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Circulating tumor cells and coagulation—Minireview

Branislav Bystricky[a,b], James M. Reuben[c], Michal Mego[a,*]

[a] 2nd Department of Medical Oncology, Faculty of Medicine, Comenius University and National Cancer Institute, Bratislava, Slovakia
[b] Department of Oncology, Trencin Hospital, Trencin, Slovakia
[c] Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

Venous thromboembolic events in cancer patients signify poor prognosis. Prophylactic treatment of ambulatory patients with anticoagulants is currently not recommended. Circulating tumor cells, either directly or indirectly, are associated with prothrombotic state. In this review, we discuss various interactions of circulating tumor cells with the coagulation pathway in cancer patient.

1. Introduction

1.1. Cancer and coagulation

Venous thromboembolic events (VTEs) are frequent complication in patients with cancer (Khorana et al., 2007). It has been shown that 5–10% of all cancer patients will develop VTE during the course of the disease (Silverstein et al., 1998). Evidence suggests that the absolute risk depends on the tumor type, the stage or extent of the cancer, and treatment with antineoplastic agents (Silverstein et al., 1998). Patients presenting with thrombotic event and cancer have lower survival rate compared to cancer without thrombosis. This lower survival rate might well be due to more aggressive tumor behavior than thrombotic event itself (Sorensen et al., 2000). Moreover, patients with cancer and VTE have increased complication rate from anticoagulation and increased risk of recurrent VTE (Prandoni et al., 2002).

* Corresponding author at: 2nd Department of Oncology, Faculty of Medicine, Comenius University and National Cancer Institute, Klenova 1, 833 10 Bratislava, Slovakia.
E-mail address: misomego@gmail.com (M. Mego).

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In 1860s, French internist Armand Trousseau first described migratory thrombophlebitis as a disorder of coagulation associated with underlying malignancy (Trousseau et al., 1867). He described several cases of migratory thrombophlebitis as a presenting sign of cancer. A few years later, he himself noticed phlebitis in his upper left extremity, a few months before he died of gastric cancer (Khorana, 2003). It took another hundred years before clot-promoting activities of tumor cells were defined. In the last 20 years, the research into thrombosis and cancer has uncovered complex cell-cell interactions, different markers of coagulation activation, and underlying molecular mechanisms. Tumor cells can activate hemostasis by several mechanisms including production of procoagulant and proaggregating factors, such as tissue factor (TF), cancer procoagulant and/or plasminogen activator inhibitors (PAI). Tumor cells can be a source of proinflammatory and proangiogenic cytokines, such as TNF-α (tumor necrosis factor) and interleukins, they can release extracellular microparticles, as well as induce release of neutrophil extracellular traps (NETs). Validated risk-score for chemotherapy associated VTE was recently adopted as part of VTE management by ASCO (American Society of Clinical Oncology) guidelines (Lyman et al., 2015). It is based on tumor type, platelet count, hemoglobin level, leucocyte count, and body mass index. However, preclinical and clinical studies suggest that circulating tumor cells (CTCs) might play a key role in initiating tumor-associated thrombosis (Mego et al., 2015a).

1.2. CTCs and coagulation

Cancer dissemination, which involves circulating tumor cells, is a crucial step for metastasis. Dissemination of cancer cells occurs predominantly via blood circulation. CTCs play important role in tumor dissemination and they represent surrogate marker for self-seeding potential (Kim et al., 2009). CTCs are very rare cells surrounded by billions of hematopoietic cells in the bloodstream. The detection of CTCs in patients with solid tumors, including breast, prostate and colon cancers, has received considerable attention over the past 15 years, and clinical studies consistently confirmed the prognostic value of CTC in different types of cancer (Cohen et al., 2008; Cristofanilli et al., 2004; de Bono et al., 2008). CTCs could be involved in coagulation activation in several ways. Firstly, CTCs express TF that activates coagulation cascade via factor VII/VIIa. Additionally, TF-factor VIIa complex activates anti-apoptotic signals and enhances cell survival in circulation. Secondly, platelets and fibrin mesh form a protective "coat" around CTCs, protecting them from lysis by natural killer (NK) cells. Platelet-CTCs microthrombi facilitate arrest and adhesion to endothelium. Platelets act as chemoattractants for CTCs, facilitating homing and exiting of tumor cells to form metastatic sites (Orellana et al., 2015). This extravasation is further enhanced by recruited neutrophils and monocytes which activate endothelial cells (Labelle and Hynes, 2012). Thirdly, factor XIII, a transglutaminase that stabilizes fibrin has been linked to metastatic cascade. Loss of function of factor XIIIa in gene-targeted immunocompetent mice diminished hematogenous metastatic potential (Palumbo et al., 2008b). It is postulated that loss of FXIII leads to a reduction in fibrin/platelets/CTCs microthrombi that favor immune system evasion. Lastly, CTCs can, via endothelial (E)-selectin, directly interact with endothelial cells (Gakhar et al., 2014).

