

Review Article

The effect of cell derived microparticles in transfusion medicine and adaptive immune system

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Received: Nov 12, 2015; Accepted: March 26, 2016

Abstract

This article reviews will focus on the concept and formation of micro particles (MPs) in circulation and their role in transfusion medicine and immune system. MPs are cell membrane derived vesicles which express markers of their parent cells and are found in circulation at low levels. Exact functions of MPs are unclear. In here, Physiological almost all types of circulating MPs including platelets MPs (PMPs), leukocytes MPs (LMPs), red blood cells MPs (RMPs) and endothelial cells MPs (EMPs) have been discussed. Furthermore, MPs present in plasma and blood products and their levels increase during storage. Thus, it can be stated that MPs are likely to cause transfusion reactions, particularly thrombotic complications and Transfusion-Related Acute Lung Injury (TRALI). Also, it is shown that the MPs may affect the immune system. However, to prove these, more and extensive studies both in vivo and in vitro need to be done.

Keywords: Microparticles, platelets, transfusion medicine, adaptive immunity

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Please cite this article as: Esmaeili M A, Yari F, Amini A, Rezvani M R . The effect of cell derived microparticles in transfusion medicine and adaptive immunity system. Arch Med Lab Sci. 2016;2(1):29-35.

Introduction

Microparticles (MPs), microvesicles or ectosomes are membrane derived vesicles that are released in blood flow. Most of cells including platelets, endothelial cells, tumor cells, erythrocytes and white blood cells (neutrophils, monocytes-macrophages and lymphocytes) produce MPs (1-3). They are found in physiological and pathological fluids (4-10) and are also produced in stored blood products (1-3). Mammalian cells secrete two extracellular vesicles; exosomes and MPs. Both are derived from the membrane, but their formation from cells membrane is different (11). Typically, MPs

range in size from 0.1 μm to 1 μm . Exosomes, another form of secretory vesicles are smaller vesicles that range in size from 0.03 μm to 0.1 μm . Indeed, MPs are larger than exosomes and are derived directly from the plasma membrane. On the other hand, apoptotic bodies range in size from 1 to 5 micrometers (12-14). MPs and exosomes can be separated by differential centrifugation, ultrafiltration, ultracentrifugation, or immune-precipitation (13, 15). According to proteomic data, MPs-bound IgM probably provide a mechanism for clearance of MPs (16). Information relating to MPs, exosomes and apoptotic bodies are described in Table 1 (12-14, 17-21). This review will focus on the concept of MPs. Special emphasis will be

put on the effects of them in transfusion medicine and adaptive immunity system.

The concept of MP and its formation

Existence of MPs was first noticed by Wolf in 1967 (22). They are commonly described as a heterogeneous population of phospholipid vesicles, which are released by budding of the parental cells plasma membrane which is called ectocytosis (17, 18). Although the MPs have been considered as cell dust with no any biological function, but it is known that they are involved in the biological activities such as hemostasis, thrombosis and inflammation (23).

MPs release is a highly regulated process (16) that prompted by stimuli such as shear stress, complement activation, injury or apoptosis. However, the rate of release of them in the blood of healthy individuals is usually low (13). The formation of MPs is secondary to disruption of the normal phospholipid asymmetry of plasma membrane. Under physiologic conditions, the aminophospholipids including phosphatidylserine (PS) and phosphatidylethanolamine (PE) are arranged on the inner leaflet of membrane, but the cholinophospholipids including phosphatidylcholine (PC) and sphingomyelin (SM) are arranged on the outer leaflet of membrane. The transbilayer lipid distribution is under the control of three phospholipidic pumps: an inward-directed pump, or flippase; an outward-directed pump, or floppase; and a lipid scramblase, responsible for non-specific redistribution of lipids across the membrane. In resting cells, flippase maintains the asymmetry of the phospholipid bilayer but floppase and scramblase are inactive, and the cytoplasm calcium concentration is low. After cell stimulation, including apoptosis, a subsequent cytosolic Ca²⁺ increase promotes the loss of phospholipid asymmetry of the plasma membrane, subsequent phosphatidylserine exposure, and a transient phospholipidic imbalance between the external leaflet at the expense of the inner leaflet, leading to budding of the plasma membrane and MPs release. Indeed, loss of membrane stability allows the possibility of formation and release MPs. Also, in platelets, a significant change in membrane associated proteins leading to the generation of MPs.

This change in red blood cells is less (23-25). The physiological role of MPs is not identified (23). However, it should be noted that Phosphatidylserine (PS) on the surface of MPs and apoptotic cells is a recognition signal for removal these vesicles and cells from the circulation by activated macrophages (26).

Effects MPs in transfusion medicine

MPs in blood components

MPs express surface markers from their parental cells. Thus, they can be classified according to the parental cell. There are four major subgroups of circulating MPs including platelets MPs (PMPs), leukocytes MPs (LMPs), red blood cells MPs (RMPs) and endothelial cells MPs (EMPs) (12, 14). It should be noted that probably all eukaryotic cells can produce MPs after stimulation or apoptosis because there is no accepted way to show the existence of MPs in tissues (27).

