Microparticles as Biomarkers of Blood Coagulation in Cancer

Shosaku Nomura, Maiko Niki, Tohru Nisizawa, Takeshi Tamaki and Michiomi Shimizu

First Department of Internal Medicine, Kansai Medical University, Hirakata, Osaka, Japan.

ABSTRACT: Cancer is associated with hypercoagulopathy and increased risk of thrombosis. This negatively influences patient morbidity and mortality. Cancer is also frequently complicated by the development of venous thromboembolism (VTE). Tumor-derived tissue factor (TF)-bearing microparticles (MPs) are associated with VTE events in malignancy. MPs are small membrane vesicles 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 through expression of procoagulative phospholipids. The detection of TF-expressing MPs in cancer patients may be clinically useful. In lung and breast cancer patients, MPs induce metastasis and angiogenesis and may be indicators of vascular complications. Additionally, MPs in patients with various types of cancer possess adhesion proteins and bind target cells to promoting cancer progression or metastasis. Overexpression of TF by cancer cells is closely associated with tumor progression, and shedding of TF-expressing MPs by cancer cells correlates with the genetic status of cancer. Consequently, TF-expressing MPs represent important markers to consider in the prevention of and therapy for VTE complications in cancer patients.

KEYWORDS: VTE, microparticle, tissue factor, cancer, hypercoagulopathy

Microparticles and Cancer

Many individuals with cancer are also in a hypercoagulable state, and the elevated risk of thrombosis conferred by hypercoagulativity increases patient morbidity and mortality.1,2 Cancer patients frequently develop venous thromboembolism (VTE).3–8 Various potential predictive biomarkers have been examined for association with VTE in cancer progression. For example, analysis of blood cells can effectively predict the risk of VTE development.9 Additionally, measurement of D-dimer, prothrombin fragment 1 + 2, and soluble P-selectin levels can accurately predict VTE risk.10 Recently, microparticle (MP) level has emerged as an accurate marker of VTE risk.11–13

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.14–16 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.17 Although most MPs in human blood originate from platelets, MPs are also released from leukocytes, erythrocytes, endothelial cells, smooth muscle cells, and cancer cells (Fig. 1).18–23 MPs have been documented in almost all thrombotic diseases occurring in venous and arterial beds.24–27 Tissue factor (TF)-MPs are related to cancer and exhibit increases in patients with certain cancers such as pancreatic cancer and breast cancer.23

Definition of MPs

MPs can range in size from 0.1 to 1.0 μm.14–16 The membrane composition of MPs reflects the membranous elements of the cell of origin.14–16 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.28,29 Some studies have analyzed the proteome of MPs and identified hundreds of proteins.30,31 Such proteins may be useful biomarkers for various disease processes.32

MPs are constitutively released from the surface of cells, and their formation can be upregulated by cellular activation and apoptosis.32,33 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.34

MP Functions

MPs possess multiple functions relevant in various clinical settings (Table 1). MPs were initially identified as associated with thrombotic disease because they contain procoagulant phospholipids. These MPs promote thrombin generation and may be involved in diffuse intravascular coagulation in disease.
states. However, MPs are detectable not only in disease states but also in healthy individuals. Berckmans et al\(^1\) identified circulating MPs in healthy human beings, with these MPs supporting low-grade thrombin generation. Sinauridze et al\(^4\) reported that platelet-derived MPs (PDMPs) have a 50–100-fold higher specific procoagulant activity (PCA) than activated platelets. Exposure of PS facilitates both the formation of coagulation complexes and promotes TF-induced coagulation.\(^3\)

MPs support coagulation by factor VII/TF-dependent and -independent pathways.\(^3\) During vascular damage, blood contacts extravascular TF, resulting in the 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.\(^3\)

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.\(^3\)

**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.\(^4\) 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 resuspension and analysis.

