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Membrane microparticles and diseases

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Abstract. – Membrane microparticles (MPs) are plasma membrane-derived vesicles shed by various types of activated or apoptotic cells including platelets, monocytes, endothelial cells, red blood cells, and granulocytes. MPs are being increasingly recognized as important regulators of cell-to-cell interactions. Recent evidences suggest they may play important functions not only in homeostasis but also in the pathogenesis of a number of diseases such as vascular diseases, cancer, infectious diseases and diabetes mellitus. Accordingly, inhibiting the production of MPs may serve as a novel therapeutic strategy for these diseases. Here we review recent advances on the mechanism underlying the generation of MPs and the role of MPs in vascular diseases, cancer, diabetes, inflammation, and pathogen infection.

Key Words:
Membrane microparticles, Vascular diseases, Cancer, Diabetes mellitus, Inflammation, Pathogen infection.

Introduction

Cells in human blood generate a variety of membrane microparticles (MPs). First identified in 1967, MPs are cell plasma membrane-derived small vesicles which are 0.1-1 mm in diameter[1]. When stimulated by various environmental factors including serine proteases, inflammatory cytokines, growth factors and stress inducers[1], nearly all kinds of mammalian cells can generate MPs. Generation of MPs has been demonstrated in platelets, monocytes, endothelial cells, red blood cells and granulocytes[2,3]. MPs may serve as a disseminated storage pool of circulating bioeffectors and are present in both healthy individuals and patients with several diseases, playing important roles in physiological homeostasis and the development of myocardial infarction, stroke and endothelial dysfunction[2,4]. MPs may vary in sizes and membrane markers depending on their cellular origins and are different from other cellular vesicles such as exosomes and apoptotic bodies in sizes, compositions, and numbers[2]. Figure 1 illustrates the typical structure of a MP, showing its bio-active substance and receptors. Apparently, the generation and release of microparticles are tightly regulated and the regulatory mechanism has been extensively studied recently.

For a long time, MPs were considered as cellular by-products without any biological functions. Recent functional assays and multicolor flow cytometric analysis of MPs have re-opened the door of extensive investigation and characterization of MPs. Researches in recent years have shown that MPs possess a broad spectrum of biological activities and may play an important role in multiple cellular processes including intercellular communication, immunity, apoptosis and homeostasis[5,6]. Given the great variation in the phenotype of MPs in different diseases such as vascular diseases, cancer, diabetes mellitus, and inflammation[7,8], analyses of changes in phenotypes and levels of MPs may provide a potentially useful tool in the diagnosis of these diseases. Here we summarize the basic properties and regulatory mechanisms underlying the generation and release of MPs. The relationship of MPs with some common diseases is specifically discussed.

Mechanisms Governing the Release of MPs

Although microparticles formation represents a physiological phenomenon, the exact mechanism governing the release of microparticles has not been clearly defined. Nevertheless, the release of MPs is thought to be a well regulated process rather than a random phenomenon. Cells can release MPs in response to various environmental stimuli and the type of MPs may change depending on a given stimulus which initiates their generation[9,10].

The compositions of the two leaflets of the membrane bilayer in a cell are different. Phos-

