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Review Article

Micro-Particles and Their Role in Various Clinical Settings

Virendra Kumar[1]*, Sanjay Melhotra[2], Ahuja Ret RC[2] and Viash AK[2]

[1]Department of Medicine, Govt Medical College, Banda, UP, India

[2]Department of Medicine, King George's Medical University, Lucknow, India

***Corresponding author:** Virendra Kumar, Department of Medicine, Govt Medical College, Banda, UP, India

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Abstract

A microparticles (MPs) submicron membrane vesicle, expresses a panel of oxidized phospholipids and proteins that plays a vital role in the normal haemostatic response to vascular injury. An important role in clinical diseases is also observed. In nearly all thrombotic diseases increased platelet-derived MP, endothelial cell-derived MP and monocyte-derived MP concentrations are reported. However, a clear importance of MPs in varied clinical conditions still remains disputed. Many studies have reported that the MPs cellular origin and composition are based on the type of disease, the disease state and medical treatment. Additionally, many different functions have also been attributed to MPs. Thus, the number and variety of clinical disorders related with elevated MPs is currently swelling.

Keywords: Microparticles; Clinical; Vascular injury; Thrombosis; Proteins

Introduction

Microparticles (MPs), small membrane-derived vesicles, are formed by several vascular or peripheral blood cells in response to cellular activation or apoptosis [1]. MPs disperse varied bioactive effectors developing from the parent cells. Therefore, MPs could change vascular function and may induce biological responses involved in vascular homeostasis [2]. Most of the MPs in human blood originate from platelets [3]. Increased levels of MPs found in a number of situations such as in inflammation, angiogenesis and transport [4-5]. In this review, author tries to summarize the microparticles various functions and role in clinical settings.

Microparticles in Health and Disease

MPs role and coagulation

MPs were initially thought to be related to disease due to their expression of phospholipids (procoagulants). Microparticles support generation of thrombin and might be involved in diffuse intravascular coagulation. Berckmans et al. [6] reported that microparticles in blood of healthy individuals support thrombin generation via TF- and FVII-independent pathways, and it may have an anticoagulant function. Monocyte-derived MPs (MDMPs) also play a part in development of platelets and fibrin-rich thrombus at sites of vascular injury by the recruitment of cells and accumulation of TF [7-8]. Del Conde et al. [9] suggest a mechanism by which all of the membrane-bound reactions of the coagulation system can be localized to the surface of activated platelets. MP surface contains proteins that inhibit coagulation and raises the possibility of MPs eventual contribution to an anticoagulant pathway [10-12]. Other mechanisms contributing to the regulation of MP procoagulant properties depends on the balance between TNF-α and anti-inflammatory cytokines, such as interleukin (IL)-10. Indeed, endogenous IL-10 was recently noted to deregulate TF expression in monocytes and TF-bound MDMP release, impeding generation of thrombin [13].

Atherothrombosis and MPs

Production of EDMPs, PDMPs and leukocyte-derived MPs can be elevated by inflammatory conditions [14-15]. A major feature in atherosclerosis is adhesion of monocytes to endothelial cells, followed by sub-endothelial transmigration. Cytokines, such as IL-1β and TNF-α, affect this process by inducing synthesis or up-regulation of leukocyte-endothelial adhesion molecules. [12]. Furthermore, treatment of endothelial cells and monocytes with PDMPs prior to co-incubation modulates monocyte-endothelial cell interactions, by increasing the expression of adhesion molecules on both cell types [12].

Circulating MPs of platelet & leukocytic origins promotes recruitment of inflammatory cells and induces cellular adhesiveness through up-regulation of cytokines and cyto-adhesions in endothelial cells and monocytes [16]. At high shear stress, PDMP rolling enables delivery of RANTES to inflamed endothelium, thus favouring adhesion of monocytes and infiltration of plaques. Development and progression of atherosclerotic plaques are associated with apoptotic cell death, thus explaining the presence of a considerable amount of procoagulant MPs within plaques. Furthermore, enhanced apoptosis or activation of leukocytes, SMCs, and endothelium contribute to the accumulation of MPs [17]. Compared with their circulating counterpart, MPs trapped within the plaque are present at much higher concentrations and display higher thrombogenic potential. In plaques, most of these MPs are from activated leukocytes, a hallmark of inflammation, and from erythrocytes, indicating occurrence of intra-plaque haemorrhage, which is a marker of vulnerability of plaques [17]. Atherosclerotic plaques also contain a considerable amount of SMC-derived MPs and EDMPs. Circulating MPs can result in vascular inflammation, endothelial dysfunction, leukocyte adhesion, and recruitment. This could contribute to plaque growth or stent-induced vascular inflammation [18].

Thrombocytopenia

Some anti-platelet antibodies can influence complement-mediated formation of PDMPs and initiate platelet destruction [19-20]. Antiphospholipid antibodies are found in antiphospholipid antibody syndrome (APS). These phospholipids are abundant on

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activated platelets, apoptotic cells, and MPs. Level of MPs is raised in patients with APS rather than thrombosis is compared with healthy controls [21-22].