The most widely used method for studying MPs is flow cytometry because of its simplicity and the wealth of

---

**Table 1. Function of microparticles (MPs).** MPs possess multiple functions relevant in various clinical settings.

| FUNCTION                        | FACTOR                           |
|---------------------------------|----------------------------------|
| Hemostasis (procoagulant activity) | PS, TF                           |
| Inflammation                    | RANTES                           |
| Cellular interaction            | CD24, CD43, integrin             |
| Angiogenesis                    | VEGF                             |
| Vascular and tissue repair      | PDGF, EGF                        |
| Thrombosis stability            | CD40L, PSLG-1                    |
| Host defence (DC activation)    | CX3CL1/CR1                       |
| Cancer metastasis (MMP activation) | TGF \(\beta_1\)                  |
| Multidrug resistance            | P-glycoprotein                    |
| Virus infection                 | mRNA, miRNA                      |
| Cell differentiation            | SDF-1                            |

**Abbreviations:** RANTES, regulated on activation, normal T-cell expressed and secreted; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; PSLG-1, P-selectin glycoprotein ligand-1; DC, dendritic cell; SDF-1, stromal cell-derived factor-1.
information that can be obtained from the population of interest. 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. 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-expressing MPs (TF-MPs) in cancer patients. A recent report showed that the level of TF-MPs measured by functional TF activity in an MP assay correlated with the development of VTE in cancer patients, whereas no correlation was found using flow cytometry to measure TF-MPs. Therefore, further investigations should consider TF-MP analysis by flow cytometry.

Various MPs and Blood Cell-derived MPs in Cancer Patients
Cancer patients possess high levels of circulating procoagulant MPs and an increased risk of thrombosis (Table 1). These procoagulant MPs may originate from various cell types and can be produced by fusion between MPs of different origins. MPs frequently detected in cancer patients include PDMPs, monocyte-derived MPs (MDMPs), and EDMPs (Fig. 1). PDMPs promote metastasis and angiogenesis in lung cancer patients and accelerate breast cancer progression by enhancing the invasive potential of cancer cells. Collectively, these results suggest that PDMPs may be a useful biomarker of cancer. Consistently, the concentration of circulating PDMPs differs by cancer stage. Kanazawa et al. reported that the number of PDMPs and MDMPs in patients with non-small cell lung cancer is 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 cell lung cancer. On the other hand, EDMPs also play an important role in various types of cancer. A pilot study concerning hepatocellular carcinoma showed that the levels of EDMPs in liver transplant patients are altered after surgery and correlated with the clinical outcome. Recently, some reports have suggested that circulating levels of EDMPs are significantly associated with one-year mortality in patients with end-stage non-small cell lung cancer. Furthermore, Reynés et al. 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.

MPs and Multidrug Resistance in Cancer Patients
Multidrug resistance (MDR) is a major obstacle to chemotherapeutic treatment in many cancer patients. Although several mechanisms of MDR acquisition have been identified, the most commonly identified MDR mechanism is overexpression of P-glycoprotein (P-gp). P-gp is present in cancers and its overexpression is negatively associated with response to chemotherapy. MPs can transfer MDR between cancer cells by transporting P-gp protein and mRNA in cancer cell-derived MPs (Table 1). Additionally, inhibitor of apoptosis protein—a negative regulator of cell death—has recently been found to be transported by cancer cell-derived MPs.

Tumor-derived MPs
There is an increasing appreciation for the notion that cancer cells themselves may be a source of procoagulant MPs. It is highly possible that cancer-derived TF-MPs are a trigger for thrombogenesis in cancer. The levels of TF-MPs in cancer patients correlate with the activation of coagulation as determined by D-dimer levels. In addition, Tesselaar et al. reported a link between TF-MPs and VTE in cancer patients. Furthermore, previous studies have reported a correlation between the levels of TF in pancreatic and brain tumors and VTE. In particular, cancer-derived TF-MPs might represent a biomarker for poorly differentiated and invasive pancreatic cancer phenotypes as well as poor survival. Therefore, the thrombogenesis in pancreatic cancer, which has one of the highest mortality rates, is a major problem. Wang et al. 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 coagulatory system or participates in thrombogenesis. Wang et al. 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.

Chemotherapy is known to be associated with an increase in thrombosis. Cytotoxic chemotherapy agents enhance
cellular TF activity and PS exposure, resulting in the release of TF-MPs. An increase in PS expression or the release of PS- or TF-positive MPs has been observed in endothelial and leukemic cells during chemotherapy. In pancreatic cancer patients, elevated circulating TF antigen levels were found in those receiving gemcitabine chemotherapy, 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. 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.

