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COMMENTARY

Von Willebrand factor and cancer: Another piece of the puzzle

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1 | CANCER-ASSOCIATED THROMBOSIS

Cancer-associated thrombosis (CAT), in the form of venous thromboembolism (VTE) or arterial events, is the most common morbidity in cancer patients and is associated with higher mortality rates.[1] It is estimated that VTE occurrence is increased 5-fold in cancer patients compared with the general population.[2] Not all cancers are created equal in terms of VTE risk. Hematological malignancies, lung, pancreas, stomach, bowel, and brain cancers are associated with higher risk. In contrast, breast and prostate cancers are considered low risk for VTE, but progression of the disease to metastatic malignancies is known to increase significantly the thrombotic risk.[3] Altogether, the high prevalence of breast cancer actually makes it the most common malignancy associated with thrombosis.

Management of the thrombotic risk in cancer patients remains broad-spectrum with the use of low molecular weight heparin (LMWH) and more recently of direct anticoagulants.[1] However, this approach does not take into account the specificity of CAT compared with regular VTE, the type of tumor or the cancer stage. A better knowledge of CAT pathophysiological mechanisms is therefore of the utmost importance to improve efficiency and specificity of therapeutic strategies. Indeed, there are some cancer-specific drivers of VTE and nonexhaustive examples include expression of tissue factor by tumor-derived extracellular vesicles that can trigger the coagulation cascade,[4] release of interleukin-6 from certain tumors, increasing platelet counts[5] and endothelial activation, and subsequently increased circulating levels of von Willebrand factor (VWF), a known risk factor for VTE.[6]

2 | VWF, AN ACTIVE PLAYER IN CANCER PROCESSES

VWF, mostly known as mediating platelet adhesion during primary hemostasis is increasingly recognized as an intriguing actor in the toxic relationship between tumor cells and the coagulation system. Indeed, links between VWF and malignant diseases are numerous. In patients, VWF levels are significantly increased in various cancer cohorts, including hematological malignancies[7] as well as solid tumors.[6] This increase is even further amplified in metastatic diseases. In experimental models, the mechanisms by which tumor cells induce VWF release from endothelial cells vary according to which types of tumor cells are used and include tumor-derived vascular endothelial growth factor A (VEGF-A) by melanoma cells[8] or tumor-derived matrix metalloproteinase-1 by colon cancer cells.[9]

Whether increased levels of VWF are just a bystander effect of endothelial activation or are an active contributor to disease progression has been assessed using experimental models. Pioneer work from the Coller's laboratory showed in 1988 that the use of antibodies against VWF led to decreased platelet/tumor interaction *in vitro* and metastasis formation in mice using colon carcinoma or melanoma cells.[10] Such observations have been confirmed in different

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models using various types of tumor cells and have highlighted the role of the VWF-platelet glycoprotein Ibα axis[6,11] as well as other potential mechanisms.[12] However, the use of VWF-deficient mice led to the surprising result that increased metastasis was associated with absence of VWF in experimental murine metastasis models of Lewis lung carcinoma or BL6-B16 melanoma cells.[13] This rather intriguing result was further explained by a VWF-mediated apoptosis of some tumor cells,[14] a finding later confirmed by Mochizuki et al., who also showed that to escape this apoptotic mechanism, some tumor cells express a VWF-cleaving protease, ADAM28, which make them resistant to VWF-induced apoptosis.[15] All these studies highlight that VWF exerts a complex role in cancer and that there is no universal truth. Depending on the type of cancer, VWF actions may be very different and may involve distinctive mechanisms. Therefore, studies targeting specific cancers should be undertaken and interpreted separately.

3 | VWF IN BREAST CANCER: MECHANISMS UNFOLDED

In this issue, Dhami and colleagues have investigated the mechanisms underlying VWF role in breast cancer and especially in metastatic breast cancer.[16] First, the authors confirmed previous studies showing markedly increased VWF antigen levels in patients with metastatic breast cancer (about 2-fold increase). Interestingly, they were able to evidence an inverse correlation between VWF levels and overall survival, highlighting the relevance of VWF as a biomarker in this patient population. Furthermore, by measuring VWF propeptide levels as well as osteoprotegerin and angiopoietin-2, all three proteins present in Weibel-Palade bodies and all concomitantly elevated, this study decisively shows that endothelial activation and Weibel-Palade bodies secretion is responsible for the increase in VWF levels.

