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**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 erythematodes, functional consequences beyond intravascular thrombosis remain to be established. In typical hemolytic uremic syndrome secondary to infection with shiga toxin producing *E. 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; Kidney disease; Glomerulonephritis; Atherosclerosis; 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[[1](#_ENREF_1)]. EVs can be secreted by virtually all cell types and contain a variety of components[[2](#_ENREF_2),[3](#_ENREF_3)]. They are already present under physiologic conditions in a variety of bodily fluids[[4](#_ENREF_4)]. EVs critically modulate local and systemic inflammatory and immune processes[[4-7](#_ENREF_4)]. 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[[8](#_ENREF_8),[9](#_ENREF_9)] and differentially increase in vascular inflammation[[10](#_ENREF_10)]. 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[[11-13](#_ENREF_11)]. 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[[10](#_ENREF_10)]. This is remarkable as most endothelial leukocyte adhesion and transendothelial migration is observed in venules[[14](#_ENREF_14)]. Vascular inflammation is central in allo-immune processes such as transplant rejection. These have recently been reviewed (among others[[15](#_ENREF_15),[16](#_ENREF_16)]). 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[[17](#_ENREF_17),[18](#_ENREF_18)]. Structural changes are most obvious in enhanced atherosclerosis development[[19-21](#_ENREF_19)]. A prominent feature in humans and mouse models with end stage kidney disease is extraosseous calcification of the arterial media[[19](#_ENREF_19),[22](#_ENREF_22)]. Chronic inflammation in atherosclerosis occurs in normal and reduced kidney function, however, both innate and adaptive leukocytes are specifically altered by renal impairment[[23-25](#_ENREF_23)].

**CHARACTERIZATION OF** EV**S**

Since the first description of “platelet-dust” in 1967[[26](#_ENREF_26)], EVs were found in diverse biological fluids[[27](#_ENREF_27)]. Important factors of EV characterization are size and surface markers indicating their cellular origin[[5](#_ENREF_5),[28-30](#_ENREF_28)]. EVs are a very heterogeneous population as both characteristics additionally vary with mode of EV generation[[31](#_ENREF_31)]. In addition, most of the currently used flow cytometry instruments are not optimal for detection of particles of submicrometer size[[32](#_ENREF_32),[33](#_ENREF_33)]. Organizations such as the Society for Extracellular Vesicles (ISEV), 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[[4](#_ENREF_4),[27](#_ENREF_27),[34](#_ENREF_34)].

Currently, two main groups of EVs are distinguished by both size and mode of generation: Exosomes and microparticles[[1](#_ENREF_1),[3](#_ENREF_3),[28](#_ENREF_28),[29](#_ENREF_29)] (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[[35](#_ENREF_35),[36](#_ENREF_36)]. Microparticles (also referred to as ectosomes, membrane vesicles, nanovesicles and shedding vesicles) measure 100-1000 nm[[3](#_ENREF_3),[30](#_ENREF_30),[35](#_ENREF_35),[37](#_ENREF_37)]. They directly bud off from the plasma membrane[[35](#_ENREF_35),[36](#_ENREF_36)]. 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[[28](#_ENREF_28),[35](#_ENREF_35)]. For example, leukocyte surface proteins such as CD14, CD36 and CD11c are found on leukocyte microparticles[[38](#_ENREF_38)]. Phosphatidylserine was initially thought to be enriched on microparticles only, but was later also found on exosomes[[3](#_ENREF_3)]. Exosomes display endosome-associated proteins like annexins, flotillins or CD63 on their surface[[28](#_ENREF_28)]. However, the expression of these proteins on microparticles cannot be completely excluded[[3](#_ENREF_3)]. In addition to a possible biological overlap, this also reflects the technical challenge of multicolor fluorescence analysis of small particles[[32](#_ENREF_32),[33](#_ENREF_33)]. Principal intravesicular contents such as cytoplasmic proteins, metabolites, RNAs, microRNAs and lipids can be found in both, exosomes and microparticles, however, in different abundance[[2](#_ENREF_2),[3](#_ENREF_3),[35](#_ENREF_35)]. In addition to exosomes and microparticles, apoptotic bodies have been described as a separate entity by some authors[[35](#_ENREF_35),[36](#_ENREF_36),[39](#_ENREF_39)]. These have been defined as large (1-5 µm) vesicles generated during apoptosis. However, other EVs also express the inner membrane marker Annexin V on their surface.

Following current recommendations[[29](#_ENREF_29)], 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[[40](#_ENREF_40)]. Uremic toxins such as p-cresol and enoxylsulfate induced EV shedding from HUVECs[[41](#_ENREF_41)]. Hemoconcentration by dialysis increased blood viscosity, thereby decreasing shear stress and EV generation[[42](#_ENREF_42)]. 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*[[43](#_ENREF_43)].

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+ platelet EV[[44-46](#_ENREF_44)], total, endothelial (CD31+, CD114+)[[43](#_ENREF_43),[46](#_ENREF_46)], platelet (CD41+), and erythrocyte (CD235+) EVs[[43](#_ENREF_43)] in patients with end stage renal disease, while in others, total plasma EV concentrations were unaltered[[47](#_ENREF_47),[48](#_ENREF_48)] or only endothelial EVs were increased[[41](#_ENREF_41)]. Also, the effect of the hemodialysis procedure is controversial with an increase in some[[47](#_ENREF_47)] but not other studies[[44](#_ENREF_44),[45](#_ENREF_45)]. 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[[49](#_ENREF_49)]. EVs of both platelet (CD42+) and endothelial (CD31+) 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[[50-53](#_ENREF_50)]. Especially endothelial EV concentrations appear to be predictive for cardiovascular prognosis[[54](#_ENREF_54)]. This was confirmed in a recent observation in a large group of 844 individuals from the Framingham offspring cohort. Endothelial EV counts (CD31+ or CD114+) 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[[43](#_ENREF_43)]. Endothelial (CD31+) EV concentration was associated with severe hypertension in a number of cohorts[[55](#_ENREF_55),[56](#_ENREF_56)]. Concentrations significantly correlated with renal damage manifesting as micro- or macro-albuminuria in this condition[[57](#_ENREF_57)].

The currently available data is also limited by a mostly cross-sectional study design that precludes detection of temporal changes in single patients[[52](#_ENREF_52)]. Measurement of EV concentration is evaluated as a predictive factor in a number of ongoing prospective trials[[58](#_ENREF_58)]. 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 months revealed that endothelial (CD31+) 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+ platelet, CD11b+ leukocyte or CD235+ erythrocyte EVs[[59](#_ENREF_59)]. Another prospective study investigated endothelial EV counts (CD31+) in a cohort of 227 patients with end stage renal disease who were scheduled for kidney transplantation[[48](#_ENREF_48)]. 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[[48](#_ENREF_48)] 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[[60](#_ENREF_60)] thus enhancing glomerular injury. Investigations of EVs in systemic lupus erythematodes (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[[61](#_ENREF_61),[62](#_ENREF_62)]. 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[[63-66](#_ENREF_63)], and also in Sjögrens syndrome[[64](#_ENREF_64)] 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[[67](#_ENREF_67)] 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[[68](#_ENREF_68)] 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[[69](#_ENREF_69)].

**ANCA ASSOCIATED VASCULITIS**

In anti-neutrophil-cytoplasmic antibody (ANCA) associated vasculitis, a number of studies have shown elevated serum EV concentrations during active disease[[47](#_ENREF_47),[70-72](#_ENREF_70)]. 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[[47](#_ENREF_47),[71](#_ENREF_71)]. Most EVs in ANCA disease were of platelet origin, but leukocyte and endothelial derived EVs were also found[[47](#_ENREF_47),[70-73](#_ENREF_70)]. Histologically, ANCA vasculitis presents as acute necrotizing vasculitis not only of the glomeruli, but arteries of all sizes with predilection of small vessels[[74](#_ENREF_74)]. The most prominent infiltrating cell types are neutrophilic granulocytes and even more abundantly, monocytes[[75](#_ENREF_75)]. 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.*, TNF primed neutrophils[[72](#_ENREF_72),[76](#_ENREF_76),[77](#_ENREF_77)]. 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[[72](#_ENREF_72)]. ANCA induced EVs also contained tissue factor and may thus promote hypercoagulability and the increased rates of thrombosis observed in patients with ANCA disease[[76](#_ENREF_76),[77](#_ENREF_77)].

**TYPICAL HUS**

Typical HUS is a complication of enteral infection with shiga toxin producing strains of *E. coli* (STEC). EVs are highly elevated in patients with active systemic disease and platelet EV attach to leukocytes, most abundantly monocytes in peripheral blood[[78-80](#_ENREF_78)]. Recent research shows that EVs are also generated from erythrocytes in this condition[[81](#_ENREF_81)], a type of EV that can activate monocytes to produce pro-inflammatory cytokines[[82](#_ENREF_82)]. 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[[80](#_ENREF_80)]. They also bore activated complement constituents, namely C3 and C9[[78](#_ENREF_78)]. Neutrophils phagocytosed them, a process that may further contribute to their activation, adhesion and vascular inflammation[[78](#_ENREF_78)]. Both leukocyte and platelet EVs contain shiga toxin and significantly contribute to its spreading into tissues including podocytes and tubular epithelium in the kidney[[83](#_ENREF_83)] thus contributing to toxicity. Whether or not shiga toxin increases or diminishes leukocyte lifespan appears to depend on experimental conditions *in vitro*[[84](#_ENREF_84)]. *In vivo*, increased rates of both monocyte and neutrophil cell death were observed during STEC-HUS[[79](#_ENREF_79)]. It is conceivable that shiga toxin transferred into the vascular wall by EVs will also influence vascular resident leukocytes[[83](#_ENREF_83)].

**THE ROLE OF EVS IN VASCULAR INFLAMMATION IN ATHEROSCLEROSIS**

EVs are abundant within the atherosclerotic wall which may enhance their biologic functions[[6](#_ENREF_6)]. EVs from human endarterectomy specimens have been isolated by serial centrifugation and analyzed by flow cytometry in comparison to material from macroscopically unaffected arteries[[85](#_ENREF_85),[86](#_ENREF_86)]. A detailed analysis determined that most plaque EVs are of leukocyte origin, including 29% macrophage (CD14+), 15% lymphocyte (CD4+), 8% granulocyte (CD66b+) provenience[[86](#_ENREF_86)]. 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[[87](#_ENREF_87)]. The analysis of plaque EV provenience was confirmed by subsequent studies including proteome analysis[[38](#_ENREF_38),[88](#_ENREF_88)].

