

REVIEW ARTICLE

The research progress of microparticles (extracellular vesicles) in the field of cardiovascular surgery

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ABSTRACT

Circulating particles (extracellular vesicles) have the function of transmitting information between cells in biological processes such as vascular regulation, inflammation, coagulation, cell proliferation and apoptosis. It contains complex and diverse components, which are closely related to the occurrence and development of cardiovascular diseases. In the future, circulating particles (extracellular vesicles) can be used as clinical markers to reflect coagulation function, inflammatory reaction, tissue and organ damage, or as clinical treatment targets to regulate vascular homeostasis, correct coagulation, improve internal environment, and protect tissue and organ function, which has important research significance. In this paper, we summarize the relevant research progress of circulating particles (extracellular vesicles) in the field of cardiovascular surgery, and discuss the role of circulating particles (extracellular vesicles) in the process of related diseases, as well as its research and application prospects in the diagnosis and treatment of related diseases.

Keywords: extracellular vesicles; circulating particles; cardiac surgery; extracorporeal circulation

1. Introduction

Circulating microparticles (MPS)/extracellular vesicles (EVS) are a kind of micro vesicles with double lipid membrane structure released when cells are stimulated or apoptotic. As early as 1967, circulating particles were discovered by wolf as a product of platelets. At that time, they were considered as non functional cell fragments, and their role was ignored. Mps/evs have the biological activity of intercellular information transmission, and play a very important role in the process of vascular regulation, inflammation, coagulation, cell proliferation and apoptosis. Mps/evs are distributed throughout the body and have diverse functions. They are divided into different subgroups according to their different maternal cell sources. In addition to the double-layer lipid membrane, mps/evs contain various contents such as cytokines, nucleic acid substances, signal proteins, etc., which reach different target organs and tissues with the blood circulation.

Inflammation, tissue damage, tumor, ischemia, etc. Can stimulate different body cells to produce mps/evs, such as tumor necrosis factor α (Tumor Necrosis Factor- α , TNF- α), Interleukin and plasminogen activator inhibitor-1 (PAI-1) stimulate endothelial cells to produce endothelium derived microparticles (EMP), and tissue factors stimulate platelets to produce platelet derived microparticles (PMP)^[1,2]. In cardiovascular diseases, such as hypertension, acute coronary syndrome, mitral valve disease, aortic stenosis, congenital heart

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disease, cardiac graft vascular disease, etc., mps/ evs has increased, and plays a role in regulating endothelial function, promoting inflammation, regulating apoptosis, etc. In the occurrence and development of cardiovascular diseases^[3-6]. Some early research results show that mps/evs play a harmful role in the physiological and pathological process of the body, especially in atherosclerosis and promoting inflammation^[7]. However, recent studies have pointed out that mps/evs can also inhibit inflammatory response and promote angiogenesis^[8,9] and play a protective role in the process of pathological development. In addition, our previous studies have shown that under different physiological and pathological conditions, mps/evs produced by the same kind of cells will show different component phenotypes^[2]. This article reviews the role of mps/evs in the pathological process of cardiovascular surgery, such as coagulation function, endothelial function, and functional damage of important organs.

2. Cardiopulmonary bypass

Extracorporeal circulation (CPB) is a life support technology that uses special devices to temporarily replace the heart to supply blood circulation and lung gas exchange function. It is also a common technology in cardiovascular surgery.

Surgical trauma itself can stimulate the production of mps/evs. However, cardiopulmonary bypass, as an independent factor, can also stimulate the production of mps/evs by body cells such as vascular endothelial cells and platelets, and participate in the biological processes such as platelet activation and aggregation, oxidative stress, inflammatory response, endothelial function regulation, which will have adverse effects on the body and affect the prognosis of patients, and the risk will increase with the extension of cardiopulmonary bypass^[10-13]. In the relevant literature, the time for the peak of mps/evs rise to return to the baseline level varies. In addition, heparinization, hypothermia and other factors during cardiopulmonary bypass may also affect platelet function^[14-16]. Some scholars have tried to use a small extracorporeal circulation tube for surgery, but it has no significant impact on the generation of mps/evs^[17]. Intraoperative use of a blood recovery device can effectively elute mps/evs, theoretically reducing the adverse effects of cardiopulmonary bypass on coagulation and inflammation, but whether it will affect the overall prognosis remains to be further studied.