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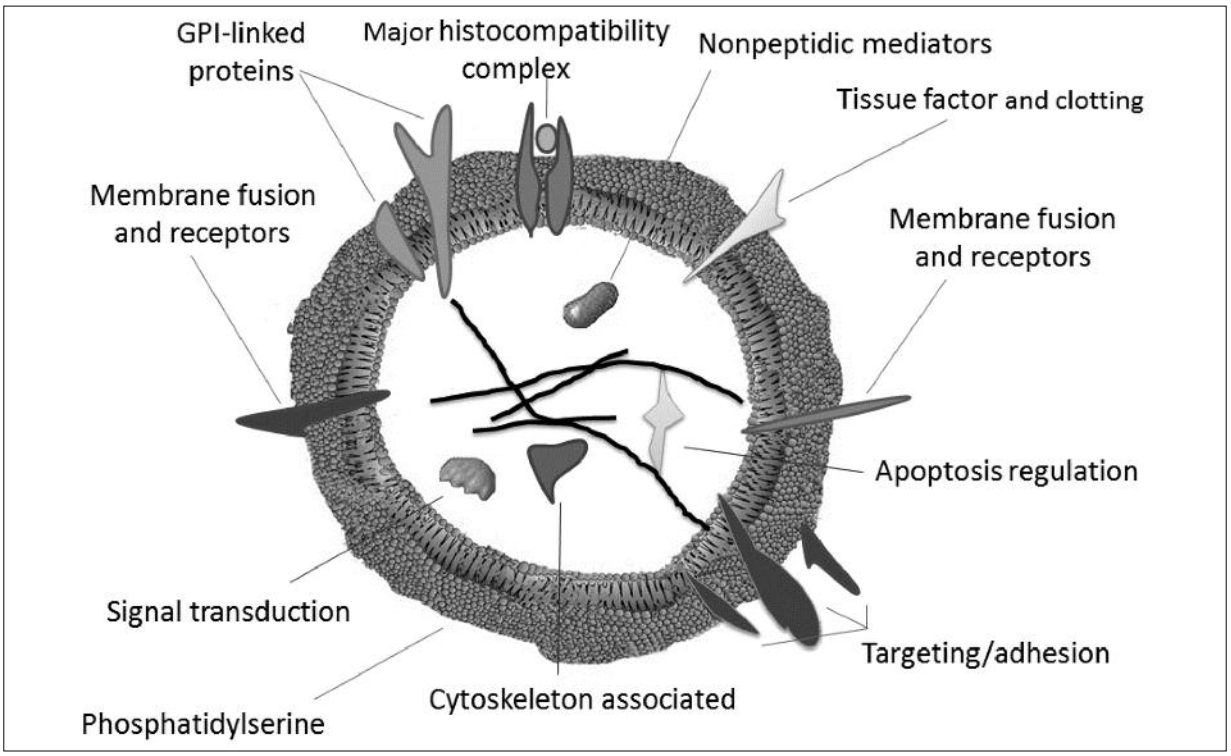

Figure 1. Structure of MPs, including the receptors/biological materials it may contain. They are a disseminated storage pool of bioactive effectors. They harbor membrane and carry cytoplasmic proteins as well as bioactive lipids implicated in a variety of fundamental processes. This representation does not include all known hijacked components. GPI, glycosylphosphatidylinositol.

phatidylcholine and sphingomyelin are mainly located in the external leaflet, while amino phospholipid and phosphatidylethanolamine are present in the inner one[11]. This distribution is controlled by three proteins, namely a *flippase* (governing their inward translocation), a *floppase* (governing their outward translocation) and a lipid *scramblase*[12]. When the cell is stimulated, the concentration of cellular calcium may increase and, thus, enhance the activities of floppase and scramblase activities and decrease the activity of flippase. As a result, the cell membrane asymmetry collapses and the surface exposure to phosphatidylserine (PS) occurs[13,14]. Membrane budding is ultimately resolved into the release of MPs. However, phosphatidylserine exposure is not always followed by release of MPs, which may be regulated by the level of intracellular calcium. It has been demonstrated that cytoskeleton reorganization plays an important role in the release of MPs[15]. Disruption of certain cytoskeleton proteins is required for membrane microparticles release. In addition, MPs may be released by cells that lose membrane integrity or injured by mechanical forces[16]. Several protein kinases may be involved in the release of MPs. For example, the myosin light chain kinase is involved in the complement-mediated microparticles release in platelets[17]. Due to the variations in the lateral composition of cell membrane, the MPs originated from the same cell may have different compositions. Proteomics analyses have revealed that the spectrum of proteins found in MPs released *in vitro* from cultured cells is influenced partly by types of the stimuli used to trigger cell vesiculation[18].

Physiological Role of MPs

MPs possess all types of receptors and bioactive substances on their surface include cytokines, signal proteins and nucleic acid, including mRNA and microRNA(miRNA), which play an important role in intercellular communication and substrate exchange[19]. MPs released from apoptotic cells may be different in lipid and protein composition from membrane vesicles shed following cell activation and might have different patho-physiological effects[19].

