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Cancer-associated thrombosis (CAT) - Section 3

# Mechanisms of cancer-associated thrombosis

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**Take home messages**

- The mechanisms leading to thrombosis associated with cancer are multiple and may depend on the nature and the stage of a tumor.
- Tissue factor, cancer cell derived microparticles and podoplanin constitute the main actors involved in thrombosis associated with cancer.
- The new concept of tumor educated platelets may lead to the identification of new pathways involved in mechanisms of cancer-associated thrombosis.

## Introduction

In 1865, Armand Trousseau was the first to establish a relationship between cancer and thrombosis. He reported that superficial thrombophlebitis is a sign of an occult visceral malignancy.[1] Currently, it is known that VTE, including DVT and PE, is a frequent clinical complication in patients suffering from cancer. The incidence of VTE is seven-fold higher in patients with cancer than in the general population. Indeed, the incidence of VTE depends on the type of cancer, with a more pronounced risk in pancreatic (20%), bladder (8%) or lung (5%) cancers.[2] Different mechanisms leading to activation of the blood coagulation cascade and/or platelets have been currently identified and play a crucial role in thrombosis associated with cancer. Cancer cells themselves can activate platelets and the coagulation system by direct interaction (in the bloodstream) or indirectly via the production of microparticles and/or secreted factors and cytokines. In turn, activated platelets participate in tumor development and formation of metastasis. Several experimental studies have investigated the use of an anti-platelet strategy in cancer progression and metastasis development. We demonstrated in mice models an interesting potential of anti P2Y12 drugs, including Clopidogrel, to treat cancer progression and metastasis development as well as to limit the occurrence of thrombosis associated with pancreatic cancer.[*3] One well-documented anti-platelet treatment that has been investigated in clinical and experimental studies is the use of the COX inhibitor aspirin. Actually, the unique therapeutic benefit of aspirin treatment of cancer patients is based on a reduction of distant metastasis and improvement in mortality, specifically in colorectal cancer. It is also suggested that this beneficial effect is due to a high dose of aspirin and to the overexpression of COX-2 by colorectal tumors.[4] Here we will describe the different mechanisms involved in cancer-associated thrombosis with a special focus on the role of Tissue factor (TF), microparticles and podoplanin (Fig. 1).

## Current state of the art

In retrospective studies, Khorana et al showed that there is a direct correlation between the increased incidence of VTE and Tissue Factor (TF) expression in pancreatic cancer patients.[5] In addition, cancer patients with the Trousseau syndrome present an augmentation of microparticles that express activated TF.[*6] Under physiological conditions, TF is the primary activator of the coagulation cascade; it also plays a critical role during the development of the vasculature, leading to embryonic lethality when it is inactivated in mice. Tissue factor, which is aberrantly expressed in many tumor cell types, is clearly involved in tumor-associated hypercoagulability and in promoting tumor angiogenesis. In an ectopic pancreatic mouse model, we previously demonstrated a key role of TF expressed by cancer-cell-derived microparticles in tumor-associated thrombosis.[*7] We showed that the cancer-cell-derived microparticles (and not their parent cells) circulate in the bloodstream and that they accumulate at laser-induced thrombi via P-selectin/PSGL-1. We also demonstrated that this TF is involved in the procoagulant state found in mice bearing tumors.[*7] The specific loss of endogenous TF expression by cancer cells leads to an important decrease of the tumor growth, a finding that correlates with those of previous studies.[8] TF is also involved in several steps of malignancy, including tumor progression, angiogenesis and the development of metastasis. In vitro studies have shown a direct correlation between the

*Funding/support: None.*
*Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.*

*HemaSphere (2019) 3:S2*
*Received: 27 February 2019 / Accepted: 31 March 2019*
***Citation:*** Mege D, Panicot-Dubois L, Dubois C. Mechanisms of Cancer-Associated Thrombosis. *HemaSphere*, 2019;3:S2. http://dx.doi.org/10.1097/HS9.0000000000000239.

