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Mini-Review

Significance of tissue factor-bearing microparticles in cancer-related coagulopathy

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ABSTRACT

Cancer patients are at increased risk of coagulopathy such as deep vein thrombosis and pulmonary embolism. Tumor-derived tissue factor (TF)-bearing microparticles (MPs) are associated with venous thromboembolic events in malignancy. MPs are small membrane vesicles that are released from many different cell types by exocytic budding of the plasma membrane in response to cellular activation or apoptosis. MPs may also be involved in clinical diseases because they express phospholipids, which function as procoagulants. A current feature of clinical applications regarding MPs is detection of TF-expressing MPs in cancer patients. In lung cancer patients, MPs induce metastasis and angiogenesis, and MPs may be a sign of vascular complications. In patients with various types of cancer, MPs possess CXCR4 and contribute to chemotaxis by stromal cell-derived factor 1, resulting in progression or metastasis of cancer. TF overexpression by cancer cells is closely associated with tumor progression, and TF-expressing MPs that are shed by cancer cells are linked to the genetic status of cancer.

KEYWORDS: tissue factor, microparticle, cancer, thrombosis, coagulopathy

INTRODUCTION

The coagulation system is often activated in cancer patients, which increases the risk of venous thromboembolism (VTE) formation [1, 2]. Such VTE in cancer patients is called “Trousseau’s syndrome” [3]. The highest frequency of VTE has been found in pancreatic cancer [1, 2, 4, 5]. Various predictive biomarkers have been examined for VTE in cancer progression. For example, analysis of blood cells is effective to predict the risk of VTE [6]. In addition, D-dimer, prothrombin fragment 1+2, and soluble P-selectin are predictive biomarkers for VTE [7], while the most recent biomarker is microparticles (MPs).

MPs are small membrane vesicles that are released from many cell types by exocytic budding of the plasma membrane in response to cellular activation or apoptosis [8-10]. MPs disseminate various bioactive effectors originating from the parent cells. Therefore, MPs can alter vascular functions and may induce biological responses involved in vascular homeostasis [11]. Although most MPs in human blood originate from platelets, MPs are also released from leukocytes, erythrocytes, endothelial cells, smooth muscle cells, and cancer cells [12-17]. MPs have been documented in almost all thrombotic diseases occurring in venous and arterial beds [18-21]. Tissue factor (TF)-MPs are related to cancer and are elevated in patients with certain cancers such as pancreatic and breast cancer [17, 22].

In this review, we address the function of MPs and some of the clinical findings in cancer patients, which suggest important roles for TF-MPs.

Definition of MPs

MPs can range in size from 0.1 to 1.0 μm [1, 2]. The membrane composition of MPs reflects the

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membranous elements of the cell of origin [1, 2]. MPs contain functional cytoadhesions, bioactive phospholipids, cytoplasmic components, and various antigens that are characteristic of the state of the originating cell and the type of stimulus [23, 24]. Some studies have analyzed the proteome of MPs and identified hundreds of proteins [25, 26]. Such proteins may be useful biomarkers for various disease processes [26].

MPs are constitutively released from the surface of cells and their formation can be upregulated by cellular activation and apoptosis [27, 28]. Plasma membranes contain various types of phospholipids. Although uncharged phospholipids are mainly present in the outer leaflet of the membrane bilayer, the inner leaflet contains negatively charged aminophospholipids such as phosphatidylserine (PS). During activation or apoptosis of cells, the normal lipid bilayer undergoes an alteration by "flipping" internal PS to the external surface. As a result, PS-exposing MPs may be released from cells [29].

MP functions

MPs were initially thought to be related to disease because they contain phospholipids that are procoagulants. These MPs support the generation of thrombin and may be involved in diffuse intravascular coagulation in disease states. However, such a coagulation system is activated not only in disease states, but also in healthy individuals. Berckmans *et al*. [30] reported that MPs circulate in healthy humans and support low-grade thrombin generation. Sinauridze *et al*. [31] reported that platelet-derived MPs (PDMPs) have a 50-100-fold higher specific procoagulant activity than activated platelets. Exposure of PS not only facilitates the formation of coagulation complexes, but also promotes the ability of TF to initiate coagulation [32].

MPs support coagulation by factor VII/TF-dependent and -independent pathways [33]. During vascular damage, blood contacts extravascular TF, resulting in activation of extrinsic coagulation and the formation of fibrin. Indeed, TF can become active upon adhesion and fusion of MPs with activated platelets. While TF is exposed by endothelial cell-derived MPs (EDMPs), TF activity is markedly inhibited by MP-associated TF pathway inhibitor (TFPI). In storage-induced PDMPs, 10% of which contain TF, TF-dependent thrombin generation is only observed in plasma with neutralization by TFPI [34]. A balance between TF and TFPI at the MP surface is likely to be crucial for the initiation of blood coagulation, and higher levels of MPs containing TF may overcome the TFPI anticoagulant pathway [35].