Mechanistic roles of EV action in atherosclerotic inflammation have mostly been ascribed to their protein content[[50](#_ENREF_50),[51](#_ENREF_51)] including large cytoplasmic protein structures such as proteasomes and inflammasomes[[89](#_ENREF_89),[90](#_ENREF_90)]. In addition, other constituents such as nucleic acids, notably microRNA[[91](#_ENREF_91),[92](#_ENREF_92)], glycosylation pattern[[93](#_ENREF_93)] and lipids[[94](#_ENREF_94)] critically contribute to EV function in atherosclerosis[[6](#_ENREF_6),[90](#_ENREF_90),[91](#_ENREF_91)]. Elevated systemic lipid levels and local deposition in the plaque makes EV lipids likely candidates for modulation of plaque development[[95](#_ENREF_95)]. 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+) were significantly decreased after lipid apheresis in humans[[96](#_ENREF_96)]. In renal impairment, lipoprotein function is markedly changed and protective functions are lost[[97](#_ENREF_97),[98](#_ENREF_98)] 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[[97](#_ENREF_97),[99-101](#_ENREF_99)]. Medial calcification is characteristic of end-stage kidney disease[[99](#_ENREF_99),[100](#_ENREF_100)]. Atherosclerotic plaques in moderate renal impairment are mostly found in the arterial intima and are histologically similar to lesions in normal renal function[[102](#_ENREF_102)], a phenotype that has been replicated in animal models of atherosclerosis[[103](#_ENREF_103),[104](#_ENREF_104)]. 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[[105-107](#_ENREF_105)]. 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 pro-atherogenic 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[[88](#_ENREF_88)]. EVs isolated from human atherosclerotic plaques can transfer ICAM-1 to endothelial cells, thus facilitating leukocyte, mainly monocyte adhesion and transmigration[[108](#_ENREF_108)]. They also expressed TNF converting enzyme and plaque EVs that increase shedding of both TNF and activated protein C from activated HUVECs[[109](#_ENREF_109)]. 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[[110](#_ENREF_110)]. Neutrophil EVs increased endothelial cell IL-6 release *in vitro*[[111](#_ENREF_111)]. 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[[112](#_ENREF_112),[113](#_ENREF_113)]. 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[[114](#_ENREF_114)]. Given NO inhibition by a range of uremic toxins[[115](#_ENREF_115)], 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 been referred to in relation to vascular leukocytes in this manuscript[[116-119](#_ENREF_116)]. 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[[120](#_ENREF_120)] and the *in vitro* pro-coagulant effect of EVs from both hemodialysis and peritoneal dialysis patients was enhanced[[46](#_ENREF_46)].

**GRANULOCYTES**

Neutrophilic granulocyte concentrations in peripheral blood and even more so, the neutrophil/lymphocyte ratio, are well-documented predictors of cardiovascular mortality[[121](#_ENREF_121),[122](#_ENREF_122)]. This relationship is also highly significant in patients with end stage renal disease[[123](#_ENREF_123)]. Recent animal data suggest that neutrophils mechanistically promote hypertension associated vascular damage and endothelial dysfunction[[124](#_ENREF_124)]. Neutrophils are essential in early atherosclerotic plaque development, probably by NET formation[[125](#_ENREF_125)]. They also generate a variety of EVs with pro- and anti-inflammatory functions[[111](#_ENREF_111),[126-128](#_ENREF_126)]. Acting directly on the parental cell type, Annexin A1 present in neutrophil EVs inhibits neutrophil rolling, adhesion and migration in mice[[126](#_ENREF_126)]. Neutrophil extravasation is promoted by close neutrophil contact with platelets and platelet EVs[[12](#_ENREF_12),[13](#_ENREF_13)] (Figure 2). Both platelets and neutrophils generate long tethers during adhesion, some of which remain as free vesicles in the environment[[129](#_ENREF_129),[130](#_ENREF_130)]. The essential role of platelet particles for directed neutrophil migration through the vessel wall is under active *in vivo* investigation by advancing imaging techniques[[11-13](#_ENREF_11),[131](#_ENREF_131),[132](#_ENREF_132)]. Thrombus formation after plaque rupture directly activates neutrophils[[133](#_ENREF_133)], a process that continues to be mechanistically explored in experimental arterial lesions[[134](#_ENREF_134)]. Antagonizing either glycoprotein Ib or IIbIIIA on platelet EV inhibited neutrophil activation[[135](#_ENREF_135),[136](#_ENREF_136)]. This may be relevant beyond acute thrombosis, as enhanced platelet activation by junctional adhesion molecule A deficiency[[137](#_ENREF_137)] increased while deletion of glycoprotein Ib decreased myeloid cell activation and atherosclerotic lesion size[[138](#_ENREF_138)]. These data suggest that platelet and platelet EV interactions with granulocytes promote also chronic 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[[139-143](#_ENREF_139)]. In atherosclerosis enhanced by renal impairment, lesional macrophage content increased[[104](#_ENREF_104),[144](#_ENREF_144)]. Angiotensin receptor I on myeloid cells[[144-146](#_ENREF_144)] and IL-17[[104](#_ENREF_104)] 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[[147](#_ENREF_147)]. 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[[148-150](#_ENREF_148)]. 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[[148-150](#_ENREF_148)]. 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*[[151](#_ENREF_151)]. *In vivo* in murine atherosclerosis, RANTES from platelet EVs coated the endothelium resulting in enhance monocyte adhesion[[152](#_ENREF_152)].

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[[153](#_ENREF_153)]. Erythrocyte EVs that are found atherosclerotic plaques[[86](#_ENREF_86)] induced TNF production in monocytes in a CD40 ligand dependent fashion[[82](#_ENREF_82)]. Platelet EVs induced secretion of cytokines that promote atherosclerotic plaque formation such as TNF, IL-1β and IL-8 in a monocytic cell line *in vitro*[[149](#_ENREF_149)]. IL-1β that is central atherogenesis[[154](#_ENREF_154)] is itself contained in EVs released from platelets[[155](#_ENREF_155),[156](#_ENREF_156)] and myeloid phagocytes[[157-159](#_ENREF_157)]. However, cytokine induction by platelet EVs is not universal as small platelet EVs inhibited human monocyte-derived phagocyte TNF and IL-10 secretion while TGFβ production was enhanced[[160](#_ENREF_160)]. Human granulocyte EVs increased macrophage TGFβ1, 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[[127](#_ENREF_127)]. Annexin 1 is a potential mediator of the anti-inflammatory effects of granulocyte EVs[[126](#_ENREF_126)]. Autocrine effects of monocytic EVs on monocyte differentiation and cytokine production varied with cell culture conditions. PMA elicited EVs from THP1 cells induced cell cycle arrest and macrophage differentiation TGFβ1 dependently[[161](#_ENREF_161)] while human monocyte EVs increased TNF and IL-6, release reactive oxygen species production and induced NF-ĸb activation[[162](#_ENREF_162)]. Interestingly, NO, a pathway that is significantly inhibited in uremia, markedly enhanced EV release from RAW264 macrophages *in vitro*[[163](#_ENREF_163)]. T lymphocyte EVs induced in both peripheral blood T lymphocytes and a human T cell line by phytohemagglutinin (PHA) and phorbol-12-myristate 13-acetate (PMA) increased TNF, IL-1β and soluble IL-1 receptor a production in monocytes in a dose-dependent manner. This was not observed for EVs from unstimulated T cells[[164](#_ENREF_164),[165](#_ENREF_165)]. Both TNF and IL-1β 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[[166](#_ENREF_166)] and the ability to take up labeled exogenous oxidized LDL particles significantly impaired in aortic macrophages[[104](#_ENREF_104)]. This was attributed to decreased cholesterol efflux, mediated by decreased expression of the transporter ABCA1[[166](#_ENREF_166)]. 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[[150](#_ENREF_150)]. In contrast, small platelet EVs with less than 50 nm diameter decreased lipid uptake via reduction of CD36 surface expression by enhanced ubiquitination[[167](#_ENREF_167)] T lymphocyte EVs from PHA-activated human T lymphocytes increased cholesterol uptake in THP-1 cell and human monocyte derived macrophages[[168](#_ENREF_168)].

Regarding antigen presentation, expression of the antigen presenting cell marker CD11c significantly increased in atherosclerotic aortas of mice with renal impairment[[104](#_ENREF_104)]. 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+ cells were significantly more frequent and longer in vessels from mice with renal impairment[[104](#_ENREF_104)]. There is a large body of evidence for a role of EVs in antigen presenting cell function[[6](#_ENREF_6)]. 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 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 γ (IFNγ) was not induced by the co-incubation. Platelet and T cell EVs were used as controls and did not elicit this response[[169](#_ENREF_169)]. Erythrocyte EVs enhanced T cell proliferation by modulation of monocyte maturation and induction of TNF[[82](#_ENREF_82)]. 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[[170](#_ENREF_170)], a protein that has been detected on human carotid plaque EVs[[88](#_ENREF_88)]. Small EVs from resting platelets exerted a contrary effect and decreasedHLA-DP, DQ, DR and CD80 expression during human PBMC differentiation[[160](#_ENREF_160)].While CD14 expression decreased similar to control cells, platelet EV also decreased endocytic capacity. Neutrophil EVs decreased immature dendritic cell phagocytic capacity and increased TGFβ release. Furthermore, LPS mediated maturation was severely impaired including surface marker expression, cytokine production and induction of T cell proliferation[[171](#_ENREF_171)] 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[[105-107](#_ENREF_105)]. B cell interaction with EVs can enhance or diminish B cell function[[172](#_ENREF_172),[173](#_ENREF_173)], however, a link to atherosclerosis remains to be defined.

Among T helper cells, IFNγ-producing TH1 cells strongly promote atherosclerotic lesion formation. In the current experimental models, there appears to be no major role for TH2 cells in atherogenesis, while regulatory T cells and their marker cytokines such as IL-10 can attenuate lesion formation[[105-107](#_ENREF_105)]. The impact of TH17 cells and their marker cytokine IL-17, which has a significant role in attraction of innate leukocytes such as neutrophilic granulocytes and monocytes[[174](#_ENREF_174)], appears to be highly context-dependent[[10](#_ENREF_10),[175](#_ENREF_175)]. Recent data show that proatherogenic lipoproteins can enhance TH17 polarization[[176](#_ENREF_176)]. IL-17 production in T cells is markedly enhanced by environmental chemicals via the aryl hydrocarbon receptor[[177-180](#_ENREF_177)]. Its ligands are well known uremic toxins[[181](#_ENREF_181),[182](#_ENREF_182)]. Indeed, the IL-17 production was significantly increased in a cohort of patients with end stage renal disease[[183](#_ENREF_183)]. Mechanistically, IL-17 was instrumental in increased myeloid cell accumulation and lesion burden in moderate renal impairment[[104](#_ENREF_104)].

