Microparticles as Novel Biomarkers and Therapeutic Targets in Coronary Heart Disease

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Introduction

Microparticles (MPs) were increased in patients with coronary heart disease (CHD), with the subtypes and quantity of MPs variate in different types of CHD. There were emerging reports indicating that MPs may play important roles in the pathogenesis of CHD. Here in this review we summarized the pro-inflammation, pro-coagulation effects of MPs, as well as their impacts on endothelial function and angiogenesis. MPs have the potential of being powerful diagnostic biomarkers and therapeutic tools in CHD patients in the future.

MPs, which were first described as “cell dust,”¹ are intact vesicles derived from the outer membrane of cells during cell activation or apoptosis. MPs are mostly derived from platelets,² whereas MPs are also present in endothelial cells, erythrocytes, granulocytes, monocytes, lymphocytes and smooth muscle cells in lower numbers.

Microparticles are composed of a phospholipid bilayer and cytosolic components such as enzymes, transcription factors, and mRNA.³ Under a resting state, phosphatidylserine is located in the inner monolayer. When the concentration of calcium rises in the cytosol, for example during cell activation or apoptosis, phosphatidylserine translocates to the outer layer, which ultimately leads to the escape of MPs from cytoskeleton and degradation by Ca²⁺ dependent proteolysis.⁴

Microparticles are found in low concentrations in the plasma under physiological conditions. However, the circulating levels are increased in pathological conditions such as atherosclerosis, sepsis, diabetes, chronic severe hypertension, preeclampsia, etc.⁵,⁶ Importantly, a recent study showed significantly higher levels of endothelial MP (EMP) but not platelet MP (PMP) in the sudden cardiac death patients compared with the ST-segment elevated myocardial infarction (STEMI) patients, suggesting a crucial role of MPs in acute coronary events.⁷ It was also found that the EMP level can predict major adverse cardiovascular and cerebral event risk in a sample of 200 CHD patients.⁷ Another study specified that only those activated EMPs (CD62E positive) but not the apoptotic EMPs could predict cardiovascular events in 300 patients with a recent stroke.⁸ MPs were increased in CHD patients comparing with non-CHD patients, with the amount of PMPs and EMPs higher in acute coronary syndrome (ACS) patients than stable angina patients.⁹ A cross-sectional study of 190 healthy males found that the PMP count was significantly correlated with the 10 years Framingham CHD risk score.¹⁰ In 488 consecutive patients with various CHD risks, plasma EMP was found to be a significant and independent predictor of future cardiovascular events during a three years follow-up, highlighting the prognostic value of EMP in CHD patients.¹¹

The reports above strongly indicate that MPs may play important roles in the pathogenesis of CHD. Here, we summarize the possible pathogenic mechanisms of MPs in modulating inflammation, coagulation, endothelial function and angiogenesis. The outline of this review is as follows: The first part describes current MPs isolation and detection methods; The second part describes possible pathogenic mechanisms of MPs.

Isolation and Detection of Microparticles

The quantification of MPs is important for establishing a consistent standard of research. Unfortunately, it is not easy
Annexin V, Biochemical information

In vivo

Concentration

−

+/−

Endothelial MP detection

CD45

Isolation MP

CD31 or CD62E

Measurement time

≥ 300 – 500 nm

Annexin V

−

CD45

−

CD41 or CD42b and CD31

−

CD31 or CD62E

−

CD144

≥ 300 – 500 nm

Annexin V

−

100,000×

−

CD144

−

18,000×

+++

CD31, CD62E or CD144

−

CD41a

Leukocyte MP

Single MP

Annexin V

+/−

−

CD45

+/−

−

GP IX (capture) CD62P, CD40 L

−

CD62P, CD61, CD63

−

Detection limit

Single quantum dot

≥ 300 – 500 nm

Size distribution

−

+/+

Methods

Scattering flow cytometry

Fluorescent flow cytometry

Impedance flow cytometry

Electron microscopy

Capture based assay

Table 1: Compare of common MP separation methods

| Methods                        | Detection limit | Size distribution | Concentration | Biochemical information | Measurement time |
|--------------------------------|-----------------|-------------------|---------------|-------------------------|------------------|
| Scattering flow cytometry      | ≥ 300 – 500 nm  | –                 | +/−           | –                       | +                |
| Fluorescent flow cytometry     | Single quantum dot | −                 | +/−           | +                       | +                |
| Impedance flow cytometry       | ≥ 300 – 500 nm  | −                 | +/−           | −                       | +                |
| Electron microscopy            | 1 nm            | +                 | −             | +/−                     | +++              |
| Capture based assay            | Single MP       | −                 | +/−           | +                       | +                |

MP: Microparticle.