Recent studies indicate that microparticles may function as veritable vectors and are involved in the intercellular exchange of biological signals and information[19]. MPs can activate cell receptors

through bioactive molecules on their surfaces, thereby, modulating cellular response and properties[20,21]. There is evidence that MPs can alter gene expression in target cells through transferring mRNA and miRNA[22]. MPs can also modulate target cell functions through directly transferring biologically active substances. It has been demonstrated that chemokine receptor CCR5 and CXCR4 can be transferred by MPs[19,23]. The transfer of these receptors has been demonstrated to facilitate HIV infection and spreading. Indeed, microparticles can transfer part of their components and contents to selected target cells, thus, mediate cell activation, phenotypic modification and reprogramming of cell function[19]. In addition, MPs can play a significant role in vascular function and inflammation by modulating nitric oxide (NO) and prostacyclin production, and stimulating cytokine release and inducing tissue factor (TF) gene expression in endothelial cells as well as regulating monocyte chemotaxis and adherence to the endothelium[24] (Figure 2).

MPs and Vascular Disease

MPs are present in both healthy people and patients with various disease conditions, but they may differ in levels and phenotypes (Table I)[25]. In patients with vascular diseases, the proportions of endothelial cell-derived MPs are found to be increased. Therefore, the endothelial cell MPs can be considered as diagnostic markers of endothelial cell dysfunction and its associated vascular diseases[25]. It has been documented that MPs induce endothelial dysfunction by impairing endothelial NO signal transduction pathway in patients with myocardial infarction[26]. Since NO signal pathway plays an important role in angiogenesis, MPs may also impair angiogenesis through inhibition of NO signal transduction. In contrast, MPs originated from human platelets are capable of promoting angiogenesis, most likely through increasing the expression of proangiogenic factors[27].

As a major blood coagulation initiator, TF (tissue factor) upregulates the expression of proangiogenic vascular endothelial growth factor and,