The effect of EVs on T cell function *in vitro* significantly varies depending on the cell of origin (Figure 2). Endothelial EVs enhanced CD4+ T cell proliferation in mixed lymphocyte reaction via modulation of dendritic cell maturation, resulting in enhanced TNF and IFNγ secretion[[169](#_ENREF_169)]. Similarly, EVs from TNF-stimulated HUVECs induced TH1 differentiation in human PBMCs[[184](#_ENREF_184)]. Erythrocyte EVs induced T cell proliferation indirectly via monocyte derived antigen presenting cell polarization. This stimulated the production of the pro-atherogenic cytokines IL-1β, IL-2, IL-7, IL-17 and IFNγ during co-culture of human PBMCs[[82](#_ENREF_82)]. In contrast, small platelet EVs directly interacted with CD4+ T cells. They decreased IFNγ, TNF and IL-6 production during polarization[[185](#_ENREF_185)]. This was at least in part due to an increase in regulatory T cells induced by EV TGFβ. EVs from antigen presenting cells promote T cell priming[[186](#_ENREF_186),[187](#_ENREF_187)]. In atherosclerosis, plasma and plaque EVs contain MHCI, MHCII and CD40L as EV surface antigens and it is therefore conceivable that these processes are also active during atherosclerosis *in vivo*[[38](#_ENREF_38),[88](#_ENREF_88)].

**CONCLUSION**

Data on mechanisms how EVs modulate leukocyte adhesion, differentiation and vascular function in inflammation have greatly enhanced our understanding of these pathophysiologic 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.

**REFERENCES**

1 **Camussi G**, Deregibus MC, Bruno S, Cantaluppi V, Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int* 2010; **78**: 838-848 [PMID: 20703216 DOI: 10.1038/ki.2010.278]

2 **Choi DS**, Kim DK, Kim YK, Gho YS. Proteomics, transcriptomics and lipidomics of exosomes and ectosomes. *Proteomics* 2013; **13**: 1554-1571 [PMID: 23401200 DOI: 10.1002/pmic.201200329]

3 **Colombo M**, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu Rev Cell Dev Biol* 2014; **30**: 255-289 [PMID: 25288114 DOI: 10.1146/annurev-cellbio-101512-122326]

4 **Yáñez-Mó M**, Siljander PR, Andreu Z, Zavec AB, Borràs FE, Buzas EI, Buzas K, Casal E, Cappello F, Carvalho J, Colás E, Cordeiro-da Silva A, Fais S, Falcon-Perez JM, Ghobrial IM, Giebel B, Gimona M, Graner M, Gursel I, Gursel M, Heegaard NH, Hendrix A, Kierulf P, Kokubun K, Kosanovic M, Kralj-Iglic V, Krämer-Albers EM, Laitinen S, Lässer C, Lener T, Ligeti E, Linē A, Lipps G, Llorente A, Lötvall J, Manček-Keber M, Marcilla A, Mittelbrunn M, Nazarenko I, Nolte-'t Hoen EN, Nyman TA, O'Driscoll L, Olivan M, Oliveira C, Pállinger É, Del Portillo HA, Reventós J, Rigau M, Rohde E, Sammar M, Sánchez-Madrid F, Santarém N, Schallmoser K, Ostenfeld MS, Stoorvogel W, Stukelj R, Van der Grein SG, Vasconcelos MH, Wauben MH, De Wever O. Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles* 2015; **4**: 27066 [PMID: 25979354 DOI: 10.3402/jev.v4.27066]

5 **Théry C**, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol* 2009; **9**: 581-593 [PMID: 19498381 DOI: 10.1038/nri2567]

6 **Robbins PD**, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol* 2014; **14**: 195-208 [PMID: 24566916 DOI: 10.1038/nri362]

7 **Suades R**, Padró T, Badimon L. The Role of Blood-Borne Microparticles in Inflammation and Hemostasis. *Semin Thromb Hemost* 2015; **41**: 590-606 [PMID: 26276937 DOI: 10.1055/s-0035-1556591]

8 **Wick G**, Romen M, Amberger A, Metzler B, Mayr M, Falkensammer G, Xu Q. Atherosclerosis, autoimmunity, and vascular-associated lymphoid tissue. *FASEB J* 1997; **11**: 1199-1207 [PMID: 9367355]

9 **Bobryshev YV**, Lord RS. Ultrastructural recognition of cells with dendritic cell morphology in human aortic intima. Contacting interactions of Vascular Dendritic Cells in athero-resistant and athero-prone areas of the normal aorta. *Arch Histol Cytol* 1995; **58**: 307-322 [PMID: 8527238]

10 **von Vietinghoff S**, Ley K. Interleukin 17 in vascular inflammation. *Cytokine Growth Factor Rev* 2010; **21**: 463-469 [PMID: 21075042 DOI: 10.1016/j.cytogfr.2010.10.003]

11 **Schmidt S**, Moser M, Sperandio M. The molecular basis of leukocyte recruitment and its deficiencies. *Mol Immunol* 2013; **55**: 49-58 [PMID: 23253941 DOI: 10.1016/j.molimm.2012.11.006]

12 **Marki A**, Esko JD, Pries AR, Ley K. Role of the endothelial surface layer in neutrophil recruitment. *J Leukoc Biol* 2015; **98**: 503-515 [PMID: 25979432 DOI: 10.1189/jlb.3MR0115-011R]

13 **Williams MR**, Azcutia V, Newton G, Alcaide P, Luscinskas FW. Emerging mechanisms of neutrophil recruitment across endothelium. *Trends Immunol* 2011; **32**: 461-469 [PMID: 21839681 DOI: 10.1016/j.it.2011.06.009]

14 **Voisin MB**, Nourshargh S. Neutrophil transmigration: emergence of an adhesive cascade within venular walls. *J Innate Immun* 2013; **5**: 336-347 [PMID: 23466407 DOI: 10.1159/000346659]

15 **Pierson RN**, Bromberg JS. Alloantibodies and Allograft Arteriosclerosis: Accelerated Adversity Ahead? *Circ Res* 2015; **117**: 398-400 [PMID: 26271536 DOI: 10.1161/CIRCRESAHA.115.307065]

16 **Halloran PF**, Reeve JP, Pereira AB, Hidalgo LG, Famulski KS. Antibody-mediated rejection, T cell-mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies. *Kidney Int* 2014; **85**: 258-264 [PMID: 23965521 DOI: 10.1038/ki.2013.300]

17 **Günthner T**, Jankowski V, Kretschmer A, Nierhaus M, Van Der Giet M, Zidek W, Jankowski J. PROGRESS IN UREMIC TOXIN RESEARCH: Endothelium and Vascular Smooth Muscle Cells in the Context of Uremia. *Semin Dial* 2009; **22**: 428-432 [DOI: 10.1111/j.1525-139X.2009.00594.x]

18 **Jourde-Chiche N**, Dou L, Cerini C, Dignat-George F, Brunet P. Vascular incompetence in dialysis patients--protein-bound uremic toxins and endothelial dysfunction. *Semin Dial* 2011; **24**: 327-337 [PMID: 21682773 DOI: 10.1111/j.1525-139X.2011.00925.x]

19 **Neven E**, De Schutter TM, De Broe ME, D'Haese PC. Cell biological and physicochemical aspects of arterial calcification. *Kidney Int* 2011; **79**: 1166-1177 [PMID: 21412217 DOI: 10.1038/ki.2011.59]

20 **Stenvinkel P**, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin J Am Soc Nephrol* 2008; **3**: 505-521 [PMID: 18184879 DOI: 10.2215/CJN.03670807]

21 **Amann K**. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol* 2008; **3**: 1599-1605 [PMID: 18815240 DOI: 10.2215/CJN.02120508]

22 **Schlieper G**, Schurgers L, Brandenburg V, Reutlingsperger C, Floege J. Vascular calcification in chronic kidney disease: an update. *Nephrol Dial Transplant* 2015; Epub ahead of print [PMID: 25916871]

23 **Betjes MG**. Immune cell dysfunction and inflammation in end-stage renal disease. *Nat Rev Nephrol* 2013; **9**: 255-265 [PMID: 23507826 DOI: 10.1038/nrneph.2013.44]

24 **Druml W**. Systemic consequences of acute kidney injury. *Curr Opin Crit Care* 2014; **20**: 613-619 [PMID: 25259720 DOI: 10.1097/MCC.0000000000000150]

25 **Kurts C**, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. *Nat Rev Immunol* 2013; **13**: 738-753 [PMID: 24037418 DOI: 10.1038/nri3523]

26 **Wolf P**. The nature and significance of platelet products in human plasma. *Br J Haematol* 1967; **13**: 269-288 [PMID: 6025241]

27 **Kim DK**, Lee J, Kim SR, Choi DS, Yoon YJ, Kim JH, Go G, Nhung D, Hong K, Jang SC, Kim SH, Park KS, Kim OY, Park HT, Seo JH, Aikawa E, Baj-Krzyworzeka M, van Balkom BW, Belting M, Blanc L, Bond V, Bongiovanni A, Borràs FE, Buée L, Buzás EI, Cheng L, Clayton A, Cocucci E, Dela Cruz CS, Desiderio DM, Di Vizio D, Ekström K, Falcon-Perez JM, Gardiner C, Giebel B, Greening DW, Gross JC, Gupta D, Hendrix A, Hill AF, Hill MM, Nolte-'t Hoen E, Hwang do W, Inal J, Jagannadham MV, Jayachandran M, Jee YK, Jørgensen M, Kim KP, Kim YK, Kislinger T, Lässer C, Lee DS, Lee H, van Leeuwen J, Lener T, Liu ML, Lötvall J, Marcilla A, Mathivanan S, Möller A, Morhayim J, Mullier F, Nazarenko I, Nieuwland R, Nunes DN, Pang K, Park J, Patel T, Pocsfalvi G, Del Portillo H, Putz U, Ramirez MI, Rodrigues ML, Roh TY, Royo F, Sahoo S, Schiffelers R, Sharma S, Siljander P, Simpson RJ, Soekmadji C, Stahl P, Stensballe A, Stępień E, Tahara H, Trummer A, Valadi H, Vella LJ, Wai SN, Witwer K, Yáñez-Mó M, Youn H, Zeidler R, Gho YS. EVpedia: a community web portal for extracellular vesicles research. *Bioinformatics* 2015; **31**: 933-939 [PMID: 25388151 DOI: 10.1093/bioinformatics/btu741]

28 **Raposo G**, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 2013; **200**: 373-383 [PMID: 23420871 DOI: 10.1083/jcb.201211138]

29 **Gould SJ**, Raposo G. As we wait: coping with an imperfect nomenclature for extracellular vesicles. *J Extracell Vesicles* 2013; **2**: [PMID: 24009890 DOI: 10.3402/jev.v2i0.20389]

30 **Choi DS**, Kim DK, Kim YK, Gho YS. Proteomics of extracellular vesicles: Exosomes and ectosomes. *Mass Spectrom Rev* 2014; **34**: 474-490 [PMID: 24421117 DOI: 10.1002/mas.21420]

31 **Pluskota E**, Woody NM, Szpak D, Ballantyne CM, Soloviev DA, Simon DI, Plow EF. Expression, activation, and function of integrin alphaMbeta2 (Mac-1) on neutrophil-derived microparticles. *Blood* 2008; **112**: 2327-2335 [PMID: 18509085 DOI: 10.1182/blood-2007-12-127183]