Galli et al. [23] carried out a study of PDMPs in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (HUS) patients by flow cytometry and noted an increased levels of PMPs in peripheral thrombocytopenia's and suggest that their presence may be clinically relevant, particularly in the microangiopathic forms. Jimenez et al. [24] measured endothelial microparticles (EMPs) generated from cultured renal and brain microvascular endothelial cells (MVECs) and also evaluated the effect of TTP plasma on them by using flow cytometry. They noted that released procoagulant EMP may play a role in the pathogenesis of TTP. Assay of EMP may be a functional marker of disease activity and endothelial injury in TTP and other thrombotic disorders. Nomura et al. [25] observed MP levels in patients following allogeneic stem cell transplantation and found only one of the 21 patients who were studied developed TMA/TTP, a continuous rise in platelets, EDMPs, and MDMPs was observed in all of the patients, for up to 4 weeks following transplantation.

Cardiovascular diseases

Microparticles role as biological messengers is buttressed by their differential and particular involvement in the pathophysiology of different cardiovascular disorders. Various studies have proposed a link between microparticles and different pathological conditions, mainly with the development of cardiovascular diseases.

Viera AJ et al. [26] noted that MPs may have clinical applications including usefulness as biomarkers, their use in enhancing cardiovascular disease risk prediction, and also as potential targets of therapy. Augustine et al. [27] have noted a slight increase in MP derived from different cell types immediately after the test followed by a rapid MP clearance from the circulation during the next hour in response to cardiac stress. Sarlon-Bartoli et al. [28] analyzed whether the plasmatic level of leukocyte-derived microparticles (LMP) is related with unstable plaques in patients with high-grade carotid stenosis and noted that LMP constitute a promising biomarker related with plaque vulnerability. These results provide clues for identifying asymptomatic subjects that are most at risk of neurologic events.

Morel et al. [29] have assessed the levels of LMP and EMP within occluded coronary arteries of ST-segment elevation myocardial infarction patients treated with primary angioplasty and has compared them with the levels of MP in peripheral blood. They reported an increase in MP within arteries, indicating the importance of those vesicles in the development of coronary atherothrombosis. Jeanneteau et al. [30,31] have evaluated in rats and humans the role of MP in the mechanism of remote ischemic conditioning (RIC), which has been described as an infraction-related cardio protective strategy. No differences were noted in the total number of MP in the group of animals undergoing RIC as compared to the control group. After phenotypic characterization of MP, elevations in the endothelial and Annexin V+ (apoptotic) subpopulations were reported in the RIC group. Similarly, elevations in EMP and Annexin V+ MP were found in the group of individuals submitted to RIC. Porto et al. [32] have evaluated the concentrations of MP in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention, and the relationship of those vesicles with micro-vascular obstruction. They noted that the MP subpopulations assessed (PMP and EMP) showed higher levels within the coronary arteries as compared to those in aortic blood. In addition, a greater release of both MP subpopulations was reported in the impaired coronary artery than in ascending aorta, indicating local MP production. Kaabi et al. [33] have evaluated the relationship between the levels of MP and treatment of stable coronary artery disease patients with external counter pulsation (ECP). That therapy has been observed effectual and safe for patients with refractory angina pectoris. They found an increase in PMP after ECP therapy, and no difference in EMP and MPM levels. Bernal-Mizrachi et al. [34] evaluate two species of EMPs (CD31+ and CD51+) in coronary artery disease patients and have noted that CD31+/CD42- EMP were more frequently expressed in patients of myocardial infarction and unstable angina, and CD51+ EMP were released in similar amounts both in acute and chronic events.

Diabetes mellitus

A few studies have reported higher concentrations of PMP related to diabetes mellitus. Ogata et al. [35] noted the levels of PMP in 92 patients with diabetic retinopathy and reported increased release of PMP in diabetic patients as compared to that in healthy individuals, and the increase was higher the more severe the retinopathy. Lumsden et al. [36] have evaluated patients with type 2 diabetes mellitus after acute coronary syndrome that had reduced levels of EMP and no PMP changes. He also submitted few unpredicted findings, which disagree with nearly all studies, can result from concomitant medications used by patients [37-39]. Some other studies have noted that the increase in the expression of adhesion molecules is linked with the monocytes activation leading to diabetic retinopathy progression. That data recommended that measuring the levels of MPM can be a handy biomarker of diabetic retinopathy progression [40]. Nomura S et al. also noted dynamic role of MPs in type 2-diabetes [41].

Conclusion

This study tries to summarize the literature that is relevant to MPs, including a growing list of clinical disorders that are linked with increased MP levels. In the beginning, MPs were thought to be little particles with procoagulant activity but the possibility that MPs (where they are formed) evoke cellular responses in the immediate microenvironments is now under observation.

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