Next, the authors sought out to dissect how breast cancer cells were able to act upon the endothelium. Using culture medium from different breast cancer cell lines, they showed how some of these cells secreted agent(s) capable of inducing VWF release from human umbilical vein endothelial cells (HUVECs). However, not all breast cancer tumor cells were able to do so. Furthermore, adding platelets to the tumor cells before collecting the supernatants resulted in a significant increase in VWF release, allowing the establishment of some kind of gradient in breast cancer cells' ability to activate HUVECs. Triple negative breast cancer cells MDA-MB-231, isolated from the most aggressive and highly metastatic type of breast cancer, were the most potent in inducing VWF release. Such cells rely at least partially on VEGF-A to activate endothelial cells, as shown by the inhibitory effect of bevacizumab, an anti-VEGF-A antibody. Coculture of MDA-MB-231 cells with platelets resulted in an even greater increase in VWF, consistent with a larger VEGF-A concentration in the supernatant. A second type of breast cancer cells, low metastatic hormone receptor positive MCF-7 cells, were less potent activators of HUVECs, consistent with the low levels of secreted VEGF-A from these cells. However, supernatants collected from MCF-7 cells incubated with platelets resulted in a significant VWF release from endothelial cells, partially through VEGF-A but also transforming growth factor-β1. Finally, nontumorigenic cell MCF-10A and control primary mammary epithelial cells were unable to induce endothelial activation and VWF release. These results highlight the diversity in breast cancer cells, the variety of mechanisms at play, and suggest a significant role for VWF in the severity of the disease.

So what advantage is there for tumor cells to induce VWF release? In their study, Dhami and colleagues also investigated this issue and observed that long VWF multimers, freshly released from Weibel-Palade bodies were able to mediate tumor cells adhesion in flow conditions. Adhesion of tumor cells constitute the first step in the process of tumor cells extravasation and subsequent metastasis, suggesting that VWF is an active contributor of disease progression (Figure 1).

Other interesting findings include the observation that supernatants from breast cancer cells induce a pro-angiogenic effect on endothelial cells, alter endothelial permeability and facilitate transendothelial migration of the tumor cells, effects mediated at least in part through VEGF-A. Whether VWF is also involved in these effects is not clear at the moment but other studies have previously linked VWF to endothelial permeability, so it cannot be excluded.[17]

Finally, and of high interest, the authors have convincingly shown that most of these effects induced by breast cancer cells supernatants can be significantly dampened by tinzaparin, an LMWH. This property of LMWHs appears to occur predominantly through their known inhibitory effect of VEGF-A activity but considering that tinzaparin was more potent than the anti-VEGF-A, bevacizumab, other pathways must also be involved. Altogether, LMWHs may be protective not only against CAT but also against tumor progression in breast cancer, similar to what has been described for melanoma.[18]

4 | VWF IN CANCER: WHAT IS NEXT?

The data presented by Dhami and colleagues bring yet another piece to the puzzle, linking VWF to malignant diseases, this time in metastatic breast cancer. Animal studies confirming such results could extend and strengthen even further the relevance of this study. However, it is becoming very clear that besides being a risk factor for CAT, VWF also contributes to other cancer-associated processes, namely tumor cell adhesion and probably metastasis.

This study raises the question whether thromboprophylaxis should be considered more systematically in breast cancer patients. Indeed, thromboprophylaxis is not very common in these patients either before or after surgery except if other prothrombotic risk factors exist.[19] However, it is important to point out that LMWH concentrations used in the present study (10-100 UI/ml) are considerably higher than those measured in clinical settings.[20] Alternatively, could direct anticoagulants have similar effects than LMWH in inhibiting VWF release, endothelial cells angiogenesis, and permeability? Could they also potentially be used to reduce not only the risk of CAT but also of tumor progression?

