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Are Microparticles the Missing Link between Thrombosis and Autoimmune Diseases? Involvement in Selected Rheumatologic Diseases

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Abstract

Microparticles (MPs) are membrane-bound vesicles with important physiologic effects. MPs exchange information intercellularly, with each kind of MP carrying antigens and receptors of the cells from which they originated. They are biologic effectors in inflammation, angiogenesis, vascular injury, and thrombosis. Thrombosis is generally caused by abnormalities in blood flow, blood composition, and/or properties of the vessel wall. Thrombosis is a well-described feature of cardiovascular disease and cerebrovascular disease. Accumulating evidence suggests that increased risk of thrombosis is also characteristic of autoimmune disorders and immune-mediated diseases affecting all age groups, although the older adults are most vulnerable. Current research has also implicated MPs as a source of autoantigenic nuclear material that can form immune complexes, activate the innate immune system, and may lead to autoimmunity. This review focuses on the contribution of MPs to both the pathogenesis of autoimmune diseases and, as the immune and coagulation systems are tightly linked, their role in hypercoagulability in the setting of autoimmunity in an aging population.

Keywords

microparticles; thrombosis; rheumatoid arthritis; systemic sclerosis; systemic; lupus erythematosus

Thrombosis, Aging, and Immunity

Thrombosis is the formation of a blood clot (thrombus) inside a blood vessel leading to obstruction of blood flow. Abnormalities in the composition of the blood (e.g., thrombophilia), properties of the vessel wall (endothelial cell [EC] injury) and/or quality of the blood flow (stasis and turbulence) can all contribute.[1] Thrombosis can affect children, young adults, and older adults; however, risk factors and frequency differ with age.[2] The number of risk factors required to increase the chance of thrombosis decreases with age.

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Aging significantly increases coagulation system proteins such as fibrinogen, factors V, VII, VIII, IX, and XIII, von Willebrand factor, high-molecular-weight kininogen, and prekallikrein levels.[3] Increased plasma fibrinogen may contribute to increased thrombosis by being a direct substrate for the clot, by increasing the viscosity of blood or by enhancing platelet connection.[4] On the contrary, increased fibrinogen levels may be a marker of intensified inflammation[5]; for example, fibrinogen increases in response to interleukin 6 (IL-6), which itself is strongly linked with age.[6]

In addition to the earlier, increased levels of plasminogen activator inhibitor 1 (PAI-1) have been implicated in endothelial dysfunction and vascular aging. Bonfigli et al showed that the presence of a 4G/5G polymorphism in the promoter region of the PAI-1 gene is associated with increased plasma levels with age.[7] Elevated levels of PAI-1 and its procoagulant activity have been recognized as hallmarks of endothelial dysfunction.[7,8] The structural and vascular wall changes during aging involve the extracellular matrix (ECM), vascular smooth muscle, and endothelium. These alterations contribute to the increased risk of thrombosis in older individuals.[9] Furthermore, the age-dependent decrease of nitric oxide production may contribute to enhanced platelet activation and arterial thrombosis as well as to increased atherosclerosis.[10,11]

Aging is also an important risk factor for immune system impairment. Aging of the immune system, referred to as immunosenescence, is associated with functional dysregulation and a reduction in immune responsiveness. This decline in immune function with advancing age contributes to the increased incidence among the elderly in morbidity and mortality from infectious diseases, cancer, and autoimmunity.[12,13] Specifically, there are changes in T-cell subpopulations, B-cell function, and cytokine production, and function in older people. The data are inconsistent with regard to B-cell number. One study demonstrated that the number of B cells is unaffected in older adults,[14] while others described a decline in total B cells, but only in men.[15–17] Ginaldi et al also demonstrated diminished B-cell immunity and decreased capacity to produce antibodies against known or new antigens in the elderly.[18] As immune competence depends on rapid expansion of clonal B- and T-cell populations, telomere loss may contribute to defective immune responses in the elderly. Accelerated T-cell aging together with telomeric shortening may predispose to diminished autoimmune responses.[19] There has also been evidence that telomere shortening might present a common biomarker for aging, immunosenescence, and autoimmune disease.[20] Taken together, in older persons who carry a complement of predisposing genes, environmental factors may alter a senescent immune system and trigger the onset of autoimmunity. In the next sections, we will discuss how autoimmune disorders predispose to hypercoagulability in both the older people and the young, with MPs as a possible link to vascular aging and risk.