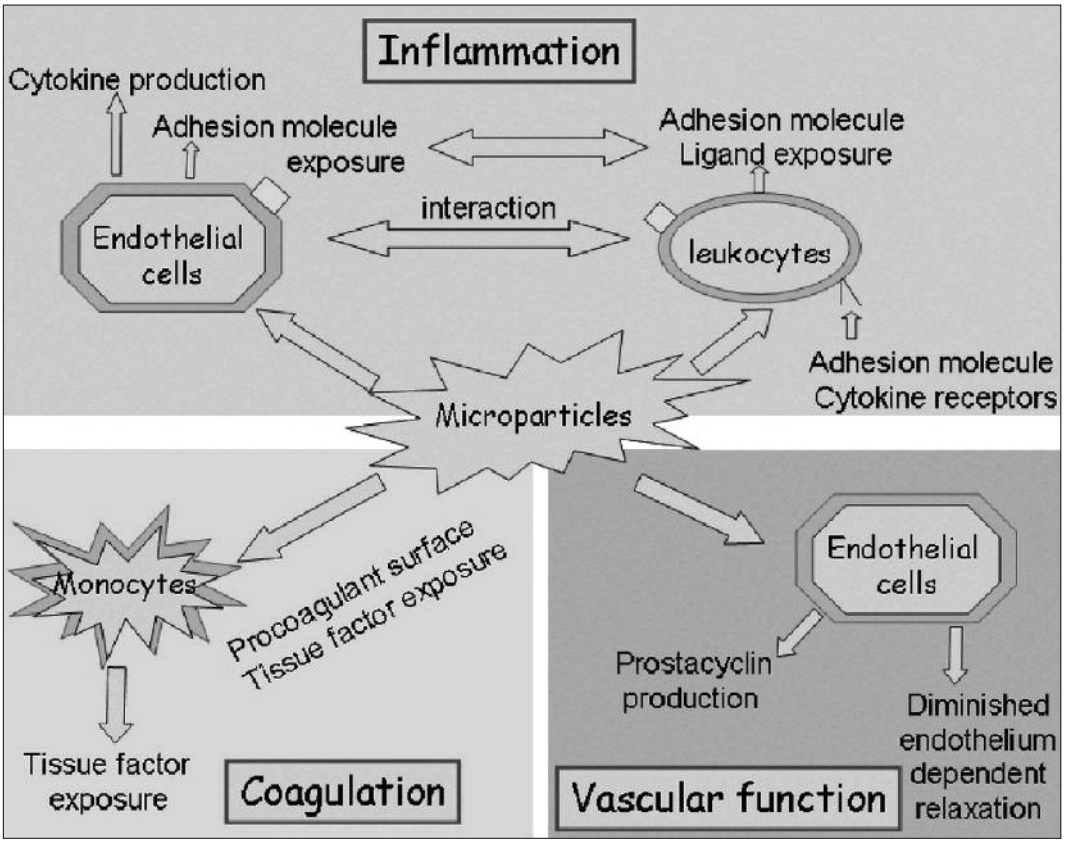

Figure 2. The functions attributed to membrane microparticles. Although many aspects of microparticle function are still unclear, a picture develops in which microparticles play an important role in inflammation, coagulation, and vascular function. Theoretically, microparticles may have various physiological functions, namely transport of membrane components from the parent cell to other cells and direct activation of inflammation, coagulation or vascular function.

Table I. Effect of microparticles on angiogenesis and vascular remodeling.

Derivation	Inducer or pathological issue	Vascular effect	Mechanisms
Platelet	Thrombin-released PMPs (healthy donor)	Neovascularization in the ischemic myocardium	VEGF, PDGF, bFGF
	Thrombin-released PMPs (healthy donor)	Angiogenesis	ERK, phosphoinositide 3-Kinase pathways
	Thrombin-released PMPs	Recruitment of hematopoietic stem cells	Not clear
	Sepsis	Endothelial and SMC apoptosis	Oxidative stress, NADPH oxidase
Endothelium	Serum deprivation	Angiogenesis induction (low-dose); angiogenesis inhibition (high-dose)	Not clear
	Serum deprivation	No effect on angiogenesis (physiological concentrations); Angiogenesis impairment (pathophysiologic concentrations)	Oxidative stress
	VEGF, FGF, serum deprivation	Proteolysis, basement membrane invasion	MMP
Tumor cells	Serum deprivation	Angiogenesis induction	Sphingomyelin

thus, plays an important role in the regulation of angiogenesis[28]. MPs can present tissue factor on their surface to promote the growth of vascular vessels. MPs from endothelial cells and platelets contain matrix metallo-proteinases, which have been demonstrated to be angiogenic *in vitro*[29].

MPs may also play an important role in blood coagulation. MPs from platelets, endothelial cells, monocytes and lymphocytes possess phosphatidylserine on their surface, which serve as a catalytic surface to promote the assembly of enzyme complex of coagulation cascade. TF is a major cellular initiator of coagulation and has been shown to be mainly localized at the surface of MPs. The TF-rich MPs can bind to activated platelets and lead to their membrane fusion. This in turn promotes further accumulation of TFs. In addition, *in vitro* studies have showed that interactions between endothelial MPs and monocytic cells can induce TF-dependent procoagulation[30]. Both experimental and clinical data suggest an involvement of endothelial MPs in the initiation/dissemination of procoagulant responses[30,31].

MPs and Cancer

MPs play an important role in cancer at different levels. MPs have been considered as a biomarker of various cancers. For example, circulating levels of MPs are elevated in gastric cancer patients[32,33]. Some studies suggest that platelet-derived MPs may contribute to cancer metastasis through a currently inconclusive mechanism[27]. In addition, platelet MPs can promote cell adhesion and proliferation of cancer cells. Hence, the number of platelet MPs may be used to predict metastasis in cancer patients. In gastric cancer patients, MPs from CD41a-positive platelets are significantly increased in stage IV compared with stage I or II/III[32].

Tumor cell-derived MPs may harbor some special proteins such as urokinases. Through these proteins, MPs regulate the invasiveness and adhesion of tumor cells. Therefore, MPs can transfer message and promote cancer progression. Moreover, doxorubicin is found to accumulate in MPs originated from cancer cells, suggesting that MP release may be also involved in drug resistance of cancer cells[34-36].

