Transfusion and Apheresis Science 52 (2015) 12–18

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Platelet microparticle: A sensitive physiological "fine tuning" balancing factor in health and disease

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ARTICLE INFO

Keywords:
Platelets
Microparticles
PMP

ABSTRACT

Platelet microparticles (PMPs) have long been regarded as inert "platelet dusts". They have now taken a center stage on the clinical research scene of transfusion medicine, being actually seen as long-stretch hands of platelets that exert a physiological role beyond the initial site of activation. These 0.05 μm to 0.8 μm microvesicles, delimited by a phospholipidic bilayer, are released by platelet membranes following activation by agonists, complement activation, or high shear forces. They can also be generated as a result of platelets and megakaryocyte senescence or cytoskeletal abnormalities. PMPs may orchestrate a delicate hemostatic balance in health, and act as procoagulant vectors in diseases triggering thrombosis. Furthermore, through their potential cargo of growth factors, microRNA and various bioactive molecules, they may promote healing in health, but, on the other side of the coin, can act as pro-inflammatory carriers and may contribute to cancer growth as an actor of the platelet-cancer loop. Through their cellular interactions they also interplay with the immune system. Their capacity to be generated by shear forces and contact with surfaces during the processing of blood and blood components, which may trigger transfusion reactions, make them also an integral part of transfusion medicine. Given their documented association with pathological conditions, PMP may serve as biomarkers for disease status or as a possible new target for anti-platelet drugs to treat cancer or inflammation.

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http://dx.doi.org/10.1016/j.transci.2014.12.015
1473-0502/

1. Introduction

Following transfusion of blood from lamb to human by the French physician Jean Denis in 1667, it is only in the early 19th century that the British obstetrician Dr. James Blundell initiated the first attempts to transfuse blood from human to human. In 1818, he performed the first successful transfusion of human blood to treat and stop post-partum bleeding [1]. The existence of platelets within the blood and their possible contribution to hemostasis was described in the 1870s, but it was not until 1910 that transfused platelets were shown to reverse the risk of bleeding in thrombocytopenic patients [2]. Platelets are quantitatively and qualitatively important blood cells that play a central role in hemostasis. They are also critically involved in physiological processes such as vascular biology, angiogenesis and tissue regeneration. Furthermore, they play important immune modulator functions [3,4]. Platelets are sensitive health markers that are prone to activation under physiological conditions involving stimulation of blood coagulation, as occurs as a result of trauma or pathologies like cancer. Therefore, platelets perform wider roles in balancing health and disease [3]. Nearly a century was needed after their discovery to show that one response of activated platelets to certain stimuli is the shedding of microparticles [PMPs] [5], described in the 1960s as "platelet dust" [6]. PMPs were initially thought to play solely a role in the normal hemostatic responses to vascular injury because they demonstrate a prothrombinase activity [7] that results from the expression of coagulant active aminophospholipids and receptors for coagulation and equally anticoagulant factors on their surface. The latter, in the microcirculation where high concentration of endothelial thrombomoduline exists, can balance a physiological action against clot formation.

PMPs can circulate in blood at a concentration of 100–1000/μl [8], with a size probably ranging from 0.05–0.10 μm to 0.8 μm [3]. Whether PMPs arise from complete conversion of a few platelets or from partial conversion of many or most platelets is unclear, but either scenario may occur [5]. Not only platelets, but also megakaryocytes, generate CD41/CD61-positive microparticles which differ from the PMPs in that they do not express the markers of granule fusion (CD62 or LAMP-1) or cytoskeletal degradation (degraded filamin A) [9]. PMPs carry several antigens characteristic of intact platelets, mainly glycoproteins (GP) IIb/IIIa (αIIbβ3) and GPIb/IX [5], and express surface receptors for both factor VIII [10] and activated factor V (factor Va), which combines with factor Xa to form the prothrombinase complex [11]. High- and low-affinity binding sites for factor IXa are also present on their surface [12]. Outreaching in the circulation, PMPs can therefore exert procoagulant effects distant from the site of platelet activation and for a longer period than that observed for activated platelets [5]. Furthermore, it is now also widely accepted that PMPs, as well as other cell-derived microparticles, mediate intercellular transfer of bioactive molecules such as lipids, surface receptors, growth factors, enzymes and could even play a role in the transmission of infectious agents, like prions [13–17]. This also explains the interest in studying the impacts of blood collection processes on the generation of PMPs [17–20]. There is also some laboratory evidence that ternary/quaternary complexes of tenase/prothrombinase may be circulating in plasma of individuals and some patients populations with hypercoagulable states. This can be measured quantitatively with chromogenic substrates sensitive to kallikrein, factor Xa, thrombin, and non-specific proteases.

2. PMPs genesis

Platelet membranes are characterized by the presence of anionic phospholipids, such as phosphatidylserine and phosphatidylethanolamine, concentrated in the inner leaflet of the plasma membrane; neutral phospholipids such as phosphatidylcholine and sphingomyelin are, on the other hand, enriched on the external leaflet. Plasma membrane asymmetry is maintained by phospholipid transporters (aminophospholipid translocases) [10]. Changes in phospholipid transporter activity that occur with platelet activation result in loss of phospholipid asymmetry with subsequent vesiculation and PMPs generation. Few mechanisms are known to promote the shedding of PMPs [21], as discussed below and summarized in Figure 1.

2.1. PMPs formation following platelet stimulation by agonists

PMPs shedding occurs after physiological activation of platelets by agonists like thrombin or collagen [7,16,22,23]. Their generation rate is not solely dependent on the type or concentration of the agonist and therefore is not a simple all-or-none phenomenon [24]. With agonist activation, phosphatidylserine expression is followed by the shedding of the membrane fragments PMPs endowed with procoagulant properties, more particularly in the hypothesis they would harbor tissue factor, the major initiator of blood coagulation reactions [25], a possibility that is still debated [26,27]. As the P2Y1 and the P2Y12 receptors are important regulators of blood clotting, differentially contributing to different platelet functions, the relative contribution of the P2Y1 and P2Y12 receptors to microparticle formation from platelets was studied [28]. Antagonist to the P2Y12 receptor, but not to the P2Y1 receptor antagonist, caused a significant decrease in the number of microparticles formed by convulxin, a snake venom toxin, and thrombin [28].