**Conclusion**

We have summarized the literature to date regarding TF-MPs, highlighting the growing list of cancer types that are associated with elevated MP levels. MPs were initially identified as small particles originating from multiple cell types and possessing PCA. MPs of multiple origins—including cancer cells—may contribute to the increased levels of TF-MPs found in cancer patients, ultimately resulting in cancer-associated coagulopathy (Fig. 2). The PCA of TF-MPs is mediated by expression of TF and the exposure of PS on the MP surface. Adhesion proteins, including CD24 and CD43, have been proposed to be involved in the binding of TF-MPs to target cells. The utilization of circulating MPs as cancer biomarkers may provide effective and noninvasive methods of cancer diagnosis, prognosis assessment, and disease surveillance to tailor and personalize therapies. However, the functional role played by TF-MPs in cancer patients needs to be understood in greater detail.

**Abbreviations**

VTE, venous thromboembolism; MP, microparticle; TF, tissue factor; PS, phosphatidylserine; mRNA, messenger RNA; CAM, cell adhesion molecule.

**Author Contributions**

Conceived and designed the experiments: SN. Analyzed the data: SN and MS. Wrote the first draft of the manuscript: SN and MN. Contributed to the writing of the manuscript: TN and TT. Agreed with manuscript results and conclusion: SN. All the authors reviewed and approved the final manuscript.

**REFERENCES**

1. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27:4839–4847.
2. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer*. 2013;119:648–655.
3. Blom JW, Vanderschueren JP, Oostindier MJ, Ousanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost*. 2006;4:529–535.
29. Abid Hussein MN, Meesters EW, Osmanovic N, Romijn FP, Nieuwland R, Menapace LA, Peteraon DR, Burnier L, Fontana P, Krivit WR, Angelillo-Scherrer A. Elevation of endothelial microparticle-associated tissue factor activity in cancer patients with venous thromboembolism. J Thromb Haemost. 2009;110:1723–1729.

30. Mackman N. New insights into the mechanisms of venous thrombosis. J Clin Invest. 2012;122:2331–2336.

31. Simanek R, Vormittag R, Ay C, et al. High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). J Thromb Haemost. 2009;8:114–120.

32. Feroni P, Martin F, Porteraen I, et al. Novel high-sensitive D-dimer determination predicts chemotherapy-associated venous thromboembolism in intermitting risk lung cancer patients. Clin Lung Cancer. 2012;13:482–487.

33. Manly DB, Wang J, Glover SL, et al. Increased microparticle tissue factor activity in cancer patients with venous thromboembolism. Thromb Res. 2010;125:511–512.

34. Geddings JF, Mackman N. Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. Blood. 2013;121:1873–1880.

35. Thaler J, Koder S, Koreczek K, Pabinger I, Ay C. Microparticle-associated tissue factor activity in patients with metastatic pancreatic cancer and its effect on fibrin clot formation. Thromb Res. 2014;163:145–150.

36. Nomura S, Ozaki Y, Ikeda Y. Function and role of microparticles in various clinical settings. Thromb Res. 2008;133:8–23.

37. Blumer L, Fassnacht P, Krivit RR, Angelillo-Scherrer A. Cell-derived microparticles in haemostasis and vascular medicine. Thromb Haemost. 2009;101:439–451.

38. Nomura S, Shimizu M. Clinical significance of procoagulant micro-particles. J Intensive Care. 2015;3:2–11.

39. Moritz O, Tost F, Hugel B, et al. Procoagulant microparticles: disrupting the vascular homeostasis equation? Arterioscler Thromb Vasc Biol. 2006;26:2594–2604.

40. Mies M, Altermann DC. Endothelial cell activation by leukocyte microparticles. J Immunol. 1999;168:4382–4387.

41. Hugel B, Socie C, Vu T, et al. Elevated levels of circulating procoagulant microparticles in patients with paroxysmal nocturnal hemoglobinuria and aplastic anemia. Blood. 1999;93:3451–3456.

42. Combes V, Simon AC, Grau GE, et al. In vitro generation of endothelial microparticles and possible prothrombotic activity in patients with lupus anticoagulant. J Clin Invest. 1999;104:93–102.

43. Sabatier F, Roux V, Anfosso F, Camoin L, Sampol J, Dignat-George F. Interaction of endothelial microvesicles with monocytic cells in vitro induces tissue factor-dependent procoagulant activity. Blood. 2002;99:3962–3970.