Characteristics of Blood-Derived Microparticles

Microparticles (MPs) are small (0.1–1.0 μm) membrane-bound vesicles with important physiologic effects. They are biological effectors in inflammation, angiogenesis, endothelial injury, and thrombosis.[8,21–23] Moreover, exposed procoagulant phospholipids and specific receptors at the surface of MPs act as biomessengers linking these processes.[24–26] Blood includes MPs derived from different cell types, mainly platelets, but also red blood cells, granulocytes, monocytes, lymphocytes, and ECs. MPs may be released during cell activation, cell injury, cell senescence, and apoptosis. Of note, MPs can be characterized by the detection of the different cell surface antigens reflecting their origin and activation method.[8]

Platelet-derived microparticles (PMPs) are the most abundant MPs in the bloodstream comprising around 70 to 90% of circulating MPs.[27–29] A population of PMPs is generated during platelet activation, whereas other PMP populations are derived from megakaryocytes during megakaryopoiesis, from platelet apoptosis, or from quiescent circulating platelets.[29,30] Although the physiologic mechanism(s) by which baseline MP levels are sustained in healthy persons remain unclear, it is known that platelet activation in thrombotic and inflammatory states leads to increased MP formation.[29] High PMP levels combined with high D-dimer and P-selectin levels correlate with the diagnosis of deep venous thrombosis (DVT).[31] Although a role for PMPs in promoting coagulation in cardiovascular (CV) disease has been described,[23,32] some species of PMP may actually inhibit coagulation by accelerating inactivation of factor Va.[33] Studies published by Knijff-Dutmer et al recently implicated PMPs in autoimmune disease.[34] The authors demonstrated elevated levels of PMPs in elderly patients with rheumatoid arthritis. Increased levels of circulating PMPs have also been identified in patients with SLE and were associated with high thrombin, suggesting activation of the coagulation system.[35,36]

Leukocyte-derived microparticles may originate from neutrophils, monocyte/macrophages, B or T lymphocytes.[37] Neutrophils (40–75% in circulating blood) migrate from the blood to sites of tissue inflammation in response to different chemotactic signals, promoting inflammation. When activated, neutrophils degranulate by exocytosis and release MPs from the cell surface by ectocytosis.[38–40] Neutrophil-derived microparticles (NMPs) expose phosphatidylserine,[41] activate the classic pathway of complement, and fix C4 and C3 fragments. Moreover, NMPs act as inflammatory mediators in activating ECs.[42,43] On the contrary, they also employ anti-inflammatory effects on macrophages[44] and, when carrying annexin A1, inhibit the interaction between neutrophils and ECs.[45,46] NMPs may also interact with resting platelets, which leads to platelet activation, increased P-selectin expression, and propagation of thrombus formation.[47]

Monocytes represent 2 to 8% of blood leukocytes. Monocyte-derived microparticles (MonoMPs) display tissue factor (TF), activated protein C, and thrombomodulin anticoagulant activity at their surface.[48] After exposure to endotoxin, there is an early increase in MonoMPs associated TF procoagulant activity. MonoMPs can also interact with neutrophils, transferring their procoagulant activity and can additionally increase endothelial thrombogenicity.[49,50]

Lymphocytes represent 25 to 40% of blood leukocytes. B lymphocyte–derived MPs, T lymphocyte–derived MPs, and MonoMPs are elevated in the circulation of patients with autoimmune disease.[51]

Red blood cell (RBC) MPs represent a minority of total (RBC) MPs in plasma (4–8%).[52] The formation of these erythrocyte-derived microparticles is also induced during the storage of blood.[53] Rubin et al demonstrated that EMPs increase the risk of a hypercoagulable state[54] and thus, may contribute to posttransfusion complications. Red cell antibody development is an additional complication of chronic transfusion in patients with sickle cell disease, for example.[55,56] The level of RBC MPs in the blood of these patients is significantly elevated and correlates with the degree of intravascular hemolysis and premature aging of red blood cells.[57–59] Interestingly, after a blood transfusion, RBC MPs have strong anti-inflammatory effects by inhibiting the release of cytokines such as TNFα, IL-8, and IL-10.[60,61]