Table 2: Compare of common separation methods for Cell-derived MPs

| Method                | Isolation MP (speed, time) | Generic MP detection | Platelet MP detection | Endothelial MP detection | Leukocyte MP detection |
|-----------------------|-----------------------------|----------------------|-----------------------|--------------------------|------------------------|
| Flow cytometry        | 18,000×g, 30 minutes        | Annexin V            | CD62P, CD61, CD63     | CD31, CD62E or CD144     | CD4, CD8, etc.         |
| Flow cytometry        | −                           | Annexin V            | −                     | CD51, CD144 or CD146     | CD45                   |
| Capture based assay   | −                           | Annexin V, tissue factor | CD62P or GPibα      | CD31 or CD62E           | CD45                   |
| Flow cytometry        | −                           | −                    | −                     | CD31 +/ CD42 − or CD62E | CD45                   |
| ELISA                 | −                           | −                    | −                     | CD144                    | CD14 (monocyte)        |
| Flow cytometry        | 100,000×g, 30 minutes       | Annexin V            | CD41a                 | CD144                    | CD14 (monocyte)        |

Elevated MP levels were also associated with many cardiovascular risk factors, which have been proven to impact endothelial function, such as obesity, hyperlipoproteinaemia, hypertension, and diabetes. It has been found that MPs from patients with acute myocardial infarction can cause endothelial dysfunction in rat aorta through the endothelial nitric oxide synthase (eNOS) pathway while MPs from nonischemic patients had no such effect. Another study showed that MPs from metabolic syndrome patients could reduce nitric oxide and superoxide anion production, resulting in endothelial dysfunction. In vivo injection of MPs from metabolic syndrome patients into mice impaired endothelium-dependent relaxation and decreased eNOS expression. These results suggested a potential link between MPs and endothelial dysfunction.

In a study of 50 patients with CHD, the levels of EMP were increased in endothelial dysfunction patients defined as a loss of vascular relaxation following acetylcholine infusion during an angiographic study. In a study of 84 patients with CHD, EMP levels were increased, and the EMP levels were correlated with severity and location of coronary artery stenosis. Higher EMP levels were noticed in patients with ACS compared with stable angina patients. Surprisingly, patients with stenosis of the left anterior descending artery
Our unpublished results showed that MPs correlate with atherosclerosis. TF played an indispensable role in the development of atherosclerosis, where the PRo-coAgulAnt PotentIAl of MIcRoPARtIcles from lymphocytes could activate the inflammatory nuclear molecule-1 expression in endothelial cells, which are sensitive markers of inflammation, complement components C3 and C4, the classical complement activation of platelets could lead to increased PMPs, which are molecules. MPs were proven able to increase the expression of adhesion molecules. Adhesion to and rolling of monocytes and neutrophils on the endothelium is an important step in atherosclerosis, and the role of MPs in inflammation in CHD patients. These reports suggest that MPs have the potential of being biomarkers as well as therapeutic targets of endothelial dysfunction in CHD patients.

**Pro-inflammatory Effects of Microparticles**

Atherosclerosis is the most frequent underlying cause of cardiovascular disease, while acute thrombosis in atherosclerotic plaque with an eroded surface is the main cause of ACSs including unstable angina and acute myocardial infarction. Inflammation was found to play a key role in the development of plaques, plaque rupture and thrombus formation. There is increasing evidence indicating that the number of MPs increases during inflammation in vivo. It is reported that MPs from leukocytes could stimulate the expression of cytokine related genes in vitro through tyrosine phosphorylation of c-Jun NH-terminal kinase-1. These cytokines included interleukin-1 (IL-1), IL-6, IL-8, monocyte chemoattractant protein-1, tissue factor (TF), tumor necrosis factor-alpha and platelet-activating factor, which all contributed to inflammation. Our unpublished results showed that inflammatory marker high-sensitivity C-reactive protein (CRP) was positively correlated with LMP in STEMI patients ($R^2 = 0.79, P < 0.01, n = 24$), indicating the potential role of MPs in inflammation in CHD patients.

Adhesion to and rolling of monocytes and neutrophils on the endothelium is an important step in atherosclerosis, and MPs were proven able to increase the expression of adhesion molecules. It was found that high shear stress-induced activation of platelets could lead to increased PMPs, which enhanced the expression of cell adhesion molecules in endothelial cells. In addition, once MPs were exposed to complement components C3 and C4, the classical complement pathway could be activated. Moreover, CRP, which is a sensitive marker of inflammation, was found on the surface of MPs. PMPs were reported to induce pro-inflammatory molecules cyclooxygenase-2 and intercellular adhesion molecule-1 expression in endothelial cells, while MPs from lymphocytes could activate the inflammatory nuclear factor-kappa B pathway. These reports suggest that MPs are involved in multiple processes of the inflammatory response.

**Pro-coagulant Potential of Microparticles**

The plaque disruption and organization of thrombi contributes to the rapid progression of atherosclerosis, where the importance of blood coagulation should not be neglected. It is found that the PMP surface is approximately 50–100 fold more pro-coagulant than the surface of activated platelets. Moreover, MPs with pro-coagulant potential were increased in the peripheral circulating blood of patients with ACSs. PMPs have been reported as a valid marker for a pro-thrombotic state through a survey of 54 stable CHD patients.