Microparticles are present in all of blood products and accumulated during storage (28-30). The mechanism of MPs release is not exactly understood; but several mechanisms are probably involved, including shear stress, calcium influx, oxidative stress and complement attack. Also, in here, there are different types of MPs in blood products such as platelet MPs (PMPs), leukocyte MPs (LMPs) or red blood cells MPs (RPMs) (31, 32).

Accumulating of MPs is considered as a storage lesion (33). The level of vesiculation in RBCs products may change with the length of storage, storage solution, pre-storage leukoreduction and donor to donor. Additive solutions minimize production of RMPs through decreased oxidative stress. Furthermore, reduced RMPs has been seen after pre-storage leukoreduction of whole blood or packed RBCs products (34, 35). In stored RBC products, RMPs are the predominant types. Nevertheless, noteworthy amount of PMPs and LMPs are produced during blood storage. After 10 days, Steep increase in the production of RMPs becomes more (28).

Platelet products are different from other blood products because they are stored between 20-24 °C with continuous gentle agitation and their life span is short, about 5 to 7 days (36). This limitation is as a

result of the following two: the first case is bacterial contamination and the second is a platelet storage lesion (37). It is believed that more than one mechanism involved in the formation of MPs that most important of them include shear stress and biological factors such as cytoskeletal reorganization, plasma membrane blebbing and Phosphatidylserine exposure (38, 39). During storage mean platelet volume (MPV) decrease due to membrane loss from dendritic forms or activation or apoptosis. These lead to fragmentation or MP formation (40).

PMPs can be connected to von Willebrand factor (vWF). VWF is a multimeric plasma glycoprotein that supports platelet adhesion at sites of vascular injury. In platelet components, it seemed that the binding of PMPs to vWF was affected from the storage media of PC (plasma and Composol). The binding capabilities of PMP were significantly higher in Composol than that of plasma at the day 4 or 7 of storage. However, PS exposure was not affected from the type of storage media (41).

It should be noted that MPs are found in fresh frozen plasma (FFP) and cryoprecipitate because they contain considerable number of cells (42). The number and type of MPs in FFP is different than those in peripheral blood (43) that depends on factors such as leukoreduction, in fact how to reduce leukocyte, and storage conditions .i.e. more storage time and freezing (44). For example, Plasma components prepared after an overnight hold of whole blood at 4 °C prior to processing contained increased levels of MPs Compared to plasma produced within 8 hours of blood donation (45). Like FFP, Cryoprecipitate contains significant amount of platelet MPs. High levels of PMPs in cryoprecipitate are considered to contribute to its therapeutic effects in bleeding patients (42).

Do MP is an agent for blood transfusion reactions?

Whether MPs are involved in a variety of blood transfusion reactions is not yet proven. But since they considered as a storage lesion and lead to changes in blood components, it is not improbable that they have a role in incidence transfusion reactions.

Thrombotic complications

MPs may contribute to transfusion related thrombotic complications because they exhibit procoagulant activity by expression of PS that cause assembly of the coagulation factors and finally thrombin formation. Thrombotic effects of PMPs are well known (46-48) but it has also been suggested for RMPs.

In a recent study, it determined that the use of aged RBC products (more than 28 days) lead to an increased incidence of deep vein thrombosis (DVT). But, its exact mechanism is still unclear. It is likely that the RMPs are involved in coagulation propagation and make this both through expression PS, and by initiating thrombin generation independently of tissue factor in a FXI-dependent manner (49). Moreover, Spinella and Colleagues reported a higher significant incidence (34%) of DVT in trauma patients receiving older blood (28 days or more) in comparison with blood <28 days old (16%)(50).

TRALI

Transfusion related acute lung injury (TRALI) is one of the most serious of transfusion reactions. Although the TRALI mechanism is still not fully understood, the findings suggest that neutrophils play an important role in its pathogenesis (51). However, it is concluded that TRALI is the result of two events which is supported by experimental and clinical studies (52). The first event is the patient's clinical condition and second event can be linked to an anti-leukocytic antibody (53, 54) or antibody-independent such as bioactive lipids, cytokines and MPs (55). It can say that MPs involved in the development TRALI because PMPs (56, 57) and RMPs (58) can activate neutrophils. Furthermore, it has been reported that CD40 Ligand (CD40L, a member of the tumor necrosis factor) is a primarily platelet-derived pro-inflammatory mediator found in soluble (sCD40L) and cell associated forms in transfused blood (59, 60) presents in platelet concentrates is a potential cause for TRALI (61) because studies have showed that the most of CD40L presents in blood is MP-associated (62).