32 **Ayers L**, Kohler M, Harrison P, Sargent I, Dragovic R, Schaap M, Nieuwland R, Brooks SA, Ferry B. Measurement of circulating cell-derived microparticles by flow cytometry: sources of variability within the assay. *Thromb Res* 2011; **127**: 370-377 [PMID: 21257195 DOI: 10.1016/j.thromres.2010.12.014]

33 **Yuana Y**, Bertina RM, Osanto S. Pre-analytical and analytical issues in the analysis of blood microparticles. *Thromb Haemost* 2011; **105**: 396-408 [PMID: 21174005 DOI: 10.1160/TH10-09-0595]

34 **Witwer KW**, Buzás EI, Bemis LT, Bora A, Lässer C, Lötvall J, Nolte-'t Hoen EN, Piper MG, Sivaraman S, Skog J, Théry C, Wauben MH, Hochberg F. Standardization of sample collection, isolation and analysis methods in extracellular vesicle research. *J Extracell Vesicles* 2013; **2**: [PMID: 24009894 DOI: 10.3402/jev.v2i0.20360]

35 **Chistiakov DA**, Orekhov AN, Bobryshev YV. Extracellular vesicles and atherosclerotic disease. *Cell Mol Life Sci* 2015; **72**: 2697-2708 [PMID: 25894694 DOI: 10.1007/s00018-015-1906-2]

36 **Gaceb A**, Martinez MC, Andriantsitohaina R. Extracellular vesicles: new players in cardiovascular diseases. *Int J Biochem Cell Biol* 2014; **50**: 24-28 [PMID: 24509128 DOI: 10.1016/j.biocel.2014.01.018]

37 **van der Pol E**, Böing AN, Harrison P, Sturk A, Nieuwland R. Classification, functions, and clinical relevance of extracellular vesicles. *Pharmacol Rev* 2012; **64**: 676-705 [PMID: 22722893 DOI: 10.1124/pr.112.005983]

38 **Mayr M**, Grainger D, Mayr U, Leroyer AS, Leseche G, Sidibe A, Herbin O, Yin X, Gomes A, Madhu B, Griffiths JR, Xu Q, Tedgui A, Boulanger CM. Proteomics, metabolomics, and immunomics on microparticles derived from human atherosclerotic plaques. *Circ Cardiovasc Genet* 2009; **2**: 379-388 [PMID: 20031610 DOI: 10.1161/CIRCGENETICS.108.842849]

39 **Loyer X**, Vion AC, Tedgui A, Boulanger CM. Microvesicles as cell-cell messengers in cardiovascular diseases. *Circ Res* 2014; **114**: 345-353 [PMID: 24436430 DOI: 10.1161/CIRCRESAHA.113.300858]

40 [**Erdbrügger U**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Erdbr%C3%BCgger%20U%5BAuthor%5D&cauthor=true&cauthor_uid=26251351), [Le TH](http://www.ncbi.nlm.nih.gov/pubmed/?term=Le%20TH%5BAuthor%5D&cauthor=true&cauthor_uid=26251351). Extracellular Vesicles in Renal Diseases: More than Novel Biomarkers? *J Am Soc Nephrol* 2015; Epub ahead of print [PMID: 26251351]

41 **Faure V**, Dou L, Sabatier F, Cerini C, Sampol J, Berland Y, Brunet P, Dignat-George F. Elevation of circulating endothelial microparticles in patients with chronic renal failure. *J Thromb Haemost* 2006; **4**: 566-573 [PMID: 16405517]

42 **Boulanger CM**, Amabile N, Guérin AP, Pannier B, Leroyer AS, Mallat CN, Tedgui A, London GM. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease. *Hypertension* 2007; **49**: 902-908 [PMID: 17309952]

43 **Amabile N**, Guérin AP, Leroyer A, Mallat Z, Nguyen C, Boddaert J, London GM, Tedgui A, Boulanger CM. Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. *J Am Soc Nephrol* 2005; **16**: 3381-3388 [PMID: 16192427]

44 **Ando M**, Iwata A, Ozeki Y, Tsuchiya K, Akiba T, Nihei H. Circulating platelet-derived microparticles with procoagulant activity may be a potential cause of thrombosis in uremic patients. *Kidney Int* 2002; **62**: 1757-1763 [PMID: 12371977]

45 **Trappenburg MC**, van Schilfgaarde M, Frerichs FC, Spronk HM, ten Cate H, de Fijter CW, Terpstra WE, Leyte A. Chronic renal failure is accompanied by endothelial activation and a large increase in microparticle numbers with reduced procoagulant capacity. *Nephrol Dial Transplant* 2012; **27**: 1446-1453 [PMID: 21873622 DOI: 10.1093/ndt/gfr474]

46 **Burton JO**, Hamali HA, Singh R, Abbasian N, Parsons R, Patel AK, Goodall AH, Brunskill NJ. Elevated levels of procoagulant plasma microvesicles in dialysis patients. *PLoS One* 2013; **8**: e72663 [PMID: 23936542 DOI: 10.1371/journal.pone.0072663]

47 **Daniel L**, Fakhouri F, Joly D, Mouthon L, Nusbaum P, Grunfeld JP, Schifferli J, Guillevin L, Lesavre P, Halbwachs-Mecarelli L. Increase of circulating neutrophil and platelet microparticles during acute vasculitis and hemodialysis. *Kidney Int* 2006; **69**: 1416-1423 [PMID: 16531979]

48 **Qamri Z**, Pelletier R, Foster J, Kumar S, Momani H, Ware K, Von Visger J, Satoskar A, Nadasdy T, Brodsky SV. Early posttransplant changes in circulating endothelial microparticles in patients with kidney transplantation. *Transpl Immunol* 2014; **31**: 60-64 [PMID: 25008980 DOI: 10.1016/j.trim.2014.06.006]

49 **Chen YL**, Chen CH, Wallace CG, Wang HT, Yang CC, Yip HK. Levels of circulating microparticles in patients with chronic cardiorenal disease. *J Atheroscler Thromb* 2015; **22**: 247-256 [PMID: 25342381 DOI: 10.5551/jat.26658]

50 **Angelillo-Scherrer A**. Leukocyte-derived microparticles in vascular homeostasis. *Circ Res* 2012; **110**: 356-369 [PMID: 22267840 DOI: 10.1161/CIRCRESAHA.110.233403]

51 **Morel O**, Morel N, Jesel L, Freyssinet JM, Toti F. Microparticles: a critical component in the nexus between inflammation, immunity, and thrombosis. *Semin Immunopathol* 2011; **33**: 469-486 [PMID: 21866419 DOI: 10.1007/s00281-010-0239-3]

52 **Viera AJ**, Mooberry M, Key NS. Microparticles in cardiovascular disease pathophysiology and outcomes. *J Am Soc Hypertens* 2012; **6**: 243-252 [PMID: 22789878 DOI: 10.1016/j.jash.2012.06.003]

53 **Amabile N**, Rautou PE, Tedgui A, Boulanger CM. Microparticles: key protagonists in cardiovascular disorders. *Semin Thromb Hemost* 2010; **36**: 907-916 [PMID: 21069633 DOI: 10.1055/s-0030-1267044]

54 **Arteaga RB**, Chirinos JA, Soriano AO, Jy W, Horstman L, Jimenez JJ, Mendez A, Ferreira A, de Marchena E, Ahn YS. Endothelial microparticles and platelet and leukocyte activation in patients with the metabolic syndrome. *Am J Cardiol* 2006; **98**: 70-74 [PMID: 16784924]

55 **Nomura S**, Inami N, Ozaki Y, Kagawa H, Fukuhara S. Significance of microparticles in progressive systemic sclerosis with interstitial pneumonia. *Platelets* 2008; **19**: 192-198 [PMID: 18432520 DOI: 10.1080/09537100701882038]

56 **Preston RA**, Jy W, Jimenez JJ, Mauro LM, Horstman LL, Valle M, Aime G, Ahn YS. Effects of severe hypertension on endothelial and platelet microparticles. *Hypertension* 2003; **41**: 211-217 [PMID: 12574084]

57 **Huang PH**, Huang SS, Chen YH, Lin CP, Chiang KH, Chen JS, Tsai HY, Lin FY, Chen JW, Lin SJ. Increased circulating CD31+/annexin V+ apoptotic microparticles and decreased circulating endothelial progenitor cell levels in hypertensive patients with microalbuminuria. *J Hypertens* 2010; **28**: 1655-1665 [PMID: 20520578 DOI: 10.1097/HJH.0b013e32833a4d0a]

58 **Martinez MC**, Tual-Chalot S, Leonetti D, Andriantsitohaina R. Microparticles: targets and tools in cardiovascular disease. *Trends Pharmacol Sci* 2011; **32**: 659-665 [PMID: 21794929 DOI: 10.1016/j.tips.2011.06.005]

59 **Amabile N**, Guérin AP, Tedgui A, Boulanger CM, London GM. Predictive value of circulating endothelial microparticles for cardiovascular mortality in end-stage renal failure: a pilot study. *Nephrol Dial Transplant* 2012; **27**: 1873-1880 [PMID: 22036944 DOI: 10.1093/ndt/gfr573]

60 **Eyre J**, Burton JO, Saleem MA, Mathieson PW, Topham PS, Brunskill NJ. Monocyte- and endothelial-derived microparticles induce an inflammatory phenotype in human podocytes. *Nephron Exp Nephrol* 2011; **119**: e58-e66 [PMID: 21849801 DOI: 10.1159/000329575]

61 **Pisetsky DS**, Ullal AJ, Gauley J, Ning TC. Microparticles as mediators and biomarkers of rheumatic disease. *Rheumatology* (Oxford) 2012; **51**: 1737-1746 [PMID: 22403183]

62 **Beyer C**, Pisetsky DS. The role of microparticles in the pathogenesis of rheumatic diseases. *Nat Rev Rheumatol* 2010; **6**: 21-29 [PMID: 19949432 DOI: 10.1038/nrrheum.2009.229]

63 **Pereira J**, Alfaro G, Goycoolea M, Quiroga T, Ocqueteau M, Massardo L, Pérez C, Sáez C, Panes O, Matus V, Mezzano D. Circulating platelet-derived microparticles in systemic lupus erythematosus. Association with increased thrombin generation and procoagulant state. *Thromb Haemost* 2006; **95**: 94-99 [PMID: 16543967]

64 **Sellam J**, Proulle V, Jüngel A, Ittah M, Miceli Richard C, Gottenberg JE, Toti F, Benessiano J, Gay S, Freyssinet JM, Mariette X. Increased levels of circulating microparticles in primary Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis and relation with disease activity. *Arthritis Res Ther* 2009; **11**: R156 [PMID: 19832990 DOI: 10.1186/ar2833]

65 **Willemze R**, Bradford RL, Mooberry MJ, Roubey RA, Key NS. Plasma microparticle tissue factor activity in patients with antiphospholipid antibodies with and without clinical complications. *Thromb Res* 2014; **133**: 187-189 [PMID: 24332063 DOI: 10.1016/j.thromres.2013.11.027]