3. Postoperative coagulation

Bleeding after cardiovascular surgery is a common complication. After thoracotomy, cardiopulmonary bypass and other processes, blood loss, hemodilution, loss of blood components, consumption of coagulant substances and so on will inevitably occur. Mps/evs not only expose the coagulation promoting phosphatidylserine, tissue factor, von Willebrand factor (VWF) on the surface of its own lipid membrane, playing a role in promoting coagulation, but also feedback and activate endothelial, platelet and other target cells, generating more circulating particles and cytokines. Promote the further development of coagulation reaction^[18] and play a very important role in hemostasis after operation. Studies have found that if the levels of PMP and red blood cell derived microparticles (RMP) decreased significantly before coronary artery bypass grafting, the greater the possibility of postoperative blood transfusion, indicating that this part of mps/evs indirectly reflects the patient's preoperative coagulation function reserve^[19].

Cardiac surgery will significantly increase the release of mps/evs and participate in a series of reactions of the body. These mps/evs have procoagulant activity, activate coagulation pathways, activate platelet aggregation, leukocyte platelet aggregation, etc.^[20-22]. Excessive consumption of coagulant substances and impairment of platelet function will cause postoperative coagulation dysfunction. In addition, we found in the study on protein components of mps/evs in patients with valve diseases that, compared with healthy people, before heart valve surgery, the plasma mps/evs components of patients contain more coagulation related

proteins, such as vwf and β 2 glycoprotein 1, which is significantly reduced after surgery, suggesting that cardiopulmonary bypass surgery will damage the coagulation function^[23]. Chung et al. applied nitric oxide and iloprost during cardiopulmonary bypass to reduce the production of mps/evs during cardiopulmonary bypass, protect platelet function, and significantly reduce postoperative drainage^[24]. These studies have verified our hypothesis that shortening cardiopulmonary bypass time, reducing the production of related mps/evs, avoiding the consumption of coagulation substances, and preserving the body's coagulation function can reduce postoperative bleeding complications. At the same time, we hope that mps/evs can be maintained at the normal physiological level and avoid excessive release, thromboembolism and other adverse consequences as far as possible.

4. Endothelial function and blood flow homeostasis

Protecting endothelial function and maintaining blood flow homeostasis are of great significance to the safety of operation and the prognosis of patients. Nitric oxide (no) is currently recognized as a key factor in the regulation of endothelial function. It plays an important role in maintaining vascular tension and endothelial activity.

Early studies have shown that mps/evs can inhibit endothelial regulatory function^[25-27]. With the deepening of our research, we found that mps/evs can uncouple enos, reduce the production of no and produce oxygen free radicals by inhibiting the akt/enos (endogenous nitroxide synthase) Hsp90 (heat shock protein 90) signal pathway, thus affecting the endothelium-dependent vasodilation function. In a recent study on patients undergoing valve surgery, we found that valve disease itself or cardiopulmonary bypass surgery can promote the body cells to produce mps/evs and act on vascular endothelial cells. In addition to inhibiting akt/enos-hsp90 pathway, mps/evs also affect Akt and PKC β II(Protein Kinase C β II). Caveolin-1 down regulates the phosphorylation of enos, resulting in the reduction of no production and endothelial dependent vasodilation dysfunction^[12]. In addition, we also found that the level of EMP increased significantly in patients with congenital heart disease, especially in patients with pulmonary hypertension. Through p38/MAPK pathway, it promotes inflammation, affects no production, damages endothelial function, and may participate in the development of pulmonary hypertension^[6]. These endothelial dysfunction will directly affect the blood flow stability after cardiac surgery, increase the occurrence of postoperative complications, and change the prognosis of patients.

Mechanical stretch can stimulate vascular smooth muscle cells, significantly increase the release of mps/evs, induce endothelial cell apoptosis through endoplasmic reticulum stress, and promote the formation of thoracic aortic aneurysm and dissection. Endoplasmic reticulum stress inhibitors can reduce the release of mps/evs caused by mechanical traction, reduce endothelial cell apoptosis, and thus inhibit the formation of thoracic aortic aneurysm and dissection^[28]. It can be seen that mps/evs also play an important role in the occurrence and development of macrovascular diseases.

5. Valvular disease

In patients with mitral stenosis or regurgitation, the content of plasma EMP increased significantly, and was positively correlated with the degree of disease. These emps in turn affect the function of valve endothelial cells and accelerate valve damage^[12]. Diehl and other scholars also found that the amount of EMP in plasma of patients with severe aortic stenosis increased significantly^[29]. However, it has also been reported that for patients with severe aortic stenosis, the degree of valve calcification is not significantly related to mps/evs and its induced thrombin production^[30]. It is suggested that there may be other pathways of action in the pathogenesis of valve stenosis, which may be closely related to the role of circulating endothelial progenitor

cells of osteoblast phenotype, leukotriene B4 and the activation of endoplasmic reticulum stress by hydroxycholesterol^[31–33]. In our study on protein components, it was also verified one by one that mps/evs before and after heart valve surgery are rich in corresponding functional proteins in terms of coagulation function, endothelial function, systemic inflammatory response, etc.^[23]. During valve surgery, cardiopulmonary bypass and myocardial arrest cause changes in hemodynamics and oxygen supply and demand balance of important organs, which will lead to a series of pathological reactions. As mentioned above, mps/evs are involved in oxidative stress, inflammatory reaction, endothelial dysfunction, coagulation dysfunction and other processes, and the excessive release of circulating particles during surgery may be unfavorable.