Recently, accumulating clinical evidence suggest a link between coagulation activation and CTCs in cancer patients (Mego et al., 2009, 2015a, 2015b). In this review, we present concepts of the molecular mechanism of the role of CTCs in coagulation activation, as well as their current clinical applications.

2. Metastatic cascade

The metastatic cascade is a series of biological steps that tumor cells must complete to exit the primary tumor and develop a new tumor at a distant site. Tumor cells must invade the basement membrane and surrounding tissue and enter the bloodstream or lymphatics. Tumor cells capable of surviving in the circulation may eventually extravasate into the bloodstream, where some of them are capable of establishing a macroscopic tumor. Invasion, the first critical step in the metastatic process, requires changes in cell-to-cell adhesion as well as cell adhesion to the extracellular matrix (ECM). Invasion is further enabled by proteolytic degradation of the ECM, which enables cancer cells to penetrate tissue boundaries. Degradation of the ECM is predominately mediated by matrix metalloproteinases (MMPs) and the urokinase plasminogen activator (uPA) system (Dass et al., 2008). A significant proportion of CTCs, detected in patients with advanced disease, exhibit amplification of urokinase-type plasminogen activator (uPA) receptor, which is responsible for plasminogen cleavage, degradation of extracellular matrix and activation of MMPs (Dass et al., 2008). Invasive potential of cancer cells is increased in the process of epithelial to mesenchymal transition (EMT). This biological program is accompanied with loss of cell polarity, cell-cell contacts and downregulation of epithelial genes accompanied by up-regulation of mesenchymal genes (Haas et al., 2012). Moreover, EMT is associated with increased cell motility, resistance to chemotherapy and cancer stem cell phenotype (Mani et al., 2008).

The microenvironment of the bloodstream is highly unfavorable to the survival of tumor cells owing to physical shear forces, immune surveillance due to the presence of immune cells, and anoikis, which all contributes to metastatic insufficiency (Mego et al., 2016a, 2016b, 2010). Upon intravasation, CTCs interact with circulating coagulation factors and platelets via tissue factors (TF), fibrin and selectins to form microemboli. In order to extravasate, CTCs secrete factors that disrupt endothelial cell junctions and increase vascular permeability thus facilitating transendothelial passage of tumor cells (Stroka and Konstantopoulos, 2014).

3. Molecular mechanism of activation of coagulation by CTC

CTCs can initiate coagulation by various means; such as surface expression of procoagulants and facilitating assembly of coagulation factors complexes on their cell membranes (Fig. 1**).** Flow cytometry experiments using breast and colon CTCs have confirmed the capability of these cells to bind coagulation factor probes, hence confirming their part in promoting procoagulant phenotype (Tormoen et al., 2012).

3.1. Tissue factor

Tissue factor is a central component in cancer-associated thrombosis. Once available in the bloodstream, it binds factor VII and coverts this zymogen to its active component, factor VIIa. This binding triggers a putative extrinsic coagulation pathway, activating factors IX, X and leading to thrombin production and ultimately to fibrin deposition. The efficiency of these reactions is increased by presence of Ca2+ and phosphatidylserine on cell membranes. For instance, factor IXa forms a complex with its cofactor VIIIa on negatively charged phosphatidylserine containing cell membranes to generate factor Xa. This step, as well as factor Xa binding of cofactor Va to form prothrombinase complex, is Ca2+ -dependent. TF expression has been upregulated in several cancers, correlating with thromboembolic events and poor prognosis. It has been shown that patients with disseminated breast and pancreatic cancer, with an episode of VTE, have a significantly increased level