66 **Combes V**, Simon AC, Grau GE, Arnoux D, Camoin L, Sabatier F, Mutin M, Sanmarco M, Sampol J, Dignat-George F. In vitro generation of endothelial microparticles and possible prothrombotic activity in patients with lupus anticoagulant. *J Clin Invest* 1999; **104**: 93-102 [PMID: 10393703 DOI: 10.1172/JCI4985]

67 **Nielsen CT**, Østergaard O, Stener L, Iversen LV, Truedsson L, Gullstrand B, Jacobsen S, Heegaard NH. Increased IgG on cell-derived plasma microparticles in systemic lupus erythematosus is associated with autoantibodies and complement activation. *Arthritis Rheum* 2012; **64**: 1227-1236 [PMID: 22238051 DOI: 10.1002/art.34381]

68 **Østergaard O**, Nielsen CT, Iversen LV, Tanassi JT, Knudsen S, Jacobsen S, Heegaard NH. Unique protein signature of circulating microparticles in systemic lupus erythematosus. *Arthritis Rheum* 2013; **65**: 2680-2690 [PMID: 23817959 DOI: 10.1002/art.38065]

69 **Nielsen CT**, Østergaard O, Rekvig OP, Sturfelt G, Jacobsen S, Heegaard NH. Galectin-3 binding protein links circulating microparticles with electron dense glomerular deposits in lupus nephritis. *Lupus* 2015; **24**: 1150-1160 [PMID: 25837289 DOI: 10.1177/0961203315580146]

70 **Brogan PA**, Shah V, Brachet C, Harnden A, Mant D, Klein N, Dillon MJ. Endothelial and platelet microparticles in vasculitis of the young. *Arthritis Rheum* 2004; **50**: 927-936 [PMID: 15022336]

71 **Erdbruegger U**, Grossheim M, Hertel B, Wyss K, Kirsch T, Woywodt A, Haller H, Haubitz M. Diagnostic role of endothelial microparticles in vasculitis. *Rheumatology* (Oxford) 2008; **47**: 1820-1825 [PMID: 18927191 DOI: 10.1093/rheumatology/ken373]

72 **Hong Y**, Eleftheriou D, Hussain AA, Price-Kuehne FE, Savage CO, Jayne D, Little MA, Salama AD, Klein NJ, Brogan PA. Anti-neutrophil cytoplasmic antibodies stimulate release of neutrophil microparticles. *J Am Soc Nephrol* 2012; **23**: 49-62 [PMID: 22052057 DOI: 10.1681/ASN.2011030298]

73 **Bertram A**, Lovric S, Engel A, Beese M, Wyss K, Hertel B, Park JK, Becker JU, Kegel J, Haller H, Haubitz M, Kirsch T. Circulating ADAM17 Level Reflects Disease Activity in Proteinase-3 ANCA-Associated Vasculitis. *J Am Soc Nephrol* 2015; **26**: 2860-2870 [PMID: 25788529 DOI: 10.1681/ASN.2014050477]

74 **Jennette JC**, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol* 2014; **10**: 463-473 [PMID: 25003769 DOI: 10.1038/nrrheum.2014.103]

75 **Zhao L**, David MZ, Hyjek E, Chang A, Meehan SM. M2 macrophage infiltrates in the early stages of ANCA-associated pauci-immune necrotizing GN. *Clin J Am Soc Nephrol* 2015; **10**: 54-62 [PMID: 25516918 DOI: 10.2215/CJN.03230314]

76 **Apostolidou E**, Skendros P, Kambas K, Mitroulis I, Konstantinidis T, Chrysanthopoulou A, Nakos K, Tsironidou V, Koffa M, Boumpas DT, Ritis K. Neutrophil extracellular traps regulate IL-1β-mediated inflammation in familial Mediterranean fever. *Ann Rheum Dis* 2016; **75**: 269-277 [PMID: 25261578 DOI: 10.1136/annrheumdis-2014-205958]

77 Huang YM, Wang H, Wang C, Chen M, Zhao MH. C5a inducing tissue factor expressing microparticles and neutrophil extracellular traps promote hypercoagulability in ANCA‐associated vasculitis. Arthritis Rheumatol 2015; 10: 2780-2790 [DOI: 10.1002/art.39239]

78 **Ståhl AL**, Sartz L, Karpman D. Complement activation on platelet-leukocyte complexes and microparticles in enterohemorrhagic Escherichia coli-induced hemolytic uremic syndrome. *Blood* 2011; **117**: 5503-5513 [PMID: 21447825 DOI: 10.1182/blood-2010-09-309161]

79 **Ge S**, Hertel B, Emden SH, Beneke J, Menne J, Haller H, von Vietinghoff S. Microparticle generation and leucocyte death in Shiga toxin-mediated HUS. *Nephrol Dial Transplant* 2012; **27**: 2768-2775 [PMID: 22234918 DOI: 10.1093/ndt/gfr748]

80 **Ståhl AL**, Sartz L, Nelsson A, Békássy ZD, Karpman D. Shiga toxin and lipopolysaccharide induce platelet-leukocyte aggregates and tissue factor release, a thrombotic mechanism in hemolytic uremic syndrome. *PLoS One* 2009; **4**: e6990 [PMID: 19750223 DOI: 10.1371/journal.pone.0006990]

81 **Arvidsson I**, Ståhl AL, Hedström MM, Kristoffersson AC, Rylander C, Westman JS, Storry JR, Olsson ML, Karpman D. Shiga toxin-induced complement-mediated hemolysis and release of complement-coated red blood cell-derived microvesicles in hemolytic uremic syndrome. *J Immunol* 2015; **194**: 2309-2318 [PMID: 25637016 DOI: 10.4049/jimmunol.1402470]

82 **Danesh A**, Inglis HC, Jackman RP, Wu S, Deng X, Muench MO, Heitman JW, Norris PJ. Exosomes from red blood cell units bind to monocytes and induce proinflammatory cytokines, boosting T-cell responses in vitro. *Blood* 2014; **123**: 687-696 [PMID: 24335232 DOI: 10.1182/blood-2013-10-530469]

83 **Ståhl AL**, Arvidsson I, Johansson KE, Chromek M, Rebetz J, Loos S, Kristoffersson AC, Békássy ZD, Mörgelin M, Karpman D. A novel mechanism of bacterial toxin transfer within host blood cell-derived microvesicles. *PLoS Pathog* 2015; **11**: e1004619 [PMID: 25719452 DOI: 10.1371/journal.ppat.1004619]

84 **Tesh VL**. The induction of apoptosis by Shiga toxins and ricin. *Curr Top Microbiol Immunol* 2012; **357**: 137-178 [PMID: 22130961 DOI: 10.1007/82\_2011\_155]

85 **Mallat Z**, Hugel B, Ohan J, Lesèche G, Freyssinet JM, Tedgui A. Shed membrane microparticles with procoagulant potential in human atherosclerotic plaques: a role for apoptosis in plaque thrombogenicity. *Circulation* 1999; **99**: 348-353 [PMID: 9918520]

86 **Leroyer AS**, Isobe H, Lesèche G, Castier Y, Wassef M, Mallat Z, Binder BR, Tedgui A, Boulanger CM. Cellular origins and thrombogenic activity of microparticles isolated from human atherosclerotic plaques. *J Am Coll Cardiol* 2007; **49**: 772-777 [PMID: 17306706]

87 **Serrano-Pertierra E**, Benavente L, Blanco-Gelaz MÁ, Fernández-Martín JL, Lahoz CH, Calleja S, López-Larrea C, Cernuda-Morollón E. Lysophosphatidylcholine Induces Vascular Smooth Muscle Cell Membrane Vesiculation: Potential Role in Atherosclerosis through Caveolin-1 Regulation. *JPB* 2014; **7**: 332 [DOI: 10.4172/jpb.1000336]

88 **Leroyer AS**, Rautou PE, Silvestre JS, Castier Y, Lesèche G, Devue C, Duriez M, Brandes RP, Lutgens E, Tedgui A, Boulanger CM. CD40 ligand+ microparticles from human atherosclerotic plaques stimulate endothelial proliferation and angiogenesis a potential mechanism for intraplaque neovascularization. *J Am Coll Cardiol* 2008; **52**: 1302-1311 [PMID: 18929241 DOI: 10.1016/j.jacc.2008.07.032]

89 **Bochmann I**, Ebstein F, Lehmann A, Wohlschlaeger J, Sixt SU, Kloetzel PM, Dahlmann B. T lymphocytes export proteasomes by way of microparticles: a possible mechanism for generation of extracellular proteasomes. *J Cell Mol Med* 2014; **18**: 59-68 [PMID: 24304442 DOI: 10.1111/jcmm.12160]

90 **Wang JG**, Williams JC, Davis BK, Jacobson K, Doerschuk CM, Ting JP, Mackman N. Monocytic microparticles activate endothelial cells in an IL-1β-dependent manner. *Blood* 2011; **118**: 2366-2374 [PMID: 21700772 DOI: 10.1182/blood-2011-01-330878]

91 **Zernecke A**, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, Hristov M, Köppel T, Jahantigh MN, Lutgens E, Wang S, Olson EN, Schober A, Weber C. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. *Sci Signal* 2009; **2**: ra81 [PMID: 19996457 DOI: 10.1126/scisignal.2000610]

92 **Ismail N**, Wang Y, Dakhlallah D, Moldovan L, Agarwal K, Batte K, Shah P, Wisler J, Eubank TD, Tridandapani S, Paulaitis ME, Piper MG, Marsh CB. Macrophage microvesicles induce macrophage differentiation and miR-223 transfer. *Blood* 2013; **121**: 984-995 [PMID: 23144169 DOI: 10.1182/blood-2011-08-374793]

93 **Bilyy RO**, Shkandina T, Tomin A, Muñoz LE, Franz S, Antonyuk V, Kit YY, Zirngibl M, Fürnrohr BG, Janko C, Lauber K, Schiller M, Schett G, Stoika RS, Herrmann M. Macrophages discriminate glycosylation patterns of apoptotic cell-derived microparticles. *J Biol Chem* 2012; **287**: 496-503 [PMID: 22074924 DOI: 10.1074/jbc.M111.273144]

94 **Huber LC**, Jüngel A, Distler JH, Moritz F, Gay RE, Michel BA, Pisetsky DS, Gay S, Distler O. The role of membrane lipids in the induction of macrophage apoptosis by microparticles. *Apoptosis* 2007; **12**: 363-374 [PMID: 17191114]

95 **Miller YI**, Choi SH, Fang L, Tsimikas S. Lipoprotein modification and macrophage uptake: role of pathologic cholesterol transport in atherogenesis. *Subcell Biochem* 2010; **51**: 229-251 [PMID: 20213546 DOI: 10.1007/978-90-481-8622-8\_8]

