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EDITORIALS

New Wrinkle Between Cancer and Blood Coagulation: Metastasis and Cleavage of von Willebrand Factor by ADAM28

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Although metastasis accounts for the death of approximately 90% of patients with cancer (1), this field of research was of little interest to most scientists for most of the 20th century. The past decade, however, has witnessed an explosion of interest in metastasis, and the complexity of the process has become mind-boggling. New concepts describing the plethora of mechanisms involved in the metastatic process (eg, premetastatic niche formation, epithelial–mesenchymal transition [EMT], protease-independent cancer cell invasion) have forced us "to think outside the box" (1). In this issue of the Journal, Mochizuki et al. (2) provide novel experimental data explaining how aggressive types of cancer cells are able to avoid apoptosis in the circulatory system at metastatic sites. Prior studies by the authors had demonstrated that increased tumor tissue and serum levels of a metalloproteinase (a disintegrin and metalloproteinase [ADAM]28), whose functions are little known, correlated with poor prognosis and metastasis in patients with breast and lung cancer (3). The authors proposed that ADAM28 contributes to tumor growth by selective digestion of insulinlike growth factor binding protein 3 and connective tissue growth factor (3). However, the molecular mechanisms by which ADAM28 promotes experimental metastases remained elusive.

Using a yeast two-hybrid system to screen a human lung cDNA library to identify how ADAM28 promotes the progression of cancer, Mochizuki et al. (2) found that ADAM28 binds to and cleaves von Willebrand's factor (VWF). The surprising aspect of this report is the demonstration that physiological levels of VWF, a prominent plasma protein associated with blood coagulation and thrombosis, induces cancer cell apoptosis. In this study (2), the in vitro experiments demonstrated that rapidly growing and metastatic human carcinoma cell lines expressing high level of ADAM28 were resistant to VWF-induced apoptosis, but apoptosis was induced when the expression or activity of ADAM28 was blocked. Less aggressive cancer cell lines did not express ADAM28 and underwent apoptosis when treated with VWF. The authors demonstrated that VWF-induced cancer cell apoptosis involved the $\alpha_V\beta_3$ integrin, leading to activation of a mitochondrial cell death pathway. Mochizuki et al. further used a mouse model of lung metastasis and demonstrated that knockdown of ADAM28 expression or activity in cancer cells resulted in diminished metastasis. This antimetastatic effect was associated with enhanced cancer cell apoptosis within blood vessels in the lung and reduced VWF degradation in the blood. The authors concluded that cleavage of proapoptotic VWF by ADAM28 enhances lung metastasis by promoting cancer cell survival within the circulatory system (2).

Let us step back in the literature to place the recent findings regarding ADAM28 and VWF (2) into perspective. Scientific investigation of matrix metalloproteinases (MMPs) emerged in the 1980s to explain how cancer cells break out of the confines of a primary tumor to enter (intravasation) and exit (extravasation) from the circulatory system and invade and proliferate at distant metastatic sites (1,4). This enthusiasm, however, was tamped down following the failure of first generation broad-spectrum MMP inhibitors in cancer clinical trials (4). ADAMs have been late comers to the large family of zinc-dependent MMPs. ADAM9, ADAM10, ADAM12, and ADAM17 are intrinsic plasma membrane proteins with established roles in regulating the cancer cell phenotype via ectodomain shedding leading to procancer effects on cell adhesion, migration, proteolysis, signaling and induction of EMT, and ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17, ADAM19, and ADAM28 are highly expressed in human malignant tumors (2,3).

VWF, a multimeric protein containing binding domains for various proteins, is secreted by endothelial cells and platelets and is well known in primary hemostasis for promoting platelet adhesion to the subendothelium and platelet aggregation (3). VWF also acts as a carrier for coagulation factor VIII. Of relevance to this Editorial, thrombotic thrombocytopenic purpura is a disease involving ADAMTS (with thrombospondin type1 motif)13 and VWF; absence or inhibition of this ADAM results in lack of cleavage of VWF multimers, leading to platelet aggregation and a hypercoagulable state (5). In contrast to ADAM28, which is capable of cleaving both native and denatured VWF, the physiological role of ADAMTS13 is limited to cleavage of denatured VWF, at sites of high shear stress in the arterial circulation.

After intravasation, tumor cells have long been known to interact with platelets and the vessel wall, before extravasation from the circulation. VWF has been implicated in the binding of platelet tumor cell thrombi to the endothelium (6,7). Furthermore, human tumor cells increase endothelial cell production of VWF, thereby enhancing adhesion of cancer cells to the endothelium (6). Relevant to the study by Mochizuki et al. (2), an in vitro interaction between VWF and cancer cells involving the Arg-Gly-Asp tripeptide sequence (a binding site for adhesion of the $\alpha_V\beta_3$ integrin) of VWF and the $\alpha_V\beta_3$ integrin on the tumor cell surface was previously characterized by Terraube et al. (7). Contrary to the expectation, cell culture studies revealed that VWF did not influence tumor cell proliferation or invasion but instead induced apoptosis (2). This in vitro observation was supported by in vivo experiments demonstrating an increased

number of pulmonary metastases in VWF-null mice compared with control mice following intravenous injection of cancer cells. Restoration of VWF plasma levels by injection of VWF inhibited metastasis. These experiments conducted by Mochizuki et al. (2) are consistent with the concept that inactivation of VWF is required in the initial establishment of metastatic foci, independently of its role in hemostasis.

Now, how are we to integrate the elegant preclinical studies of Mochizuki et al. (2) to expand our understanding of clinical metastasis? Let us go back to the basics. The mouse pulmonary colonization model used by Mochizuki et al. (2) is considered the "gold standard" in analyzing cancer dissemination. The fact that mouse lung metastasis occurs within weeks, whereas human metastases develop over years, is cause for concern. Furthermore, the extensive proliferation of metastatic cancer cells intravascularly in mouse lungs (8) appears different from pathological examination of human metastases.

What other data is needed to "nail down" the role of ADAM28 cleavage of VWF in cancer? An association of VWF levels in blood and tissues and ADAM28 levels in patient tumor tissue with indolent vs aggressive cancers would be revealing. One area of concern deals with an old observation that humans with type O blood group have substantially lower plasma levels of VWF than other ABO groups (9), which, according to Mochzuki et al. (2), might lead to diminished tumor cell apoptosis, hence more aggressive cancers. But, on the contrary, patients with type O blood do not display enhanced tumor aggressiveness (9–11). Other investigators reported increased serum levels of VWF antigen and multimers in patients with cancer, but the issue of correlation of VWF with prognosis is disputed (12).

From a wider perspective, how are we to make sense of the enlarging number of genes being implicated in the metastatic process? Will it turn out that individual human tumors require different proteins to complete the metastatic process or will a small panel of "driver genes" be identified? We have the cell and molecular technology, animal models, and clinical tools to solve the problem, but the path to drug discovery for treatment of metastasis and the dream of turning cancer into a "chronic disease" (13) might turn into quite an obstacle.

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Non-Hodgkin Lymphoma in Early Life

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The non-Hodgkin lymphomas (NHLs) are a heterogeneous group of B-cell and T-cell neoplasms that vary by morphological appearance, etiology, biology, and clinical manifestations. Worldwide, the incidence of NHL began to increase circa 1950 (1,2), approximately doubling in the United States between 1975 and 2000 (3,4), and then stabilizing with an age-standardized rate near 20 per 100 000 person-years (3). The age-standardized incidence rate, however, is an age-specific weighted average that may