In a study, Xie RF and Colleagues showed that PMPs, which carried the sCD40L, primed the formyl-Met-Leu-Phe (fMLP)-activated PMN respiratory

Table 1. Differentiation of MPs from Exosomes and Apoptotic bodies

Feature	MPs	Exosomes	Apoptotic bodies
Size	0.1-1 μm	0.03-0.01 μm	1-5 μm
Overlap in size	bacteria	viruses	platelets
Shape	Various shapes	Cup-shaped	Heterogeneous
Origin	Plasma membrane by #ectocytosis	Plasma membrane by exocytosis	Cellular
Structure	Phospholipid bilayer	Phospholipid bilayer	Cellular fragments
Sedimentation	18000-20000 g	100000-200000 g	16000 g
Release	Cellular activation and *early apoptosis	Constitutive and/or Cellular activation	Terminal apoptosis

budding from the cell plasma membrane surface

* Of note, apoptosis itself involves vesicle release

burst. In this study, they obtained the PMP from the 20000 g fraction by centrifugation of the stored platelet-free plasma. PMP was accumulated in the stored apheresis platelet concentrates as a vector of sCD40L that might interact with neutrophils and play an important role in developing TRALI (63).

In another study, it was shown that among antibody-independent factors (cytokines, PMPs, RMPs, LMPs), only RMPs released from RBC products are suggested as potential mediators of TRALI, although, this needs to be investigated further (64).

Effects MPs in adaptive immunity

In the immune system, direct membrane contact is indeed the leading way for two cells to communicate. Nevertheless, soluble mediators are also an essential link for this communication such as cytokines, chemokines, and hormones and so on. It was found that MPs derived from polymorphonuclear leukocytes, erythrocytes, platelets, and tumor cells have many effects on the innate immune system and on the induction of the adaptive immunity (65, 66). Although exact function of MPs in adaptive immunity is still unknown, they play a role in pathological conditions. For example, budding phenomenon from cell membrane is triggered or enhanced under specific physiological conditions such as injury, inflammation, or cancer (67). They also affect the immune system by changing the behavior of cells (68). For instance, it has demonstrated that following TLR activation platelets

produce IL1 β that is released through PMP production. Also, Platelets contribute to the inflammatory response to LPS through production of MPs that promote endothelial cell activation (69).

In 2007, Cognasse and colleagues showed that Platelets have an immuno regulatory role because they express CD40L (CD154), which is a central marker to B cells and adaptive immunity function. Indeed, they determined that platelets can activate peripheral blood B cells and increase production of antibodies. In this study, co-culturing of platelets with B cells lead to mutual activation of each (70).

However, there was the question of how platelets in the body can affect the immune system whereas mobility of them is limited to circulation. In 2008, Sprague and colleagues were probably given that platelets modulate inflammation and adaptive immunity at least in part by release membrane vesicles. In this study, it is shown that activated platelets release factors into the supernatant, resulting in production of IgG. Actually, platelet-derived membrane vesicles (PDMV) can be responsible immunity interactions so that they are sufficient to induce IgG production, enhance GC formation in vivo (71).

In a study, it was found that PMPs can cause activation B cells. PMPs were isolated from platelet concentrates obtained from the Tehran Blood Transfusion Center. In here, it was found that PMPs could affect B cell activation during in vitro co-culture. As with platelets, in a comparison between test (B cells/PMPs) and control (B cells) cells, it was observed that the expression of activation markers

CD27 and CD86 increased during the seven-day co-culture period whereas the expression of IgD antibody decreased (72).

In a recent study, it was determined that PMPs stimulate the production of antibodies by B-lymphocytes. During 5-day coculture significant increase was observed in the production of IgG antibodies in the test samples (B cells+MPs) compared to the control (B cells in the absence of PMPs). In fact, PMPs can induce IgG production from B cells during in vitro co-culture (73).

However, it should be noted that exosomes are involved in the immune system. For instance, data has indicated the exosomes of mast cell have mitogenic activity on B and T lymphocytes both in vitro and in vivo (74).

Conclusion

MPs are cell membrane derived vesicles which express markers of their parent cells. Briefly, it can be said that MPs induce balance between health and disease, although, exact function of MPs is unknown. Studies were shown that they have roles in the modulation of innate and adaptive immunity, especially of PMPs which express CD40L marker. Since MPs are found in blood products, they can also cause transfusion reactions including of TRALI and Thrombotic complications. Nevertheless, details associated with their duties in adaptive immunity system is unclear. Furthermore; numerous questions remain unanswered, for example:

- 1-What is the precise function of these two sub-groups of vesicles (i.e. MPs and exosomes)?
- 2-Do solid tissues also produce vesicles? If they produce, what are their functions?
- 3-Are all types of MPs and exosomes play a role in adaptive immunity system?
- 4-In absence of these vesicles especially MPs, how is the function of the adaptive immune system?

However, according to the MPs demonstrated effects on the immune system and various diseases, they should be considered more important. A few studies have been done on the impact PMPs on the acquired immunity and still more studies need to be done in vitro and in vivo, especially in the clinical trial.

Conflict of Interests

Authors declare any conflict of interest.

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