96 **Connolly KD**, Willis GR, Datta DB, Ellins EA, Ladell K, Price DA, Guschina IA, Rees DA, James PE. Lipoprotein-apheresis reduces circulating microparticles in individuals with familial hypercholesterolemia. *J Lipid Res* 2014; **55**: 2064-2072 [PMID: 25121984 DOI: 10.1194/jlr.M049726]

97 **Kon V**, Yang H, Fazio S. Residual Cardiovascular Risk in Chronic Kidney Disease: Role of High-density Lipoprotein. *Arch Med Res* 2015; **46**: 379-391 [PMID: 26009251 DOI: 10.1016/j.arcmed.2015.05.009]

98 **Pawlak K**, Mysliwiec M, Pawlak D. Oxidized low-density lipoprotein (oxLDL) plasma levels and oxLDL to LDL ratio - are they real oxidative stress markers in dialyzed patients? *Life Sci* 2013; **92**: 253-258 [PMID: 23295961 DOI: 10.1016/j.lfs.2012.12.002]

99 **Kon V**, Linton MF, Fazio S. Atherosclerosis in chronic kidney disease: the role of macrophages. *Nat Rev Nephrol* 2011; **7**: 45-54 [PMID: 21102540 DOI: 10.1038/nrneph.2010.157]

100 **Schiffrin EL**, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation* 2007; **116**: 85-97 [PMID: 17606856]

101 **Coresh J**, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038-2047 [PMID: 17986697 DOI: 10.1001/jama.298.17.2038]

102 **Campean V**, Neureiter D, Varga I, Runk F, Reiman A, Garlichs C, Achenbach S, Nonnast-Daniel B, Amann K. Atherosclerosis and vascular calcification in chronic renal failure. *Kidney Blood Press Res* 2005; **28**: 280-289 [PMID: 16534222]

103 **Buzello M**, Törnig J, Faulhaber J, Ehmke H, Ritz E, Amann K. The apolipoprotein e knockout mouse: a model documenting accelerated atherogenesis in uremia. *J Am Soc Nephrol* 2003; **14**: 311-316 [PMID: 12538731]

104 **Ge S**, Hertel B, Koltsova EK, Sörensen-Zender I, Kielstein JT, Ley K, Haller H, von Vietinghoff S. Increased atherosclerotic lesion formation and vascular leukocyte accumulation in renal impairment are mediated by interleukin-17A. *Circ Res* 2013; **113**: 965-974 [PMID: 23908345 DOI: 10.1161/CIRCRESAHA.113.301934]

105 **Libby P**, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. *Immunity* 2013; **38**: 1092-1104 [PMID: 23809160 DOI: 10.1016/j.immuni.2013.06.009]

106 **Sheedy FJ**, Moore KJ. IL-1 signaling in atherosclerosis: sibling rivalry. *Nat Immunol* 2013; **14**: 1030-1032 [PMID: 24048132 DOI: 10.1038/ni.2711]

107 **Weber C**, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. *Nat Med* 2011; **17**: 1410-1422 [PMID: 22064431 DOI: 10.1038/nm.2538]

108 **Rautou PE**, Leroyer AS, Ramkhelawon B, Devue C, Duflaut D, Vion AC, Nalbone G, Castier Y, Leseche G, Lehoux S, Tedgui A, Boulanger CM. Microparticles from human atherosclerotic plaques promote endothelial ICAM-1-dependent monocyte adhesion and transendothelial migration. *Circ Res* 2011; **108**: 335-343 [PMID: 21164106 DOI: 10.1161/CIRCRESAHA]

109 **Canault M**, Leroyer AS, Peiretti F, Lesèche G, Tedgui A, Bonardo B, Alessi MC, Boulanger CM, Nalbone G. Microparticles of human atherosclerotic plaques enhance the shedding of the tumor necrosis factor-alpha converting enzyme/ADAM17 substrates, tumor necrosis factor and tumor necrosis factor receptor-1. *Am J Pathol* 2007; **171**: 1713-1723 [PMID: 17872973]

110 **Distler JH**, Jüngel A, Huber LC, Seemayer CA, Reich CF, Gay RE, Michel BA, Fontana A, Gay S, Pisetsky DS, Distler O. The induction of matrix metalloproteinase and cytokine expression in synovial fibroblasts stimulated with immune cell microparticles. *Proc Natl Acad Sci USA* 2005; **102**: 2892-2897 [PMID: 15701693]

111 **Mesri M**, Altieri DC. Endothelial cell activation by leukocyte microparticles. *J Immunol* 1998; **161**: 4382-4387 [PMID: 9780216]

112 **Martin S**, Tesse A, Hugel B, Martínez MC, Morel O, Freyssinet JM, Andriantsitohaina R. Shed membrane particles from T lymphocytes impair endothelial function and regulate endothelial protein expression. *Circulation* 2004; **109**: 1653-1659 [PMID: 15023873]

113 **Boulanger CM**, Scoazec A, Ebrahimian T, Henry P, Mathieu E, Tedgui A, Mallat Z. Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. *Circulation* 2001; **104**: 2649-2652 [PMID: 11723013]

114 **Nolan S**, Dixon R, Norman K, Hellewell P, Ridger V. Nitric oxide regulates neutrophil migration through microparticle formation. *Am J Pathol* 2008; **172**: 265-273 [PMID: 18079439]

115 **Kielstein JT**, Fliser D, Veldink H. PROGRESS IN UREMIC TOXIN RESEARCH: Asymmetric Dimethylarginine and Symmetric Dimethylarginine: Axis of Evil or Useful Alliance? *Semin Dial* 2009; **22**: 346-350 [DOI: 10.1111/j.1525-139X.2009.00578.x]

116 **Lacroix R**, Dubois C, Leroyer AS, Sabatier F, Dignat-George F. Revisited role of microparticles in arterial and venous thrombosis. *J Thromb Haemost* 2013; **11** Suppl 1: 24-35 [PMID: 23809108 DOI: 10.1111/jth.12268]

117 **Shantsila E**, Kamphuisen PW, Lip GY. Circulating microparticles in cardiovascular disease: implications for atherogenesis and atherothrombosis. *J Thromb Haemost* 2010; **8**: 2358-2368 [PMID: 20695980 DOI: 10.1111/j.1538-7836.2010.04007.x]

118 **Niccolai E**, Emmi G, Squatrito D, Silvestri E, Emmi L, Amedei A, Prisco D. Microparticles: Bridging the Gap between Autoimmunity and Thrombosis. *Semin Thromb Hemost* 2015; **41**: 413-422 [PMID: 25965903 DOI: 10.1055/s-0035-1549850]

119 **Vajen T**, Mause SF, Koenen RR. Microvesicles from platelets: novel drivers of vascular inflammation. *Thromb Haemost* 2015; **114**: 228-236 [PMID: 25994053 DOI: 10.1160/TH14-11-0962]

120 **Gao C**, Xie R, Yu C, Wang Q, Shi F, Yao C, Xie R, Zhou J, Gilbert GE, Shi J. Procoagulant activity of erythrocytes and platelets through phosphatidylserine exposure and microparticles release in patients with nephrotic syndrome. *Thromb Haemost* 2012; **107**: 681-689 [PMID: 22370875 DOI: 10.1160/TH11-09-0673]

121 **Ruggiero C**, Metter EJ, Cherubini A, Maggio M, Sen R, Najjar SS, Windham GB, Ble A, Senin U, Ferrucci L. White blood cell count and mortality in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2007; **49**: 1841-1850 [PMID: 17481443]

122 **von Vietinghoff S**, Ley K. Homeostatic regulation of blood neutrophil counts. *J Immunol* 2008; **181**: 5183-5188 [PMID: 18832668]

123 **Reddan DN**, Klassen PS, Szczech LA, Coladonato JA, O'Shea S, Owen WF, Lowrie EG. White blood cells as a novel mortality predictor in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 1167-1173 [PMID: 12748351]

124 **Karbach S**, Croxford AL, Oelze M, Schüler R, Minwegen D, Wegner J, Koukes L, Yogev N, Nikolaev A, Reißig S, Ullmann A, Knorr M, Waldner M, Neurath MF, Li H, Wu Z, Brochhausen C, Scheller J, Rose-John S, Piotrowski C, Bechmann I, Radsak M, Wild P, Daiber A, von Stebut E, Wenzel P, Waisman A, Münzel T. Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. *Arterioscler Thromb Vasc Biol* 2014; **34**: 2658-2668 [PMID: 25341795 DOI: 10.1161/ATVBAHA.114.304108]

125 **Warnatsch A**, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. *Science* 2015; **349**: 316-320 [PMID: 26185250 DOI: 10.1126/science.aaa8064]

126 **Dalli J**, Norling LV, Renshaw D, Cooper D, Leung KY, Perretti M. Annexin 1 mediates the rapid anti-inflammatory effects of neutrophil-derived microparticles. *Blood* 2008; **112**: 2512-2519 [PMID: 18594025 DOI: 10.1182/blood-2008-02-140533]

127 **Gasser O**, Schifferli JA. Activated polymorphonuclear neutrophils disseminate anti-inflammatory microparticles by ectocytosis. *Blood* 2004; **104**: 2543-2548 [PMID: 15213101]

128 **Lőrincz ÁM**, Schütte M, Timár CI, Veres DS, Kittel Á, McLeish KR, Merchant ML, Ligeti E. Functionally and morphologically distinct populations of extracellular vesicles produced by human neutrophilic granulocytes. *J Leukoc Biol* 2015; **98**: 583-589 [PMID: 25986013 DOI: 10.1189/jlb.3VMA1014-514R]

129 **Sundd P**, Gutierrez E, Koltsova EK, Kuwano Y, Fukuda S, Pospieszalska MK, Groisman A, Ley K. 'Slings' enable neutrophil rolling at high shear. *Nature* 2012; **488**: 399-403 [PMID: 22763437 DOI: 10.1038/nature11248]

130 **Tersteeg C**, Heijnen HF, Eckly A, Pasterkamp G, Urbanus RT, Maas C, Hoefer IE, Nieuwland R, Farndale RW, Gachet C, de Groot PG, Roest M. FLow-induced PRotrusions (FLIPRs): a platelet-derived platform for the retrieval of microparticles by monocytes and neutrophils. *Circ Res* 2014; **114**: 780-791 [PMID: 24406984 DOI: 10.1161/CIRCRESAHA.114.302361]

131 **Hyun YM**, Sumagin R, Sarangi PP, Lomakina E, Overstreet MG, Baker CM, Fowell DJ, Waugh RE, Sarelius IH, Kim M. Uropod elongation is a common final step in leukocyte extravasation through inflamed vessels. *J Exp Med* 2012; **209**: 1349-1362 [PMID: 22711877 DOI: 10.1084/jem.20111426]

132 **Sreeramkumar V**, Adrover JM, Ballesteros I, Cuartero MI, Rossaint J, Bilbao I, Nácher M, Pitaval C, Radovanovic I, Fukui Y, McEver RP, Filippi MD, Lizasoain I, Ruiz-Cabello J, Zarbock A, Moro MA, Hidalgo A. Neutrophils scan for activated platelets to initiate inflammation. *Science* 2014; **346**: 1234-1238 [PMID: 25477463 DOI: 10.1126/science.1256478]