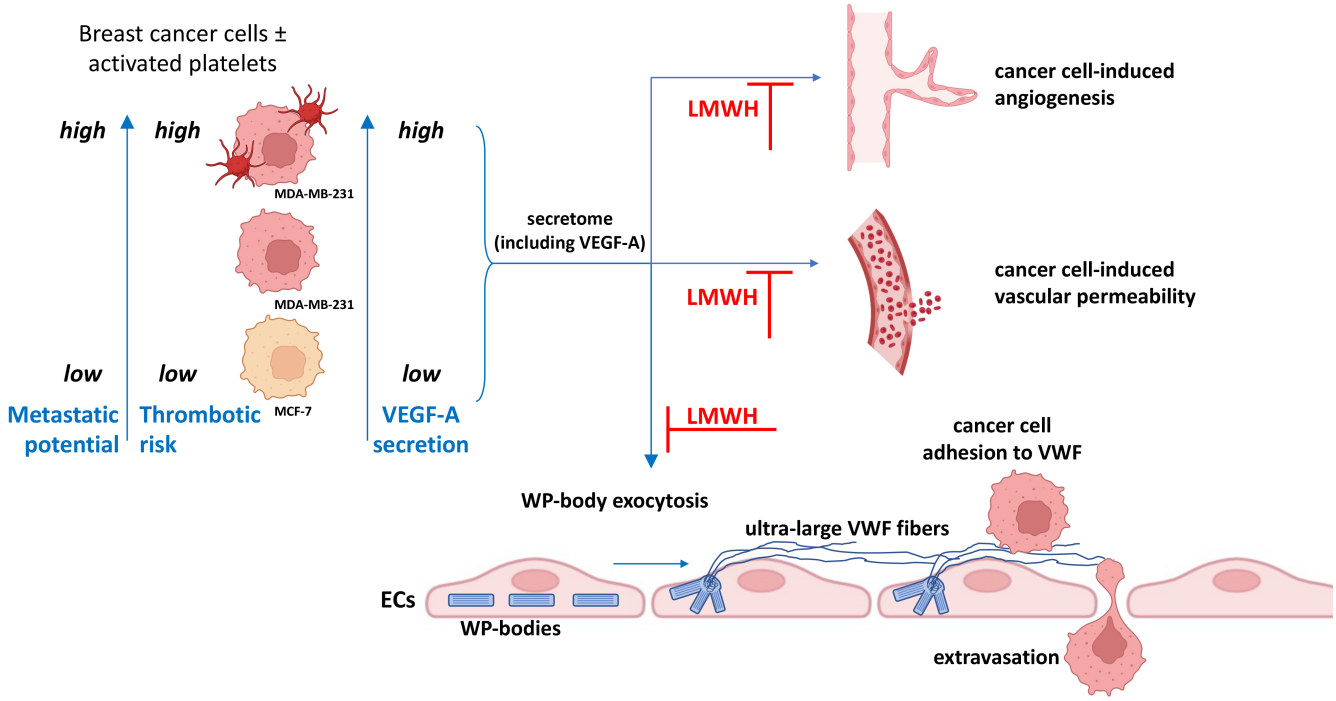

FIGURE 1 Crosstalk between breast cancer cells and the endothelium. Different types of breast cancer cells derived from tumors with varying aggressiveness and associated with various thrombotic risk exert different actions on endothelial cells. Secretome from most aggressive tumor cells induce endothelial activation, von Willebrand factor (VWF) release, promote angiogenesis, and induce endothelial permeability. Incubation of tumor cells with platelets exacerbates these effects which are partially mediated by tumor-derived vascular endothelial growth factor A (VEGF-A) and transforming growth factor-β1 (TGF-β1). VWF strings released from endothelial cells mediate tumor cell adhesion, thereby facilitating extravasation and possibly metastasis. Low molecular weight heparin (LMWH) tinzaparin inhibits tumor-derived VEGF-A mediated effects on endothelial cells, lowering cancer cells progression. Portions of this figure were created using Biorender.com.

For limiting disease progression, direct inhibition of VWF appears very elusive at the moment considering the multiplicity of mechanisms involved in the progression of malignant disorders. Additional studies refining further our knowledge of VWF involvement in cancer are more than ever necessary. Also, observations of patients with von Willebrand disease (VWD) could potentially be useful. Despite the heterogeneity of malignant diseases, can we get any information about whether VWD patients are at lower/higher risk of developing cancer? Alternatively, is cancer progression different in patients with VWD? Such studies will obviously be extremely complicated to carry out but if at least, an international surveillance database existed on the subject, the clinical relevance of VWF role in cancer could potentially be established beyond experimental models.

AUTHOR CONTRIBUTIONS

C.V.D., S.R., and J.P. wrote the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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