MPs and Diabetes Mellitus

In diabetes mellitus, a wide variety of blood or vascular cells, including monocytes, endothelial cells, platelets, and islets of Langerhans, release MPs[37,38]. Shedding of MPs from these cells is triggered by a variety of cytokines or stimuli, such as oxLDL (oxidized Low Density Lipoproteins), remnants lipoproteins, IL-1 , tumor necrosis factors (TNF family), oxidative stress, advanced glycation end products and hyperglycemia[39]. Levels of MPs from CD14+ monocytes and CD41a+ and CD42+ platelet are elevated in patients with type 2 diabetes[40,41]. In addition, MPs are present in the circulation of patients with type 1 diabetes and type 2[42,43]. However, the phenotype and procoagulant potential of MPs may vary with the type of diabetes or glycemic control. In patients with types 2 diabetes, only the number of PS+ MPs is significantly increased. In contrast, in patients with type

1 diabetes, levels of MPs are significantly elevated for PS+ and CD41+ platelets and CD51+ endothelial cells. There are also studies showing that the procoagulant activity in MPs is correlated with glucose imbalance in patients with type 1 diabetes.

An increase in the level of circulating MPs has been suggested to be one of the procoagulant determinants in patients with diabetes. Hypercoagulable state of diabetes can be initiated or maintained by elevated levels of MPs from TF-positive platelets. Moreover, increases in levels of insulin and glucose may increase the procoagulant activity of TF, suggesting that in diabetes TF exposed to MPs is highly pro-thrombogenic. The recognitions of a role for MPs may not only be important to a better understanding of the pathogenesis of diabetes, but may also have significant clinical implications in the prevention and treatment of this disease[19].

MPs and Inflammation and Immunity

It is now well established that MPs play a crucial role in inflammation. As a source of aminophospholipids and also a preferential substrate for phospholipase A2, MPs are involved in the release of lysophosphatidic acid, which, in turn, triggers platelet aggregation and the inflammatory process. MPs are able to deliver arachidonic acid, leading to an increased expression of endothelial cyclooxygenase type 2[19].

Cytokines also participate in the generation of MPs including PMPs with pro-inflammatory properties. It is documented that the released MPs contains interleukin-1, an important inflammatory factor[44,45]. In addition, there is evidence showing that MPs shed by platelets can stimulate the production of proinflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α. These cytokines in turn activate inflammatory cells to generate more MPs, forming a positive feedback loop[46,47]. MPs can also promote the expression of cell adhesion molecules in endothelial cells; MPs released by leukocytes have been demonstrated to contribute to the activated phenotype of rheumatoid arthritis synovial fibroblasts. MPs released by leukocytes may stimulate the expression of proangiogenic chemokines of CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, and CXCL8[48]. Taken together, MPs from certain cells may induce and intensify inflammatory response. This suggests that MPs can act as agonists of inflammation. However, the underlying mechanism remains unclear.

It has been previously demonstrated that neutrophils can release a large amount of MPs at the site of inflammation, triggering cell apoptosis. MP release is one of the early hallmarks of cells undergoing apoptosis, and shedding from senescent cells is correlated to the degree of apoptosis[49]. It is, therefore, reasonable to believe that systems in charge of the elimination of cell waste products may gain information from qualitative or quantitative variations of MPs.

Upon activation, neutrophils release MPs at the site of inflammation *in vivo*. These MPs, termed *ectosomes*, bind efficiently to opsonized bacteria and may be designed to focus antimicrobial activity onto opsonized surfaces[50]. In addition, ectosomes can specifically adhere to monocytic and endothelial cells, making them more active players in inflammation and cell signaling[20]. It has been proposed that ectosomes are re-

