine from rat arterial endothelial cells contained high levels of heat shock protein 70 (HSP70) that increased monocyte adhesion *in vitro*<sup>[151]</sup>. *In vivo* in murine atherosclerosis, RANTES from platelet EVs coated the endothelium resulting in enhance monocyte adhesion<sup>[152]</sup>.

Macrophage phenotype has a decisive role in plaque growth and stability of the lesion. In renal impairment, histologic analysis of the plaque showed that markers of M1 macrophage polarization were up-regulated with corresponding down-regulation of M2 markers<sup>[153]</sup>. Erythrocyte EVs that are found atherosclerotic plaques<sup>[86]</sup> induced TNF $\alpha$  production in monocytes in a CD40 ligand dependent fashion<sup>[82]</sup>. Platelet EVs induced secretion of cytokines that promote atherosclerotic plaque formation such as TNF $\alpha$ , IL-1 $\beta$  and IL-8 in a monocytic cell line *in vitro*<sup>[149]</sup>. IL-1 $\beta$  that is central atherogenesis<sup>[154]</sup> is itself contained in EVs released from platelets<sup>[155,156]</sup> and myeloid phagocytes<sup>[157-159]</sup>. However, cytokine induction by platelet EVs is not universal as small platelet EVs inhibited human monocyte-derived phagocyte TNF $\alpha$  and IL-10 secretion while TGF $\beta$  production was enhanced<sup>[160]</sup>. Human granulocyte EVs increased macrophage TGF $\beta$ 1, but not IL-6 or IL-8 expression and blocked pro-inflammatory responses induced by zymosan or LPS. The authors

also noted large donor variations in response to EVs suggesting that genetic factors may have a significant influence<sup>[127]</sup>. Annexin 1 is a potential mediator of the anti-inflammatory effects of granulocyte EVs<sup>[126]</sup>. Autocrine effects of monocytic EVs on monocyte differentiation and cytokine production varied with cell culture conditions. phorbol-12-myristate 13-acetate (PMA) elicited EVs from THP1 cells induced cell cycle arrest and macrophage differentiation TGF $\beta$ 1 dependently<sup>[161]</sup> while human monocyte EVs increased TNF $\alpha$  and IL-6, release reactive oxygen species production and induced nuclear factor (NF)- $\kappa$ b activation<sup>[162]</sup>. Interestingly, NO, a pathway that is significantly inhibited in uremia, markedly enhanced EV release from RAW264 macrophages *in vitro*<sup>[163]</sup>. T lymphocyte EVs induced in both peripheral blood T lymphocytes and a human T cell line by phytohemagglutinin (PHA) and PMA increased TNF $\alpha$ , IL-1 $\beta$  and soluble IL-1 receptor a production in monocytes in a dose-dependent manner. This was not observed for EVs from unstimulated T cells<sup>[164,165]</sup>. Both TNF $\alpha$  and IL-1 $\beta$  generation were inhibited by HDL, connecting these studies directly to regulation of inflammation in the atherosclerotic plaque.

Regarding lipid phagocytosis, lipid and cholesterol content in peritoneal macrophages from atherosclerotic mice with renal impairment was significantly higher than in control animals<sup>[166]</sup> and the ability to take up labeled exogenous oxidized LDL particles significantly impaired in aortic macrophages<sup>[104]</sup>. This was attributed to decreased cholesterol efflux, mediated by decreased expression of the transporter ABCA1<sup>[166]</sup>. Platelet EVs increased uptake of oxidized LDL if present during macrophage differentiation *in vitro*. This protocol also increased CD14, CD36 and CD68 surface receptor expression<sup>[150]</sup>. In contrast, small platelet EVs with less than 50 nm diameter decreased lipid uptake *via* reduction of CD36 surface expression by enhanced ubiquitination<sup>[167]</sup> T lymphocyte EVs from PHA-activated human T lymphocytes increased cholesterol uptake in THP-1 cell and human monocyte derived macrophages<sup>[168]</sup>.

Regarding antigen presentation, expression of the antigen presenting cell marker CD11c significantly increased in atherosclerotic aortas of mice with renal impairment<sup>[104]</sup>. T cell proliferation was significantly higher in their then aortas of atherosclerotic control mice. In addition, life cell imaging demonstrated that aortic T cell interactions with CD11c<sup>+</sup> cells were significantly more frequent and longer in vessels from mice with renal impairment<sup>[104]</sup>. There is a large body of evidence for a role of EVs in antigen presenting cell function<sup>[6]</sup>. While many studies focused on tumor antigens, some may be directly relevant to atherosclerosis. Endothelial EVs from a human microvascular cell line induced by TNF $\alpha$  enhanced antigen presenting cell maturation, indicated by morphologic maturation, up-regulation of HLA-DR, CD83 and CCR7 and IL-6 secretion in a cell line and human plasmacytoid dendritic cell, but not in myeloid cells. While the stimulated cells were capable of inducing mixed lymphocyte reaction, interferon  $\gamma$  (IFN $\gamma$ ) was not induced by the co-incubation. Platelet and T cell EVs were used as controls and did not