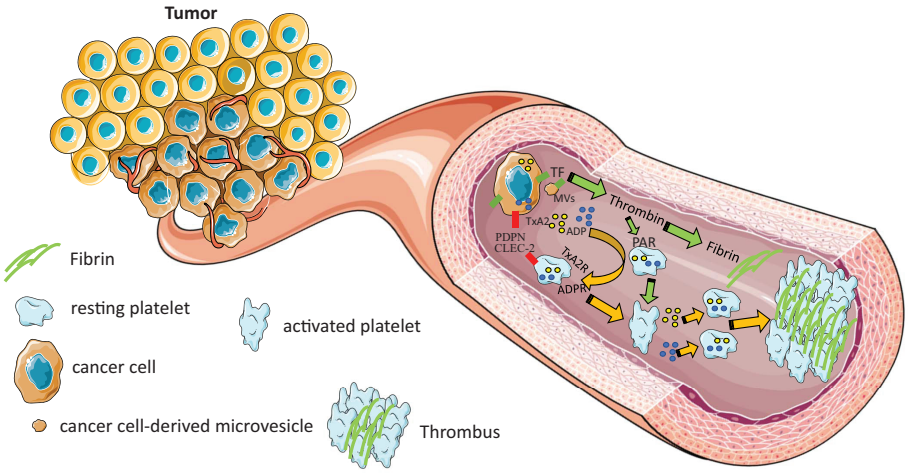


**Figure 1. Main mechanisms involved in cancer-associated thrombosis**. Circulating cancer cells once in bloodstream may directly induce activation and aggregation of platelets via the expression of Podoplanin (PDN) and the secretion of the platelet agonists ADP and thromboxane A2 (TxA2). The activation of the blood coagulation cascade is induced by the expression by the cancer cell of Tissue factor (TF) and the release of cancer cell-derived microvesicles (MVs) expressing TF and negatively charged phospholipids. This figure was obtained using Servier medical art. http://smart.servier.com/.

expression of TF and the production of VEGF. It is also suggested that the angiogenic phenotype promoted by TF is due to the upregulation of VEGF in addition to the downregulation of thrombospondin. Others have suggested that the promotion of tumoral angiogenesis by TF occurs through both coagulation-dependent and coagulation-independent pathways. The coagulation-dependent pathway involves the activation of FVIIa by TF, which induces thrombin generation and the activation of platelets. The other mechanism is the phosphorylation of PAR-2 and -1 as a result of cytoplasmic domain signaling of TF.[*9,10]

Depending on the tumor, other mechanisms, TF and/or microparticles independents, may also activate platelets leading to the formation of a thrombus. These mechanisms include the production by the tumor of the platelet agonists ADP and Thromboxane A2 (TXA2), the secretion of Matrix metalloproteinases (MMPs) participating in the Tumor Cell Induced Platelet Aggregation (TCIPA) and of Cathepsin cysteine proteases, such as cathepsin B and K, which cleave the Tissue Factor Pathway Inhibitor (TFPI) and favor the activation of the TF pathway.[*3,11]

Cancer cells also express many adhesive molecules that enable their interaction with the blood host cells, including platelets, endothelial cells and immune cells. To date, there are few mechanisms described for the interaction of cancer cells with platelets in the bloodstream.

Glycoproteins (GPs), expressed on both platelets and cancer cells, are described to mediate cancer cell–platelet interactions. The GPIbα, which is a component of the platelet receptor GPIb-V-IX, was reported to contribute to TCIPA and tumor progression, but its specific role remains contradictive. Podoplanin (PDPN) is a mucin-type sialoglycoprotein. PDPN, which was initially described in the lymphatic vessel formation during embryogenesis, is upregulated in various types of cancer, including colorectal, bladder and lung carcinomas and contributes to TCIPA, tumor growth and metastasis. Podoplanin can directly bind the platelet receptor C-type lectin-like receptor (CLEC-2) and induces platelet activation and aggregation.[12] Finally, in response to all of the biomolecules released and/or expressed by tumor cells and tumor microenvironments, the notion of tumor-educated platelets had recently emerged.[*13] Indeed, cancer cells by acting on megakaryocytes can increase platelet production and modify the platelet "RNAsome". Thus, a tumor could modify the physiology and the phenotype of platelets that is closely associated with the pro-thrombotic state of cancer.

## Future perspective

Although different mechanisms leading to the formation of a thrombus have been identified in different types of cancers, the exact contribution and the interplay between the different pathways still need to be determined according to the nature and stage of a cancer. The emerging concept of tumor educated platelets is subject of intensive research in different labs and will mostly lead to the identification of new important pathways involved in thrombosis and cancer.

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