Microparticles in Thrombosis and Immunity

MPs are markers of cellular activation or of damage in the vascular compartment. In this compartment, MPs are major bioactive effectors of inflammation, vascular tone, angiogenesis, and thrombosis.[62] The procoagulant properties of MPs involve phosphatidylserine, a procoagulant aminophospholipid needed for the assembly of blood clotting enzyme complexes, and TF, which when present is a major initiator of the coagulation cascade.[22] Endothelial MPs express phospholipids that bind coagulation factors leading to a prothrombotic state.[63] They also increase the procoagulant activity of TF, which is expressed in atherosclerotic plaques, macrophages, smooth muscle cells, and ECM. Recently, it was shown that endothelial MPs expressing both activators and inhibitors of coagulation have fibrinolytic properties that counteract their procoagulant activities, which may enable them to also contribute to hemostatic balance.[64] A recent clinical study done by Forest et al[65] revealed a reduced basal level of circulating endothelial MPs but preserved MP procoagulant activity in elderly patients compared with young patients.

MPs represent a source of immunologically active molecules that can influence cells and affect various processes such as inflammation, coagulation, antigen presentation, and apoptosis. Specifically, MPs may contribute to the pathogenesis of autoimmune diseases and inflammatory disorders as will be discussed in the next section. Depending on the source of the MPs, the cell type, and the local microenvironment, MPs can stimulate inflammation by various mechanisms: activation of the complement cascade, transfer of cell surface receptors, augmentation of leukocyte rolling, and cytokine stimulation.[21] In contrast, under different conditions, MPs may exert anti-inflammatory effects by the induction of apoptosis in B and T cells via Fas–FasL interaction.[66] Although multiple studies have demonstrated increased levels of MPs in patients with autoimmune diseases, more work is needed to understand the complex interplay of MPs with immune cells and their effectors.

Microparticles and Autoimmunity

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint pain, swelling, and deformity. Inflammation in RA contributes to accelerated atherosclerosis with increased mortality; in fact, CV disease is the most frequent cause of death in RA patients.[67,68] MPs are a target of investigation in RA as they can transfer molecules to target cells, which then amplify a variety of biological mechanisms such as inflammation, apoptosis, and cell proliferation, impacting immune responses.[69] Most studies have shown that RA patients, even in early stages of disease, have increased levels of MPs compared with healthy controls. Patients with active RA tended to have higher PMPs than nonactive RA patients.[34,70] In contrast, Pamuket al observed similar or lower PMPs in RA patients versus healthy controls, and speculated that PMPs were expressed for a short period in peripheral blood before being removed from circulation.[68] Of note, MP numbers, particularly PMPs, are similar between RA and other autoimmune diseases.[34,69,70]

RA-associated MPs have been isolated from both synovial fluid and peripheral blood. Generally, MP numbers are higher in synovial fluid than peripheral blood.[71] Synovial fluid from RA patients and controls contain MPs originating from many cell types: granulocytes, monocytes, T cells, B cells, erythrocytes, and platelets,[72,73] and appears to stimulate joint inflammation in multiple ways. For example, collagen-stimulated PMPs can stimulate production of IL-6 and IL-8 in fibroblast-like synoviocytes, contributing to joint inflammation.[72] MPs released from platelets activated by collagen receptor glycoprotein VI appear to be important in the pathogenesis of inflammatory arthritis. Synovial fluid MPs have much higher levels of bound C1q, C3, and C4 compared with plasma MPs from either RA patients or healthy controls.[71] In addition, granulocyte MPs are implicated in local hypercoagulation through thrombin generation via factor VII. As thrombin can induce an inflammatory response, granulocyte MPs may indirectly stimulate inflammation by this mechanism.[73]

RA patients have a higher proportion of first-time CV events compared with control populations.[74–77] They suffer higher than anticipated myocardial infarctions (MIs) and these incidents are equal between males and females.[74] Although we do not yet have data on MP association with MIs, there is an association between high levels of plasma MPs and the risk of venous thromboembolism (VTE).[78] In western countries, RA patients have a twofold increase in VTE incidents compared with controls, and a similar study in Taiwanese RA patients demonstrated a threefold and twofold increase in DVT and pulmonary embolism, respectively.[79–81] Patients with significantly elevated MP levels (greater than the 90th percentile) exhibited a fivefold increase in VTEs compared with patients with low MP levels (below the 10th percentile).[78] As RA patients have higher levels of MPs compared with healthy controls, this may contribute to increased incidence of VTE in this population, although a causal relationship has not yet been established.[82] The high levels of MPs, both in peripheral blood and synovial fluid, indicate that RA patients could be in a more prothrombotic state compared with healthy controls, leaving them more susceptible to VTE events. MPs are one possible link between inflammation and hypercoagulability, and more work is needed to define the role of MPs in thromboembolic events.