Identification of MPs in a clinical setting

An identification method for MPs is important for clinical studies. Appropriate sampling conditions, processing, and sample storage are essential [8]. MPs can be directly quantified in platelet-poor plasma obtained by serial centrifugation of citrated whole blood. Alternatively, washed MPs can be isolated from platelet-poor plasma by ultracentrifugation before re-suspension and analysis.

The most widely used method for studying MPs is flow cytometry because of its simplicity and the wealth of information that can be obtained from the population of interest [36]. Platelet-poor plasma or MP suspensions are labeled with fluorescently conjugated monoclonal antibodies. The major advantage of flow cytometry is double staining of MPs to determine the origin/cellular source of the MPs. Annexin V binding is used to confirm the phospholipid properties of MPs, although most endothelial MPs do not contain this antigen. Antibodies against specific surface antigens expressed on the cells of origin are used to identify the MP subtype. Flow cytometry also allows the criterion of size to be applied to MP analysis by assessment of the forward light scatter of MPs. Identification of events of a specific size is most accurately performed using calibration beads of a known diameter for comparison [8, 37]. Additionally, a variety of cell-specific antibodies have been applied to MP analyses, and their specificity is likely to influence the results.

Several studies have applied flow cytometry to detect TF-MPs in cancer patients [38-40]. A recent report showed that the level of TF-MPs measured by functional TF activity in a MP assay correlated with the development of VTE in cancer patients, whereas no correlation was found using flow cytometry to measure TF-MPs [41]. Therefore, further investigations should consider TF-MP analysis by flow cytometry.

Cancer- and blood cell-derived MPs

Cancer patients exhibit high levels of circulating procoagulant MPs, which correlate with the risk of thrombosis [22, 39, 42-46]. These procoagulant MPs may originate from various cell types, and be produced by fusion between MPs of different origins [22, 46]. High frequency MPs in cancer patients are PDMPs, monocyte-derived MPs (MDMPs), and EDMPs (Figure 1) [47-49]. In lung cancer patients, PDMPs induce metastasis and angiogenesis [47]. PDMPs can also mediate the progression of breast cancer by enhancement of the invasive potential in cancer cells [48]. In addition, PDMPs contribute to chemotaxis by stromal cell-derived factor 1, resulting in progression or metastasis of cancer [49]. These results suggest that PDMPs can be used as a biomarker of cancer. Indeed, the concentration of circulating PDMPs differs according to the cancer stage [50]. Kanazawa *et al.* [51] reported that the numbers of PDMPs and MDMPs in patients with non-small cell lung cancer are significantly higher than those in patients with small cell lung cancer. They concluded that elevated MDMPs are a sign of vascular complication in lung cancer patients, particularly those with non-small lung cancer. On the other hand, EDMPs also play an important role in patients with various types of cancer. A pilot study concerning hepatocellular carcinoma (HCC) showed that the levels of EDMPs in liver transplant patients are altered after surgery and correlated with the clinical outcome [52]. Recently, some reports have suggested that circulating levels of EDMPs are significantly associated with 1-year mortality in patients with end-stage non-small cell lung cancer [53, 54]. Furthermore, Reynes *et al.* [55] reported that EDMPs have a prognostic value in patients with glioblastoma. The exact production mechanism of these blood cell-derived MPs in cancer patients is unknown. However, these MPs may participate in the generation of TF-MPs.

Tumor-derived MPs

There is an increasing appreciation for the notion that cancer cells themselves may be a source of procoagulant MPs [56-58]. It is highly possible that cancer-derived TF-MPs are a trigger for thrombogenesis in cancer [38, 39, 59-61]. The levels of TF-MPs in cancer patients correlate with activation of coagulation as determined by D-dimer levels [39]. In addition, Tesselaar *et al.* [22] reported a link between TF-MPs and VTE in cancer patients. Furthermore, previous studies have reported