Transcatheter aortic valve implantation (Tavi) is an effective alternative treatment for high-risk groups of aortic valve surgery. Studies have found that EMP decreased significantly after Tavi, while PMP remained at a high level for a long time. The decrease of EMP may be related to the fact that Tavi can effectively improve aortic valve function, improve overall hemodynamics, and reduce cross valve pressure difference and stress. The newly implanted valve itself will cause thrombosis, especially the tip position of the implant, which can be used to explain why PMP is maintained at a high level^[34].

6. Coronary atherosclerotic heart disease

Mps/evs participate in endothelial inflammatory response, inflammatory cell migration, vascular injury and repair, endothelial and vascular smooth muscle cell proliferation and migration, and play an important role in the occurrence and development of coronary atherosclerotic heart disease^[35–39].

Coronary artery bypass graft surgery (CABG), namely coronary artery bypass grafting, is the most effective treatment for coronary heart disease. The operation methods can be divided into off-pump and on pump coronary artery bypass grafting.

Whether it is off pump or on pump, CABG will increase the level of mps/ evs, showing a downward trend after operation, but still higher than the preoperative level. However, studies have shown that Off-pump CABG does not cause oxidative stress, but mps/evs contained in the plasma of on pump CABG patients can induce oxidative stress and promote the production of superoxide^[10].

The patency of transplanted vessels is directly related to the overall prognosis of patients. Camera et al. found that mps/evs was closely related to the patency of bridging vessels in patients undergoing coronary artery bypass grafting. During the follow-up, the content of mps/evs in some subpopulations of plasma increased significantly in patients with bridge vessel occlusion. For example, PMP transmits biological information to target cells during platelet activation and participates in cell proliferation, angiogenesis and inflammatory response. According to the research results, this study screened out six phenotypes: Cd40l+/cd41+, cd62p+/cd41+, tf+/cd41+, tf+, annexinv+/tf+, annexinv+/tf+/cd41+ and calculated the “particle score”, which was used to predict the risk of bridge vessel blockage after coronary artery bypass grafting and guide the follow-up treatment plan^[40].

7. Cardiac graft vascular disease

Allogeneic heart transplantation is the most effective treatment for end-stage heart disease. Cardiac allograft vasculopathy (CAV) is the main cause affecting the long-term prognosis of heart transplantation patients. It is the result of endothelial cell damage and repair mediated by immune and non immune factors. Natural immune and specific immune cells can affect inflammatory reaction, vascular fibrosis, vascular smooth muscle proliferation, etc., and promote the occurrence of CAV^[41–45].

During the process of endothelial injury and repair, endothelial cells continued to activate and release mps/evs. Some studies have pointed out that mps/evs in heart transplant patients have more apoptotic activity than those in patients with coronary heart disease and heart failure^[46,47]. However, Singh et al. found that in patients with CAV, mps/evs were more inclined to endothelial activation than apoptosis^[48]. This study suggests that EMP of this phenotype can be used as a marker to predict whether postoperative patients suffer from CAV. However, the role and mechanism of the phenotypic changes of mps/evs in the development of CAV are not completely clear and need to be further studied.

8. Functional impairment of important organs

Functional injury of important organs is a serious complication after cardiac surgery, which is directly related to the success or failure of the operation. Mps/evs can promote the occurrence and development of these complications by promoting inflammatory reaction and oxidative stress.

Our recent research found that the content of mps/evs in plasma increased after patients underwent cardiopulmonary bypass, and the increase of mps/evs 12 hours after operation was closely related to the occurrence of acute heart failure. Mps/evs can be expected to be a new generation marker for predicting postoperative heart failure.

In addition, mps/evs can affect endothelial function and promote inflammatory reaction by inhibiting enos activity and chemotactic granulocyte aggregation, leading to pulmonary edema, endothelial alveolar barrier damage, and then acute lung injury^[49]. Moreover, mps/evs can also promote inflammation during the development of lung injury^[50].