Systemic Sclerosis

Systemic sclerosis (SSc) is a relatively rare connective tissue disease most commonly affecting skin, lung, and kidney. The disease is characterized by autoantibody production, activation of immune cells, and subsequent tissue fibrosis, and vasculopathy. While the exact pathogenesis is unclear, EC dysfunction and damage are clearly involved and appear to play an early role in disease. The role of MPs in endothelial damage and inflammation in SSc patients has not been well studied, but several reports have revealed that MPs are altered in SSc. It is not yet clear whether they are surrogate markers of disease damage or mediating important biological processes such as inflammation and thrombosis. The data at this time suggest that MPs may play a role in pathogenesis. In a recent study of 121 SSc patients and 49 healthy controls, MPs were characterized, and levels were overall reduced approximately 20 to 40% in SSc patients.[83] However, nonbinding MPs (AnxV-) were increased in SSc patients, and correlated with elevated plasma levels of sE- and sP-selectin (in diffuse SSc), suggesting an increased level of vascular activation in this group. A separate study found that plasma MP levels in SSc are overall increased and, additionally, levels correlated with skin fibrosis. Guiducci et al studied 37 SSc patients and 15 healthy controls and found the total number of MPs (from different cellular sources) was increased twofold over healthy controls.[84] Given that vascular and thrombotic diseases are associated with increased MPs, the investigators excluded patients with a known history of coronary artery disease, peripheral artery disease, stroke, and/or thrombotic diseases such as APS. Not surprisingly, they did detect an increase in arterial hypertension in the SSc patients versus controls.

Pulmonary arterial hypertension (PAH) is a well-known complication of both limited and diffuse SSc. PAH is associated with activated platelets, an inflammatory vasculopathy and EC dysfunction that lead to increased risk of thromboembolism. PAH patients also have an approximate twofold increase in MP in agreement with the study by Guiducci et al.[85] Further classifying the MPs revealed that PAH patients with thromboembolic disease had higher levels of endothelial-derived MPs compared with nonembolic PAH patients, suggesting an association between MPs and risk of increased disease-related coagulopathy, as well as possible PAH progression.

With regard to potential mechanisms of MP impact on vascular injury in SSc, two recent studies have proposed a role for MP-produced high mobility group box 1 (HMGB1) as a regulator of crosstalk between platelets and leukocytes leading to increase in the inflammatory vasculopathy in SSc patients. Maugeri et al found that HMGB1(+) MPs isolated from SSc patients, but not HMGB1(−) MPs from controls, activated neutrophils, suggesting that these MPs participate in microvascular injury and inflammation via HMGB1 activity in SSc which may contribute to the prothrombotic atmosphere in these patients.[86]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by heterogeneous, multiorgan involvement with a strong female predominance. The pathogenesis of SLE is characterized by autoantibody production, specifically antinuclear antibodies (ANA) and antibodies to double-stranded DNA (anti-dsDNA) that then form immune complexes. Immune complexes stimulate cytokine production, notably a type 1 interferon response, and deposit in the kidneys and other organs causing cellular injury. Current research has implicated MPs as a source of autoantigenic nuclear material that then can form immune complexes.[87] MPs are released via a blebbing process during cellular death or activation and can contain DNA, RNA, growth factors, and cytokines. MPs can transfer these biologically active molecules, influencing inflammation, and coagulation, as stated earlier. As MPs can contain nucleic acid material, they can inappropriately activate the innate immune system and potentially lead to autoimmunity.[67] It is hypothesized that the autoantigenic material in MPs is increased in SLE patients due to both an increase in cell death and an impaired ability to clear apoptotic debris.[87]