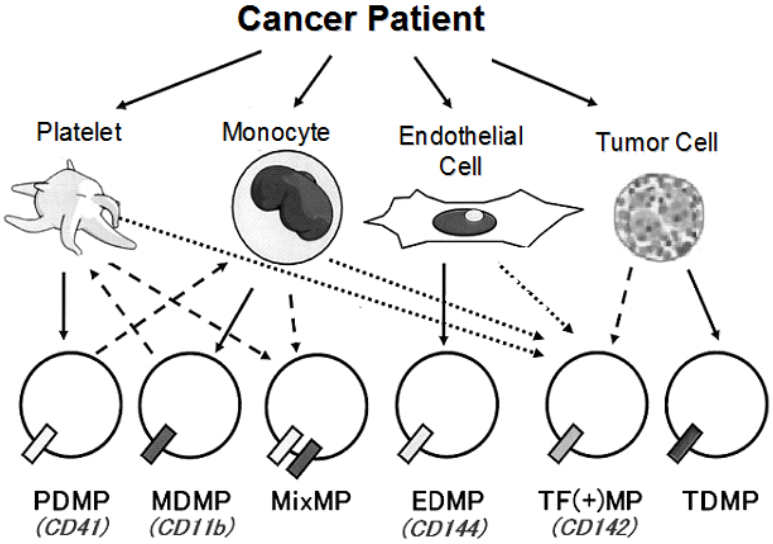

Figure 1. Origin of MPs in cancer patients. Production of PDMPs, MDMPs, EDMPs and TDMPs can be increased in cancer patients. These MPs contribute to the generation of TF-MPs in cancer patients. PDMP: platelet-derived microparticle; MDMP: monocyte-derived microparticle; EDMP: endothelial cell-derived microparticle; TDMP: tumor-derived microparticle.

a correlation between the levels of TF in pancreatic and brain tumors and VTE [62, 63]. In particular, cancer-derived TF-MPs might represent a biomarker for poorly differentiated and invasive pancreatic cancer phenotypes as well as poor survival [64]. Therefore, the thrombogenesis in pancreatic cancer, which has one of the highest mortality rates, is a major problem. Wang *et al.* [65] reported interesting experimental results concerning the VTE of pancreatic cancer. They analyzed the expression of TF in four pancreatic cancer-derived cell lines to clarify the mechanism of VTE formation with cancer invasion *in vivo*. As a result, they found an increase in the expression of TF in two of the four cell lines, and TF-MPs were detected in the culture medium. Moreover, most TF in the culture medium was the TF-combined form. Based on these results, activation of the coagulatory system through elevation of the thrombin-antithrombin III complex (TAT) suggested a dependence on TF-MPs. It is unknown how TF in tumors activates the coagulating system or participates in thrombogenesis. Wang *et al.* [65] indicated that it is unclear whether TF on the tumor surface and/or soluble TF are directly involved in thrombogenesis. In contrast, cancer-derived TF-MPs appear to participate in triggering thrombogenesis directly, and play an important role in the abnormality of the coagulation system in cancer. Consequently, TF-MP is a very important marker in the consideration of prevention or therapy of VTE complication in cancer [22, 64, 66-69].

Chemotherapy is known to be associated with an increase in thrombosis [1, 70]. Cytotoxic chemotherapy agents enhance cellular TF activity and PS exposure, resulting in the release of TF-MPs [71]. An increase in PS expression or the release of PS- or TF-positive MPs has been observed in endothelial and leukemic cells during chemotherapy [72, 73]. In pancreatic cancer patients, elevated circulating TF antigen levels were found in those receiving gemcitabine chemotherapy [74], while a detectable rise in plasma TF measured by TF expression levels or MP-associated PCA during chemotherapy was deemed predictive of subsequent VTE events [45]. However, other mechanisms in addition to the increase in the levels of circulating TF-MPs may be involved in thrombosis during chemotherapy, such as the release of nucleic acids and increase in cellular PS exposure [46, 61, 66].

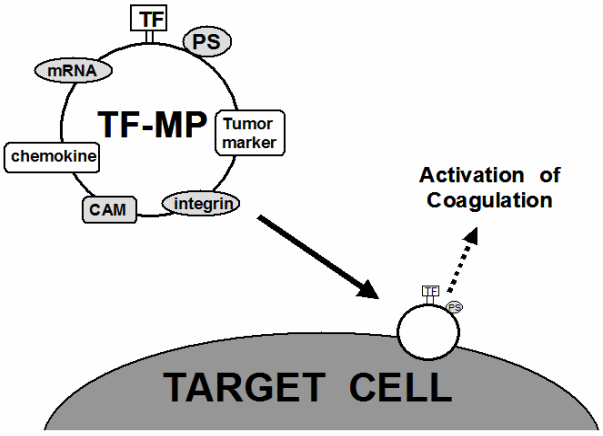

Figure 2. Role of TF-MPs in activation of target cells and organs. TF-MPs can carry some substances, such as integrin, cell adhesion molecule, chemokines, phospholipids, and TF. TF mainly contributes to activation of the extrinsic coagulation system. TF: tissue factor; PS: phosphatidylserine; mRNA: messenger RNA; CAM: cell adhesion molecule.

CONCLUSION

We have summarized the literature to date that is relevant to TF-MPs, including a growing list of cancer types that are associated with elevated MP levels. MPs were initially thought to be small particles with a procoagulant activity, emanating from various cell types. MPs of different origins including cancer cells may contribute to the generation of TF-MPs in cancer patients, resulting in cancer-related coagulopathy (Figure 2). However, the functional role of TF-MPs in cancer patients still needs to be understood in more detail.

CONFLICT OF INTEREST STATEMENT

The author declares no competing financial interests.

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