Mps/evs extracted from patients' plasma after valve replacement surgery can inhibit the phosphorylation process of Akt, cause overexpression of FOXO3a (forkhead box protein 3A) and dephosphorylation of FOXO3a, cause more FOXO3a to enter the nucleus, activate downstream signal pathways, cause a large number of endothelial cells to release chemokines CXCL4 and CCL5, stimulate neutrophil chemotactic aggregation, and cause kidney damage. The study also found that the use of dexmedetomidine during valve surgery can reduce the effect of mps/evs on FOXO3a, effectively slow down neutrophil chemotaxis, and reduce the risk of postoperative renal insufficiency^[51]. Some scholars have found that the changes of mps/evs in pediatric cardiac surgery may be related to age. Studies have shown that children with renal injury have higher plasma mps/evs concentration, while infants with renal injury have lower mps/evs^[52]. This suggests that the mechanism of regulation of body response to injury stimulation may be different in patients of different ages.

The incidence of cerebral infarction or cerebral hemorrhage in perioperative period of cardiac surgery is low, but the consequences are often very serious. Among them, atherosclerotic plaque rupture is an important cause of postoperative cerebral infarction, especially in the elderly or high-risk patients with metabolic diseases. Studies have shown that endothelial derived particles and leukocyte derived particles can be used as markers to predict the stability of carotid atherosclerotic plaque, which is helpful for preoperative evaluation of the disease condition and clinical intervention^[53,54].

Since the biological processes involved in mps/evs can evolve and develop in various important organs and tissues, we hope to find out the taxonomic types in which various organs and tissues play a corresponding role in the future to better explain their role in the development and evolution of diseases.

9. Left ventricular assist

Left ventricular assist devices (LVAD) is a mechanical cardiac assist device that provides support for circulation when the left ventricle cannot meet the needs of system perfusion, so that the failed heart can recover its function, or temporarily replace its function when waiting for heart transplantation.

Mps/evs levels were higher in patients with end-stage heart failure than in healthy people or patients with stable angina pectoris. However, different scholars have reported different results on the changes of mps/evs content in patients with heart failure after receiving LVAD. Ivak et al. found that even though mps/evs decreased in 3 months after operation and rose in 6 months after operation, there was no significant difference in the whole study^[55]. Sansone et al. observed that after receiving LVAD treatment, mps/evs of platelet phenotype, leukocyte phenotype, endothelial cell phenotype and erythrocyte phenotype were significantly increased. These mps/evs exhibit endothelial cell activation and apoptosis promoting properties^[56]. In addition, studies have found that the elevated mps/evs level of exposed phosphatidylserine (PS) may be related to the occurrence of adverse events after LVAD, and may become a new marker^[57].

10. Composition and particle size

Studying mps/evs has its diversity and complexity. Analyzing and verifying its components is of great significance for studying the functions of mps/evs in different physiological and pathological processes.

Early proteomic studies on mps/evs began with isolated human umbilical vein endothelial cells^[58]. Later, some scholars extracted mps/evs from the blood of healthy volunteers for more comprehensive proteomic analysis to further verify the function of mps/evs in physiological processes^[59]. In our recent study, in addition to the healthy population, mps/evs extracted from valve patients before and after cardiopulmonary bypass surgery were analyzed from the aspects of cell composition, molecular function and biological process through protein component determination, which verified the function of mps/evs in the process of complement activation, immune response, endothelial response, coagulation and hemostasis^[23]. Studies have found that the content and distribution of DNA components of mps/evs in patients with cardiac surgery under different pathological conditions also have significant changes, and have an important connection with the body's inflammatory response^[60]. Mps/evs contain long non coding RNA (lnc RNA) and microRNA (mirna), which play an important role in regulating vascular endothelial function, angiogenesis, aging and other processes^[61-67], and have the application prospect of new markers or therapeutic targets. In addition, under the action of some drugs, the production, function and components of mps/ evs will also be affected^[68-71].

Recently, we have also made relevant research on the particle size of mps/evs before and after cardiopulmonary bypass, and found that the content changes of mps/evs with different particle sizes after operation are different, and there is a correlation with the dose of positive inotropic drugs after operation, suggesting that the classification of mps/evs with different particle sizes may become a reference index for predicting postoperative cardiac function^[72].

11. Summary

With the in-depth study of mps/evs, more and more functional features of mps/evs have been excavated. Mps/evs involves many biological processes, such as vascular regulation, inflammation, coagulation, cell proliferation and apoptosis. Its components are complex and diverse, and its role in the occurrence and development of related diseases is still not completely clear. In the future exploration, it is far from enough to simply study the concentration and content of mps/evs. When studying and analyzing the action mechanism of each subgroup in different biological processes, it needs to be verified in combination with phenotype,

protein component, nucleic acid component, particle size and other aspects, which will be more convincing. At present, mps/evs is expected to become a new method to help make decisions on surgical treatment plans, evaluate disease status, and verify treatment effects. Mps/evs can also be used as a new therapeutic target in regulating vascular homeostasis, correcting coagulation, improving internal environment, protecting tissue and organ functions, etc.

Conflict of interest

The authors declare no conflict of interest.

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