133 **Döring Y**, Drechsler M, Soehnlein O, Weber C. Neutrophils in atherosclerosis: from mice to man. *Arterioscler Thromb Vasc Biol* 2015; **35**: 288-295 [PMID: 25147339 DOI: 10.1161/ATVBAHA.114.303564]

134 **Totani L**, Piccoli A, Dell'Elba G, Concetta A, Di Santo A, Martelli N, Federico L, Pamuklar Z, Smyth SS, Evangelista V. Phosphodiesterase type 4 blockade prevents platelet-mediated neutrophil recruitment at the site of vascular injury. *Arterioscler Thromb Vasc Biol* 2014; **34**: 1689-1696 [PMID: 24925970 DOI: 10.1161/ATVBAHA.114.303939]

135 **Lo SC**, Hung CY, Lin DT, Peng HC, Huang TF. Involvement of platelet glycoprotein Ib in platelet microparticle mediated neutrophil activation. *J Biomed Sci* 2006; **13**: 787-796 [PMID: 16897582]

136 **Salanova B**, Choi M, Rolle S, Wellner M, Luft FC, Kettritz R. Beta2-integrins and acquired glycoprotein IIb/IIIa (GPIIb/IIIa) receptors cooperate in NF-kappaB activation of human neutrophils. *J Biol Chem* 2007; **282**: 27960-27969 [PMID: 17644514]

137 **Karshovska E**, Zhao Z, Blanchet X, Schmitt MM, Bidzhekov K, Soehnlein O, von Hundelshausen P, Mattheij NJ, Cosemans JM, Megens RT, Koeppel TA, Schober A, Hackeng TM, Weber C, Koenen RR. Hyperreactivity of junctional adhesion molecule A-deficient platelets accelerates atherosclerosis in hyperlipidemic mice. *Circ Res* 2015; **116**: 587-599 [PMID: 25472975 DOI: 10.1161/CIRCRESAHA.116.304035]

138 **Koltsova EK**, Sundd P, Zarpellon A, Ouyang H, Mikulski Z, Zampolli A, Ruggeri ZM, Ley K. Genetic deletion of platelet glycoprotein Ib alpha but not its extracellular domain protects from atherosclerosis. *Thromb Haemost* 2014; **112**: 1252-1263 [PMID: 25104056 DOI: 10.1160/TH14-02-0130]

139 **Gautier EL**, Jakubzick C, Randolph GJ. Regulation of the migration and survival of monocyte subsets by chemokine receptors and its relevance to atherosclerosis. *Arterioscler Thromb Vasc Biol* 2009; **29**: 1412-1418 [PMID: 19759373 DOI: 10.1161/ATVBAHA.108.180505]

140 **Packard RR**, Maganto-García E, Gotsman I, Tabas I, Libby P, Lichtman AH. CD11c(+) dendritic cells maintain antigen processing, presentation capabilities, and CD4(+) T-cell priming efficacy under hypercholesterolemic conditions associated with atherosclerosis. *Circ Res* 2008; **103**: 965-973 [PMID: 18832748 DOI: 10.1161/CIRCRESAHA.108.185793]

141 **Koltsova EK**, Kim G, Lloyd KM, Saris CJ, von Vietinghoff S, Kronenberg M, Ley K. Interleukin-27 receptor limits atherosclerosis in Ldlr-/- mice. *Circ Res* 2012; **111**: 1274-1285 [PMID: 22927332 DOI: 10.1161/CIRCRESAHA.112.277525]

142 **Wu H**, Gower RM, Wang H, Perrard XY, Ma R, Bullard DC, Burns AR, Paul A, Smith CW, Simon SI, Ballantyne CM. Functional role of CD11c+ monocytes in atherogenesis associated with hypercholesterolemia. *Circulation* 2009; **119**: 2708-2717 [PMID: 19433759 DOI: 10.1161/CIRCULATIONAHA.108.823740]

143 **Koltsova EK**, Hedrick CC, Ley K. Myeloid cells in atherosclerosis: a delicate balance of anti-inflammatory and proinflammatory mechanisms. *Curr Opin Lipidol* 2013; **24**: 371-380 [PMID: 24005215 DOI: 10.1097/MOL.0b013e328363d298]

144 **Suganuma E**, Zuo Y, Ayabe N, Ma J, Babaev VR, Linton MF, Fazio S, Ichikawa I, Fogo AB, Kon V. Antiatherogenic effects of angiotensin receptor antagonism in mild renal dysfunction. *J Am Soc Nephrol* 2006; **17**: 433-441 [PMID: 16371432]

145 **Yamamoto S**, Kon V. Mechanisms for increased cardiovascular disease in chronic kidney dysfunction. *Curr Opin Nephrol Hypertens* 2009; **18**: 181-188 [PMID: 19374004]

146 **Yamamoto S**, Yancey PG, Zuo Y, Ma LJ, Kaseda R, Fogo AB, Ichikawa I, Linton MF, Fazio S, Kon V. Macrophage polarization by angiotensin II-type 1 receptor aggravates renal injury-acceleration of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2856-2864 [PMID: 21979434 DOI: 10.1161/ATVBAHA.111.237198]

147 **Robbins CS**, Hilgendorf I, Weber GF, Theurl I, Iwamoto Y, Figueiredo JL, Gorbatov R, Sukhova GK, Gerhardt LM, Smyth D, Zavitz CC, Shikatani EA, Parsons M, van Rooijen N, Lin HY, Husain M, Libby P, Nahrendorf M, Weissleder R, Swirski FK. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. *Nat Med* 2013; **19**: 1166-1172 [PMID: 23933982 DOI: 10.1038/nm.3258]

148 **Barry OP**, Praticò D, Savani RC, FitzGerald GA. Modulation of monocyte-endothelial cell interactions by platelet microparticles. *J Clin Invest* 1998; **102**: 136-144 [PMID: 9649567]

149 **Nomura S**, Tandon NN, Nakamura T, Cone J, Fukuhara S, Kambayashi J. High-shear-stress-induced activation of platelets and microparticles enhances expression of cell adhesion molecules in THP-1 and endothelial cells. *Atherosclerosis* 2001; **158**: 277-287 [PMID: 11583705]

150 **Vasina EM**, Cauwenberghs S, Feijge MA, Heemskerk JW, Weber C, Koenen RR. Microparticles from apoptotic platelets promote resident macrophage differentiation. *Cell Death Dis* 2011; **2**: e211 [PMID: 21956548 DOI: 10.1038/cddis.2011.94]

151 **Zhan R**, Leng X, Liu X, Wang X, Gong J, Yan L, Wang L, Wang Y, Wang X, Qian LJ. Heat shock protein 70 is secreted from endothelial cells by a non-classical pathway involving exosomes. *Biochem Biophys Res Commun* 2009; **387**: 229-233 [PMID: 19555663 DOI: 10.1016/j.bbrc.2009.06.095]

152 **Mause SF**, von Hundelshausen P, Zernecke A, Koenen RR, Weber C. Platelet microparticles: a transcellular delivery system for RANTES promoting monocyte recruitment on endothelium. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1512-1518 [PMID: 15890969]

153 **Yamamoto S**, Zhong J, Yancey PG, Zuo Y, Linton MF, Fazio S, Yang H, Narita I, Kon V. Atherosclerosis following renal injury is ameliorated by pioglitazone and losartan via macrophage phenotype. *Atherosclerosis* 2015; **242**: 56-64 [PMID: 26184694 DOI: 10.1016/j.atherosclerosis.2015.06.055]

154 **Zimmer S**, Grebe A, Latz E. Danger signaling in atherosclerosis. *Circ Res* 2015; **116**: 323-340 [PMID: 25593277 DOI: 10.1161/CIRCRESAHA.116.301135]

155 **Brown GT**, McIntyre TM. Lipopolysaccharide signaling without a nucleus: kinase cascades stimulate platelet shedding of proinflammatory IL-1β-rich microparticles. *J Immunol* 2011; **186**: 5489-5496 [PMID: 21430222 DOI: 10.4049/jimmunol.1001623]

156 **Boilard E**, Nigrovic PA, Larabee K, Watts GF, Coblyn JS, Weinblatt ME, Massarotti EM, Remold-O'Donnell E, Farndale RW, Ware J, Lee DM. Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. *Science* 2010; **327**: 580-583 [PMID: 20110505 DOI: 10.1126/science.1181928]

157 **Pizzirani C**, Ferrari D, Chiozzi P, Adinolfi E, Sandonà D, Savaglio E, Di Virgilio F. Stimulation of P2 receptors causes release of IL-1beta-loaded microvesicles from human dendritic cells. *Blood* 2007; **109**: 3856-3864 [PMID: 17192399]

158 **MacKenzie A**, Wilson HL, Kiss-Toth E, Dower SK, North RA, Surprenant A. Rapid secretion of interleukin-1beta by microvesicle shedding. *Immunity* 2001; **15**: 825-835 [PMID: 11728343]

159 **Qu Y**, Franchi L, Nunez G, Dubyak GR. Nonclassical IL-1 beta secretion stimulated by P2X7 receptors is dependent on inflammasome activation and correlated with exosome release in murine macrophages. *J Immunol* 2007; **179**: 1913-1925 [PMID: 17641058]

160 **Sadallah S**, Eken C, Martin PJ, Schifferli JA. Microparticles (ectosomes) shed by stored human platelets downregulate macrophages and modify the development of dendritic cells. *J Immunol* 2011; **186**: 6543-6552 [PMID: 21525379 DOI: 10.4049/jimmunol.1002788]

161 **Ansa-Addo E**, Inal J. T. cruzi interference with host cell membrane integrity triggers the release of Plasma Membrane-derived Vesicles: A mechanism for entry into mammalian cells. *J Immunol* 2010; **184**: 137

162 **Bardelli C**, Amoruso A, Federici Canova D, Fresu L, Balbo P, Neri T, Celi A, Brunelleschi S. Autocrine activation of human monocyte/macrophages by monocyte-derived microparticles and modulation by PPARγ ligands. *Br J Pharmacol* 2012; **165**: 716-728 [PMID: 21745193 DOI: 10.1111/j.1476-5381.2011.01593.x]

163 **Gauley J**, Pisetsky DS. The release of microparticles by RAW 264.7 macrophage cells stimulated with TLR ligands. *J Leukoc Biol* 2010; **87**: 1115-1123 [PMID: 20335312 DOI: 10.1189/jlb.0709465]

164 **Scanu A**, Molnarfi N, Brandt KJ, Gruaz L, Dayer JM, Burger D. Stimulated T cells generate microparticles, which mimic cellular contact activation of human monocytes: differential regulation of pro- and anti-inflammatory cytokine production by high-density lipoproteins. *J Leukoc Biol* 2008; **83**: 921-927 [PMID: 18223103 DOI: 10.1189/jlb.0807551]