MPs have been studied in lupus prone murine models to determine if they can form immune complexes. Specifically, one study showed that plasma from MRL/lpr lupus prone mice contains MPs that bear immunoglobulin G (IgG).[88] Using another murine model C3H/lpr, MPs were found in the plasma along with significant levels of IgG, implicating MPs in the formation of immune complexes, likely with ANA.[67,89] Human studies demonstrated that MPs derived from apoptotic cells in vitro could bind to SLE patient plasma to form immune complexes.[87] In a follow-up study, investigators found im complexes composed of MPs bound to IgG in SLE plasma. MP levels from SLE patient plasma were greater than control plasma, and also had higher levels of anti-IgG binding and IgG-positive MPs. Furthermore, the number of IgG-positive MPs was positively correlated with anti-DNA antibodies.[87] Another group investigated MPs as a source of immune complexes in SLE plasma and found that a specific MP subpopulation correlated with SLE disease activity scores.[90] They also found increased levels of IgG, IgM, and C1q bound to cell-derived MPs in SLE patient plasma compared with healthy controls. Levels of IgG-positive MPs correlated with the presence of anti-dsDNA,[36] all suggesting a role for MPs in immune complex formation. SLE patients have a unique profile of increased MPs containing Ig and complement proteins compared with patients with RA and SSc or healthy controls. Systematic profiling of the protein composition of MPs revealed increased representation of immunoglobulin and complement of the classical pathway in SLE patients. This highlights that MPs may play a role in activating Toll-like receptor (TLR)-7 and -9, stimulating the release of IFNα from plasmacytoid dendritic cells[91] key events in lupus pathogenesis. Thus, both murine and human studies suggest that MPs play a role in the pathogenesis of SLE and better understanding this role may help identify new targets for treatment.

In addition to autoantibody-mediated immune complex formation and organ damage, patients with SLE have an increased risk of CV disease that is not fully explained by traditional risk factors such as age and hypertension.[92–94] SLE is considered an independent risk factor for CV disease. The increased risk is likely due to an interplay between inflammation and endothelial dysfunction, but hypercoagulability may also contribute.[95] Endothelial microparticles (EMPs) have been implicated as a potential biomarker for endothelial damage in SLE. EMPs play a role in intracellular signaling and allow transfer of proteins such as vascular endothelial growth factor and endothelial nitric oxide synthase.[96,97] One study investigated whether active SLE was associated with increased levels of EMPs and endothelial dysfunction, as measured by brachial artery flow-mediated dilatation (FMD).[95] Patients with active SLE had significantly higher levels of both total MPs and EMPs as well as impaired FMD, compared with controls. There was a moderate correlation between number of EMPs and FMD. Furthermore, when active SLE patients were treated with more aggressive immunosuppressive therapy resulting in decreased disease activity, both total MPs and EMPs significantly declined and were comparable to controls. This study showed that EMP levels could be potential biomarkers for endothelial dysfunction in SLE with needed studies to establish the role of EMPs in the pathogenesis of vascular dysfunction. This study additionally suggests that suppressing inflammation and reducing disease activity in SLE decreases EMP levels and may have a beneficial effect on endothelial function leading to reduced vascular risk factors.

Summary and Conclusion

Increased level of MPs is observed in vascular as well as immune and autoimmune disorders (►Table 1). The immune and coagulation systems are tightly linked suggesting the role of MPs in this connection. However, the direct association between elevated levels of MP generation and formation of immune and coagulation systems are tightly linked suggesting the role of MPs in this connection. However, this interplay is understudied and further investigation of cellular and molecular mechanisms of these correlations is needed. These findings can be crucial in understanding and providing a basis to identify new targets for the treatment of autoimmune diseases.

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Table 1

Summary of origin and characteristic of MPs in RA, SSc, and SLE

Autoimmune diseases	Blood- and cell-derived MP	References
RA	↑ PMPs in synovial fluid, peripheral blood	34,70,82
	↓ PMPs in peripheral blood	68
	↑ MonoMPs	72,73
	↑ LMPs	72,73
SSc	↓ PMPs, ↓ EMPs	83
	↑ LMPs, ↑ PMPs	84,86
SLE	↑ MPs in peripheral blood	87
	↑ EMPs	95–97

Abbreviations: EMPs, endothelial-derived microparticles; LMPs, leukocyte-derived microparticles; MPs, microparticles; PMPs, platelet-derived microparticles; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.