44. Angelillo-Scherrer A. Leukocyte-derived microparticles in vascular homeostasis. Cir Res. 2012;110:68–74.

45. Zouides HH, Leeper HA, Neuberg D, et al. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. Clin Cancer Res. 2009;15:6830–6840.

46. Matsumoto N, Nomura S, Kamihata H, Kimura Y, Iwasaka T. Increased level of tissue factor-dependent microparticles in acute coronary syndrome. Thromb Haemost. 2004;91:146–154.

47. Crittinons JD, Heresi GA, Velasquez H, et al. Involvement of platelet-derived microparticles in patients with paroxysmal nocturnal hemoglobinuria and aplastic anemia. J Thromb Haemost. 2012;10:1147–1155.

48. Korn G, Balk H, Heuser I, et al. Tissue factor expression in circulating microparticles in cancer patients with and without venous thromboembolism. Thromb Res. 2011;127:473–477.

49. van Doornmaal F, Kleinjan A, Berckmans RJ, et al. Coagulation activation and microparticle-associated coagulant activity in cancer patients. An exploratory prospective study. Thromb Res. 2012;108:160–165.

50. Korn G, Balk H, Heuser I, et al. Enhanced effect of platelet-derived microvesicles on the invasive potential of breast cancer cells. Arterioscler Thromb Vasc Biol. 2009;29:158–165.

51. Abarona K, Mottore B, Procopatricles, thrombosis and cancer. Best Pract Res Clin Haematol. 2009;22:61–69.

52. Tilley RE, Holcher T, Belani R, Nieuwland R. Tissue factor activity is increased in a combined platelet and microparticle sample from cancer patients. Thromb Res. 2008;122:628–633.

53. Zwickler J. Predictive value of tissue factor bearing microparticles in cancer associated thrombosis. Thromb Res. 2010;125(suppl 2):S89–S91.

54. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. J Thromb Haemost. 2008;6:1983–1985.

55. Rak J. Microparticles in cancer. Semin Thromb Hemost. 2010;36:888–906.

56. Janowska-Wieczorek A, Marquez-Curris LA, Wysoczynski M, Ratnacaz MZ. Enhancing effect of platelet-derived microparticles on the invasive potential of breast cancer cells. Transfus. 2006;46:1199–1202.

57. Kalinkovich EV, Avarad A, et al. Functional CXCR4-expressing microparticles and SDF-1 correlate with circulating acute myelogenous leukemia cells. Cancer Res. 2006;66:11031–11020.

58. Medsuzar S, Mege D, Barboza R, et al. Involvement of platelet-derived microparticles in tumor progression and thrombosis. Semin Oncol. 2014;41:346–358.

59. Kanazawa S, Nomura S, Kawanuma M, Muramatsu Y, Yamaguchi K, Fukuhara S. Monocyte-derived microparticles may be a sign of vascular complication in cancer patients with lung cancer. J Gastrointestin Liver Dis. 2013;22:145–149.

60. Brodsky SV, Facchito ME, Heydt D, et al. Dynamics of circulating microparticles in liver transplant patients. J Gastrointestin Liver Dis. 2008;17:261–268.

61. Sang HC, Wang CC, Chang HC, et al. Levels of circulating microparticles are increased in lung cancer patients with possible metastatic activity. Dis Markers. 2013;33:301–310.

62. Wang CC, Sang HC, Hsiao CC, et al. Circulating endothelial-derived activated microparticles: a useful biomarker for predicting one-year mortality in patients with advanced non-small cell lung cancer. Biomed Res Int. 2014;2014:734701.