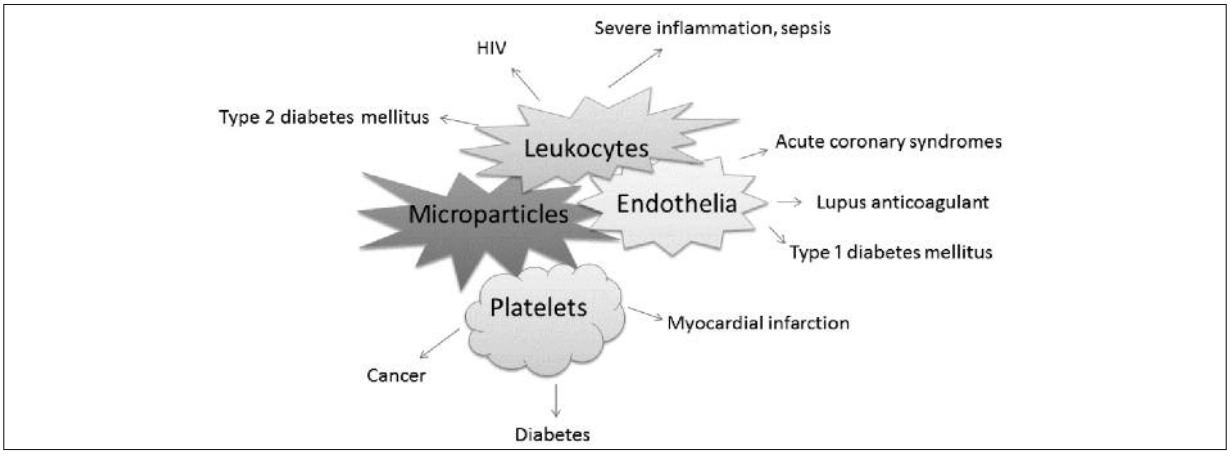

Figure 3. Cellular origin of circulating microparticles in different pathological states, including cancer, diabetes, HIV infection, myocardial infarction, etc

leased from the plasma membrane through the same mechanisms described above for MPs and also bear a significant proportion of PS.

MPs and Infection

MPs have been shown to be associated with some infectious diseases such as malaria and AIDS. Malaria infection may cause overwhelming response of the host to sepsis and influence blood coagulation. Previous evidence shows that malaria infection can promote the formation of MPs from platelets, red blood cells, and macrophages, which may induce systematic inflammation and cause activation of blood coagulation[51,52]. MPs are implicated in HIV infection, propagation and escape from the classical vaccine process and, thus, play important roles in the development of AIDs. MPs originated from CCR5-positive cells can transfer CCR5 to CCR5-deficient peripheral blood mononuclear cells, causing them to be susceptible to HIV infection[53,54]. Patients of HIV infection with a high level of circulating MPs and a low number of circulating CD4+ cells are less likely to develop AIDS-associated complications[55,56]. In addition, procoagulant activity in MPs released by granulocytes and platelets is increased in patients with meningococcal sepsis[57,58]; endothelial MPs have been shown to be extremely important in patients with severe inflammatory response syndrome[59].

Conclusions

Figure 3 summarizes the cellular origin of circulating microparticles in different pathological states. The data accumulated over the last few years on the beneficial and deleterious roles played by microparticles respectively in physiological and pathological conditions (in particular in vascular and inflammatory diseases), suggest that MPs could be friends or foes of the human body, depending on their cellular origins and their generation triggers. On the basis of previous studies in this area, we suggest that microparticles may serve as a new and effective therapeutic target in the treatment of several cardiovascular, renal and infectious and inflammatory diseases.

The development of methodological approaches has greatly promoted the progress of investigations on MPs. At present, flow cytometry analysis and microplate affinity assays are the most commonly used methods, a lot of novel biomarkers have been used to examine MPs. Techniques about assays of MPs have been reviewed in a series of publications[60,61]. As a product from an active process rather than a passive or random phenomenon in the cell, MPs may play important roles in self-defense, stress response, tissue regeneration and inflammation through modulating intercellular communication, initiating cell signaling and transferring receptors and other cytoplasmic proteins. These studies have greatly enriched our understanding of MPs. Nevertheless, questions regarding the adverse effects of MPs, the nature and content of blood transfusion products need to be answered in further investigations.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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