165 **Carpintero R**, Gruaz L, Brandt KJ, Scanu A, Faille D, Combes V, Grau GE, Burger D. HDL interfere with the binding of T cell microparticles to human monocytes to inhibit pro-inflammatory cytokine production. *PLoS One* 2010; **5**: e11869 [PMID: 20686620 DOI: 10.1371/journal.pone.0011869]

166 **Zuo Y**, Yancey P, Castro I, Khan WN, Motojima M, Ichikawa I, Fogo AB, Linton MF, Fazio S, Kon V. Renal dysfunction potentiates foam cell formation by repressing ABCA1. *Arterioscler Thromb Vasc Biol* 2009; **29**: 1277-1282 [PMID: 19667109 DOI: 10.1161/ATVBAHA.109.188995]

167 **Srikanthan S**, Li W, Silverstein RL, McIntyre TM. Exosome poly-ubiquitin inhibits platelet activation, downregulates CD36 and inhibits pro-atherothombotic cellular functions. *J Thromb Haemost* 2014; **12**: 1906-1917 [PMID: 25163645 DOI: 10.1111/jth.12712]

168 **Zakharova L**, Svetlova M, Fomina AF. T cell exosomes induce cholesterol accumulation in human monocytes via phosphatidylserine receptor. *J Cell Physiol* 2007; **212**: 174-181 [PMID: 17299798]

169 **Angelot F**, Seillès E, Biichlé S, Berda Y, Gaugler B, Plumas J, Chaperot L, Dignat-George F, Tiberghien P, Saas P, Garnache-Ottou F. Endothelial cell-derived microparticles induce plasmacytoid dendritic cell maturation: potential implications in inflammatory diseases. *Haematologica* 2009; **94**: 1502-1512 [PMID: 19648164 DOI: 10.3324/haematol.2009.010934]

170 **Kaneider NC**, Kaser A, Tilg H, Ricevuti G, Wiedermann CJ. CD40 ligand-dependent maturation of human monocyte-derived dendritic cells by activated platelets. *Int J Immunopathol Pharmacol* 2003; **16**: 225-231 [PMID: 14611725]

171 **Eken C**, Gasser O, Zenhaeusern G, Oehri I, Hess C, Schifferli JA. Polymorphonuclear neutrophil-derived ectosomes interfere with the maturation of monocyte-derived dendritic cells. *J Immunol* 2008; **180**: 817-824 [PMID: 18178820]

172 **Messer L**, Alsaleh G, Freyssinet JM, Zobairi F, Leray I, Gottenberg JE, Sibilia J, Toti-Orfanoudakis F, Wachsmann D. Microparticle-induced release of B-lymphocyte regulators by rheumatoid synoviocytes. *Arthritis Res Ther* 2009; **11**: R40 [PMID: 19291304 DOI: 10.1186/ar2648]

173 **Köppler B**, Cohen C, Schlöndorff D, Mack M. Differential mechanisms of microparticle transfer toB cells and monocytes: anti-inflammatory propertiesof microparticles. *Eur J Immunol* 2006; **36**: 648-660 [PMID: 16479543]

174 **Onishi RM**, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. *Immunology* 2010; **129**: 311-321 [PMID: 20409152 DOI: 10.1111/j.1365-2567.2009.03240.x]

175 **Taleb S**, Tedgui A, Mallat Z. IL-17 and Th17 cells in atherosclerosis: subtle and contextual roles. *Arterioscler Thromb Vasc Biol* 2015; **35**: 258-264 [PMID: 25234818 DOI: 10.1161/ATVBAHA.114.303567]

176 **Lim H**, Kim YU, Sun H, Lee JH, Reynolds JM, Hanabuchi S, Wu H, Teng BB, Chung Y. Proatherogenic conditions promote autoimmune T helper 17 cell responses in vivo. *Immunity* 2014; **40**: 153-165 [PMID: 24412615 DOI: 10.1016/j.immuni.2013.11.021]

177 **Quintana FJ**, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, Caccamo M, Oukka M, Weiner HL. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature* 2008; **453**: 65-71 [PMID: 18362915 DOI: 10.1038/nature06880]

178 **Basu R**, Hatton RD, Weaver CT. The Th17 family: flexibility follows function. *Immunol Rev* 2013; **252**: 89-103 [PMID: 23405897 DOI: 10.1111/imr.12035]

179 **Esser C**, Rannug A, Stockinger B. The aryl hydrocarbon receptor in immunity. *Trends Immunol* 2009; **30**: 447-454 [PMID: 19699679 DOI: 10.1016/j.it.2009.06.005]

180 **Nguyen NT**, Nakahama T, Le DH, Van Son L, Chu HH, Kishimoto T. Aryl hydrocarbon receptor and kynurenine: recent advances in autoimmune disease research. *Front Immunol* 2014; **5**: 551 [PMID: 25400638 DOI: 10.3389/fimmu.2014.00551]

181 **Schroeder JC**, Dinatale BC, Murray IA, Flaveny CA, Liu Q, Laurenzana EM, Lin JM, Strom SC, Omiecinski CJ, Amin S, Perdew GH. The uremic toxin 3-indoxyl sulfate is a potent endogenous agonist for the human aryl hydrocarbon receptor. *Biochemistry* 2010; **49**: 393-400 [PMID: 20000589 DOI: 10.1021/bi901786x]

182 **Sallée M**, Dou L, Cerini C, Poitevin S, Brunet P, Burtey S. The aryl hydrocarbon receptor-activating effect of uremic toxins from tryptophan metabolism: a new concept to understand cardiovascular complications of chronic kidney disease. *Toxins* (Basel) 2014; **6**: 934-949 [PMID: 24599232 DOI: 10.3390/toxins6030934]

183 **Chung BH**, Kim KW, Sun IO, Choi SR, Park HS, Jeon EJ, Kim BM, Choi BS, Park CW, Kim YS, Cho ML, Yang CW. Increased interleukin-17 producing effector memory T cells in the end-stage renal disease patients. *Immunol Lett* 2012; **141**: 181-189 [PMID: 22004873 DOI: 10.1016/j.imlet.2011.10.002]

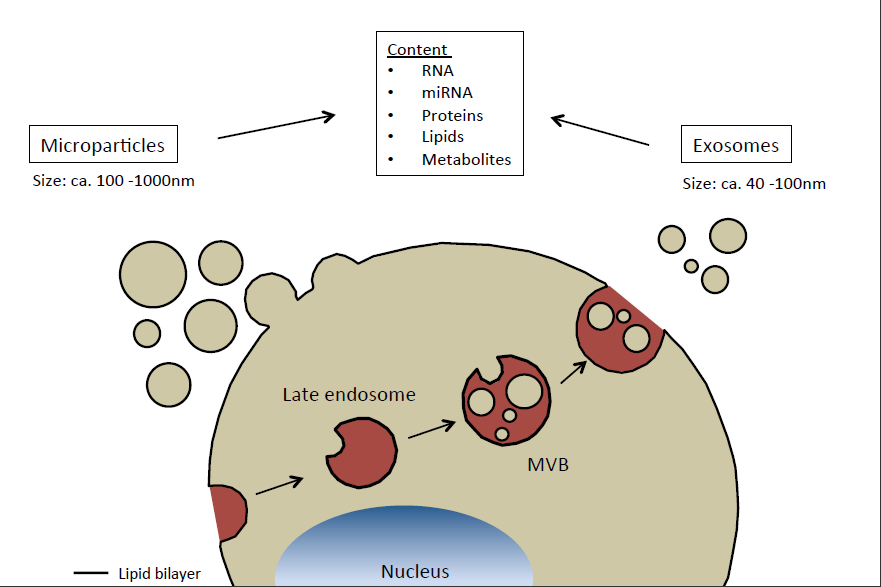
184 **Lu Y**, Li L, Yan H, Su Q, Huang J, Fu C. Endothelial microparticles exert differential effects on functions of Th1 in patients with acute coronary syndrome. *Int J Cardiol* 2013; **168**: 5396-5404 [PMID: 24012161 DOI: 10.1016/j.ijcard.2013.08.050]

185 **Sadallah S**, Amicarella F, Eken C, Iezzi G, Schifferli JA. Ectosomes released by platelets induce differentiation of CD4+T cells into T regulatory cells. *Thromb Haemost* 2014; **112**: 1219-1229 [PMID: 25209750 DOI: 10.1160/TH14-03-0281]

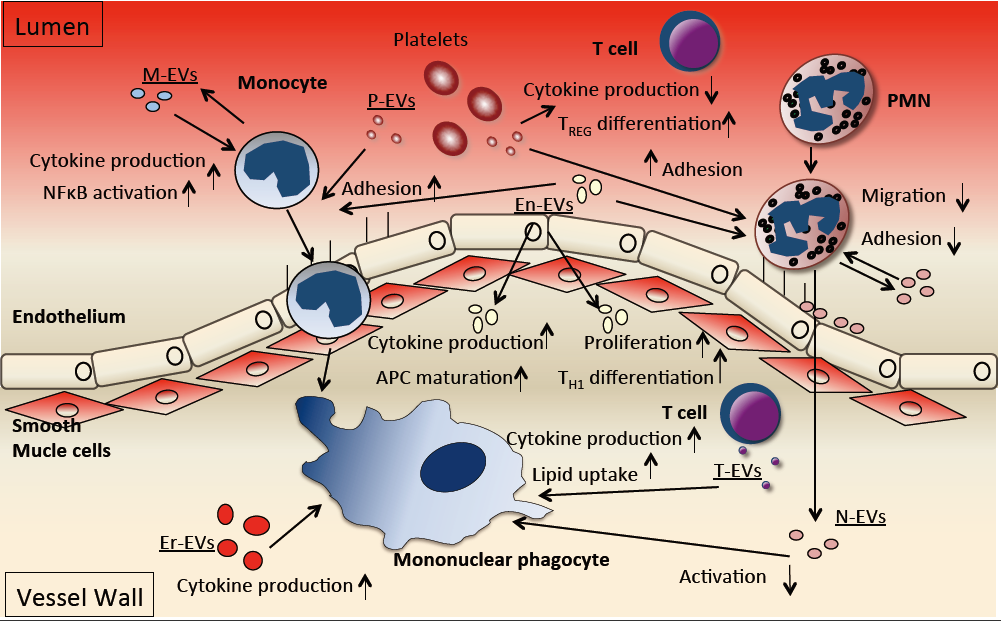
186 **Théry C**, Duban L, Segura E, Véron P, Lantz O, Amigorena S. Indirect activation of naïve CD4+ T cells by dendritic cell-derived exosomes. *Nat Immunol* 2002; **3**: 1156-1162 [PMID: 12426563]

187 **Segura E**, Nicco C, Lombard B, Véron P, Raposo G, Batteux F, Amigorena S, Théry C. ICAM-1 on exosomes from mature dendritic cells is critical for efficient naive T-cell priming. *Blood* 2005; **106**: 216-223 [PMID: 15790784]

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**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 (MVBs) 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.



**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 granuloctes (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.