elicit this response<sup>[169]</sup>. Erythrocyte EVs enhanced T cell proliferation by modulation of monocyte maturation and induction of TNF $\alpha$ <sup>[82]</sup>. In a somewhat different setting, platelet EV recovered from thrombin-activated platelet supernatants induced HLA-DR expression in immature DCs during differentiation from human PBMC. This was mediated by CD40L<sup>[170]</sup>, a protein that has been detected on human carotid plaque EVs<sup>[88]</sup>. Small EVs from resting platelets exerted a contrary effect and decreased HLA-DP, DQ, DR and CD80 expression during human PBMC differentiation<sup>[160]</sup>. While CD14 expression decreased similar to control cells, platelet EV also decreased endocytic capacity. Neutrophil EVs decreased immature dendritic cell phagocytic capacity and increased TGF $\beta$  release. Furthermore, LPS mediated maturation was severely impaired including surface marker expression, cytokine production and induction of T cell proliferation<sup>[171]</sup> extending the protective neutrophil effect from endothelium to monocyte derived phagocytes.

In summary, EVs of different cellular origins modulate mononuclear phagocyte functions that promote atherosclerosis in renal impairment.

## LYMPHOCYTES

T cells are major modifiers of plaque formation among adaptive immune cells while the role for B cells is controversial<sup>[105-107]</sup>. B cell interaction with EVs can enhance or diminish B cell function<sup>[172,173]</sup>, however, a link to atherosclerosis remains to be defined.

Among T helper cells, IFN $\gamma$ -producing T<sub>H1</sub> cells strongly promote atherosclerotic lesion formation. In the current experimental models, there appears to be no major role for T<sub>H2</sub> cells in atherogenesis, while regulatory T cells and their marker cytokines such as IL-10 can attenuate lesion formation<sup>[105-107]</sup>. The impact of T<sub>H17</sub> cells and their marker cytokine IL-17, which has a significant role in attraction of innate leukocytes such as neutrophilic granulocytes and monocytes<sup>[174]</sup>, appears to be highly context-dependent<sup>[10,175]</sup>. Recent data show that proatherogenic lipoproteins can enhance T<sub>H17</sub> polarization<sup>[176]</sup>. IL-17 production in T cells is markedly enhanced by environmental chemicals *via* the aryl hydrocarbon receptor<sup>[177-180]</sup>. Its ligands are well known uremic toxins<sup>[181,182]</sup>. Indeed, the IL-17 production was significantly increased in a cohort of patients with end stage renal disease<sup>[183]</sup>. Mechanistically, IL-17 was instrumental in increased myeloid cell accumulation and lesion burden in moderate renal impairment<sup>[104]</sup>.

The effect of EVs on T cell function *in vitro* significantly varies depending on the cell of origin (Figure 2). Endothelial EVs enhanced CD4<sup>+</sup> T cell proliferation in mixed lymphocyte reaction *via* modulation of dendritic cell maturation, resulting in enhanced TNF $\alpha$  and IFN $\gamma$  secretion<sup>[69]</sup>. Similarly, EVs from TNF $\alpha$ -stimulated HUVECs induced T<sub>H1</sub> differentiation in human PBMCs<sup>[184]</sup>. Erythrocyte EVs induced T cell proliferation indirectly *via* monocyte derived antigen presenting cell polarization. This stimulated the production of the pro-atherogenic cytokines IL-1 $\beta$ , IL-2,

IL-7, IL-17 and IFN $\gamma$  during co-culture of human PBMCs<sup>[82]</sup>. In contrast, small platelet EVs directly interacted with CD4<sup>+</sup> T cells. They decreased IFN $\gamma$ , TNF $\alpha$  and IL-6 production during polarization<sup>[185]</sup>. This was at least in part due to an increase in regulatory T cells induced by EV TGF $\beta$ . EVs from antigen presenting cells promote T cell priming<sup>[186,187]</sup>. In atherosclerosis, plasma and plaque EVs contain MHC I, MHC II and CD40L as EV surface antigens and it is therefore conceivable that these processes are also active during atherosclerosis *in vivo*<sup>[38,88]</sup>.

## CONCLUSION

Data on mechanisms how EVs modulate leukocyte adhesion, differentiation and vascular function in inflammation have greatly enhanced our understanding of these pathophysiological processes. Experimental results suggest a number of mechanisms that enhance EV generation and modulate their function in renal patients. While analytic tools continue to be optimized and therapeutic options are limited to inhibition of platelet EVs at this point, EV counts start to serve as activity and prognostic markers in different conditions.

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