63. Reymer G, Vila F, Fleitas T, et al. Circulating endothelial cells and procoagulant microparticles in patients with glioblastoma: prognostic value. PLoS One. 2013;8:e60934.
62. Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med. 2002;53:615–627.
63. Ambudkar SV, Sauna ZE, Gottesman MM, Szakacs G. A novel way to spread drug resistance in tumor cells: functional intercellular transfer of P-glycoprotein ABCB1. Trends Pharmacol Sci. 2005;26:471–478.
64. Gillet JP, Efferté T, Remacle T. Chemotherapy-induced resistance by ATP-binding cassette transporter genes. Biochim Biophys Acta. 2007;1775:237–262.
65. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer. 2002;2:48–58.
66. Behrwy M, Combes V, Lee E, et al. Membrane microparticles mediate transfer of P-glycoprotein to drug sensitive cancer cells. Leukemia. 2009;23:1643–1649.
67. Jaiwal R, Gong J, Sambasivam S, et al. Microparticle-associated nucleic acids mediate trait dominance in cancer. PLoS ONE. 2013;8:e61515.
68. Fulda S, Vucic D. Targeting IAP proteins for therapeutic intervention in cancer. Nat Rev Drug Discov. 2012;11:109–124.
69. de Souza PS, Cruz ALS, Viola JPB, Maia RC. Microparticles induce multifactorial resistance through oncogenic pathways independently of cancer cell type. Cancer Sci. 2015;106:60–68.
70. Yu JL, Rak JW. Shedding of tissue factor (TF)-containing microparticles rather than alternatively spliced TF is the main source of TF activity released from human cancer cells. J Thromb Haemost. 2004;2:2065–2067.
71. Davila M, Amirkhosravi A, Coll E, et al. Tissue factor-bearing microparticles derived from tumor cells: impact on coagulation activation. J Thromb Haemost. 2008;6:1517–1524.
72. Thomas GM, Panicot-Dubois L, Lacroit R, Dignat-George F, Lombardo D, Dubois C. Cancer cell-derived microparticles bearing P-selectin glycoprotein ligand 1 accelerate thrombus formation in vivo. J Exp Med. 2009;206:1913–1927.
73. DelConde I, Bharwani LD, Dietzen DJ, Pendurthi U, Thagarajan P, López JA. Microvesicle-associated tissue factor activity and Trousseau’s syndrome. J Thromb Haemost. 2007;5:70–74.
74. Sartori MT, Della Puppa A, Ballin A, et al. Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: a potential prothrombotic role. Thromb Haemost. 2013;110:378–385.
75. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res. 2007;13:2870–2875.
76. Khorana AA, Ahrendt SA, Ryan CK, et al. Intratumoral tissue factor expression and risk of venous thromboembolism in brain tumor patients. Thromb Res. 2013;131:162–165.
77. Thaler J, Preusser M, Ay C, et al. Intratumoral tissue factor expression and risk of venous thromboembolism in brain tumor patients. Thromb Res. 2013;131:162–165.
78. Wang JG, Geddings JE, Alemán MM, et al. Tumor-derived tissue factor activates coagulation and enhances thrombosis in a mouse xenograft model of human pancreatic cancer. Blood. 2012;119:5543–5552.
79. Date K, Hall J, Greenman J, Maraveyas A, Madden LA. Tumour and microparticle tissue factor expression and cancer thrombosis. Thromb Res. 2013;131:109–115.
80. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. Thromb Res. 2013;128:180–184.
81. Davila M, Robles-Carrillo L, Urruh D, et al. Microparticle association and heterogeneity of tumor-derived tissue factor in plasma: is it important for coagulation activation? J Thromb Haemost. 2014;12:186–196.
82. Falanga A, Marchetti M, Russo L. Venous thromboembolism in the hematologic malignancies. Curr Opin Oncol. 2012;24:702–710.
83. Boles JC, Williams JC, Hollingsworth RM, et al. Anthracycline treatment of the human mononcytic leukemia cell line THP-1 increases phosphatidylserine exposure and tissue factor activity. Thromb Res. 2012;129:197–203.
84. Fu Y, Zhou J, Li H, et al. Daunorubicin induces procoagulant activity of cultured endothelial cells through phosphatidylserine exposure and microparticles release. Thromb Haemost. 2010;104:1235–1241.
85. Zhou J, Shi J, Hou J, et al. Phosphatidylserine exposure and procoagulant activity in acute promyelocytic leukemia. J Thromb Haemost. 2010;8:773–782.
86. Maraveyas A, Ettelaie C, Echrish H, et al. Weight-adjusted dalteparin for prevention of vascular thromboembolism in advanced pancreatic cancer patients decreases serum tissue factor and serum-mediated induction of cancer cell invasiveness. Blood Coagul Fibrinolysis. 2010;21:452–458.
87. Aigner S, Sthoeger ZM, Fogel M, et al. CD24, a mucin-type glycoprotein, is a ligand for P-selectin on human tumor cells. Blood. 1997;89:1385–1395.
88. Nomura N, Nomura Y, Suda Y, et al. Acute promyelocytic leukemia NALL-1. Blood. 2007;109:162–165.