Tissue factor on monocyte MPs, which is a receptor for factor VII and factor VIIa, was proven to be crucial in coagulation. MPs correlate with atherosclerosis clinically. STEMI patients have high levels of pro-coagulant MPs, and an increased risk of fibrinolysis failure. MPs were also present in atherosclerotic plaques, which are considered to promote TF-dependent coagulation, leading to thrombosis and arterial occlusion. TF played an indispensable role in coagulation; its function was dependent on platelet P-selection receptor P-selectin glycoprotein 1, which was on the surface of monocyte MPs. PMPs and EMPs provided binding sites for coagulation factors IXa, VIII, Va, and IIa. EMPs also express ultra-large von Willebrand factor multimers, which can promote platelet aggregation.

**Microparticles and Angiogenesis**

Angiogenesis is a complicated process that includes endothelial cell proliferation, migration, differentiation, and morphological change. Angiogenesis processes after myocardial infarction can improve heart function. In recent studies, MPs were found to be involved in angiogenic processes such as tumor neovascularization, diabetic retinopathy, wound healing, and CHD. MPs derived from many types of cells are found to have angiogenic functions. In a rat myocardial infarction model, ligating the left anterior descending coronary artery, PMPs injection into the peri-ischemic region resulted in a marked increase in new capillaries. MPs were found to be involved in almost all steps of angiogenesis through PI3-kinase and extracellular signal-regulated kinase pathways. EMPs could promote vessel formation through elevating matrix metalloproteinase-2 (MMP-2) and MMP-9 activity, which catalyze matrix degradation and angiogenesis. MPs derived from Shh, which act as an inter-cellular signal responsible for cellular fate decisions, can up-regulate angiogenic growth factors vascular endothelial growth factor (VEGF) and angiopoietins. It was further confirmed that treatment of endothelial cells with MPs derived from Shh induced and accelerated the formation of capillary-like structures through up-regulation of pro-angiogenic factors VEGF, heparocyte growth factor, and fms-like tyrosine kinase (FLT)-1. This pro-angiogenic function could be inhibited by blocking the Shh signaling with cyclopamin.

However, there are some contradictory results as well. EMPs were also reported to play an antiangiogenic role through up-regulation of antiangiogenic reactive oxygen species. The differences may be due to different concentrations of EMPs because lower concentrations of EMPs were reported to promote angiogenesis, whereas higher concentrations could suppress angiogenesis.
### Perspectives

Given the correlation between MPs and the development of CHD, MPs have the potential of being biomarkers for CHD [Table 3]. For example, EMPs were reported as a predictor of future cardiovascular events in a population with high Framingham risk scores.[11] In ACS patients, circulating Annexin V positive MPs were strongly correlated with the occurrence of myocardial infarction or death.[3,72] In asymptomatic subjects, circulating LMPs predicted subclinical atherosclerosis as evaluated by plaque numbers in several vascular sites.[3] However, the prognostic potential of MPs has not yet been elucidated, additional clinical outcome studies are necessary.

In consideration of their active involvement in multiple processes of atherosclerosis, MPs have been proposed as new therapeutic targets in the treatment of CHD. First, MPs could work as vectors for gene therapy. It has been reported that MPs from lung cells contain mRNA that could be released into bone marrow cells, and modulate their phenotypes.[73-76] Moreover, engineered MPs generated in vitro could also incorporate mRNA into target cells and modify their phenotype.[76] Recently, it was reported that inhaled and oral MPs have been developed to deliver therapeutics.[77,78] Second, it has been reported that transfection of glioma cells with the oncogenic form of the epidermal growth factor receptor (EGFR) induces MPs over-expressing EGFR, which could be transferred to cells lacking this receptor.[76] This finding demonstrated a natural way to generate MPs over-expressing certain receptor molecules. Moreover, due to their pro-coagulation function, MPs may ameliorate platelet function in diseases such as thrombocytopenia.[79]

In addition to the molecular application of MPs mentioned above, several drugs may influence the release of MPs. Statins, for instance, could reduce the expression of GPIIIa antigen, P-selectin and TF on PMPs in patients with diabetes, dyslipidemia or peripheral arterial occlusive disease.[80,82] while statins exert controversial effects on EMP levels.[85,86] PMPs release could be reduced by ticlopidine and clopidogrel.[85,86] Aspirin could reduce the number of EMPs and PMPs in patients with CHD.[87] However, an important question remains how to control particular MPs to an ideal level, so as to achieve benefit actions and limit adverse effects. Also, the comprehensive effects of MPs need to be fully evaluated before clinical use. MPs as powerful diagnostic and therapeutic tools may benefit more CHD patients in the future.

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High levels of circulating endothelial

Platelets amplify inflammation in arthritis

Microparticles derived from endothelial

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