Sharing Tissue Factor
A Winning Strategy in Tumorigenesis

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Existence of a close relationship between increased clotting and malignancy has been clearly recognized for over a century. Many tumor cell types express tissue factor (TF), a procoagulant protein, on their cell surfaces. Tissue factor is a transmembrane cellular receptor for coagulation factor VIIa/VIIa. Binding of factor VIIa to TF triggers the activation of coagulation cascade leading ultimately to the generation of thrombin which in turn stimulates platelet activation and cleaves fibrinogen. Thus, there is no surprise that the activation of coagulation by tumor cell TF or by membrane fragments shed from tumor cells carrying TF contributes to cancer-associated thrombotic disorders.1,2 The close association between cancer and TF has also raised the possibility that TF may contribute to the pathogenesis of cancer beyond thrombosis. In fact, there are a number of reports in the literature showing that TF expressed by tumor cells plays an important role in both primary tumor growth and metastasis (see reviews3–5). The prometastatic effect of TF involves both activation of the coagulation pathway (eg, mechanisms linked to thrombin generated by TF) and effects mediated through the direct signaling activity of TF, probably via the cytoplasmic domain of TF.6 Recent studies have shown that direct TF-FVIIa protease-induced cell signaling is a major contributor to tumor growth in breast cancer.7 However, there are a couple of convincing reports in the literature that provide evidence that is contrary to the general belief that tumor-derived TF is crucial for primary tumor growth or metastasis. Toomey et al8 using embryonic stem (ES) cells that do not express TF, showed that tumor-derived TF was not required for either tumor growth or metastasis. In a more recent study, Palumbo et al9 showed that tumor TF was neither required for primary tumor growth nor necessary for the initial seeding of embolized tumor cells within lungs. However, tumor TF, in cooperation with circulating hemostatic factors, has been shown to promote metastasis by increasing the survival of micrometastasis.9 These studies, however, do raise an important question: Does tumor-derived TF contribute to primary tumor growth and angiogenesis? Obtaining the answer to this question is not as simple as the question posed. Various host cells, some of them often present within the tumor mass, also express TF, and TF from these cells may contribute to tumor growth and angiogenesis. Thus, it is difficult to separate tumor TF-mediated effects from that of the host TF-mediated effects. There are no specific agents that can specifically inhibit the tumor TF but not the host TF or vice versa. Because TF gene deletion results in embryonic lethality, the use of TF knock-out mice to examine the effect of host-TF in cancer pathogenesis is also not an option. However, the development of a unique strain of mice,10 in which the endogenous mouse gene has been substituted with a human TF minigene, that expresses very low levels of TF (1%) has provided an unique opportunity to examine the effects of host-TF on tumor growth and angiogenesis.

See accompanying article on page 1975

In an article published in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Yu et al11 took advantage of the availability of low-TF mice and ES cells lacking TF, to investigate the contribution of tumor-derived TF and host-related TF on both tumor growth and angiogenesis. Their data reported in the article provide novel information that may prove helpful in resolving the controversy on the importance of tumor-derived TF to tumor growth and angiogenesis. The data show that the growth rate of TF-expressing transplantable tumors or their extent of metastasis was unchanged in low-TF mice, as compared to that in wild-type mice, suggesting that host TF is not essential for tumor growth or metastasis. Nonetheless, host TF appears to influence a number of tumor/context-specific alterations, including tumor blood vessel size, spleen size, and tolerance to toxicity of the anticancer agent cyclophosphamide (CTX). Consistent with the observation that host TF does not contribute significantly to either primary tumor growth or metastasis, subcutaneous injection of TF-expressing tumorigenic ES cells gave rise aggressive and angiogenic teratomas in both the wild-type and low-TF mice. As reported earlier,3 TF+ ES cells grew prolifically as a vascular teratoma in SCID mice with wild-type levels of TF. However, the tumor growth was aborted after inoculation if TF− ES cells were injected to low-TF mice. Overall, the data suggest that TF is essential to primary tumor growth and angiogenesis, but tumor-derived TF per se is not an absolute requirement for tumor growth or metastasis because host TF can perform the same function, at least in certain of types of cancer.

This complementarity of host- and tumor-derived TF in tumor growth and metastasis appears to be the consequence of TF sharing between tumor and host cell compartments. The authors11 have provided an acceptable, although not robust, evidence for TF sharing between tumor cells and host cells by showing the presence of human TF in host (mouse) blood vessels in a model involving a human epithelial cell carcinoma (A431) xenograft developed in severe combined immunodeficiency (SCID) mice. It would have been more
impressive if the authors could have shown such TF transfer in the other in vivo model systems that they employed to generate the primary data of the study. A potential mechanism by which TF can be transferred from one cell to the other cell is through the exchange of TF-containing microvesicles, as shown recently for inflammatory cells and platelets. Data from in vitro studies provided in the present article, which showed shedding of TF containing microvesicles from A431 carcinoma cells and the transfer of the microvesicle-TF to mouse endothelial cells, further support the authors’ contention. Although it is possible that there could be converse exchange, ie, transfer of TF from host cells to tumor cells, no evidence has been presented for this in the present study. Indeed if TF does transfer from the host cells to tumor cells, it is unclear which host cell types share TF with tumor cells. Endothelial cells and circulating blood cells in general do not express TF, although it could be induced in these cells in certain types of cancer. A limitation of the present study is that there is no direct evidence indicating that the exchange of TF is critical for tumorigenesis. It is possible that host- and tumor-derived TF can complement each other without exchanging TF from one cell to the other but by sharing cellular mediators elaborated by TF. Either way, TF sharing between host and tumor cells can explain why some of the earlier studies found that tumor-derived TF is essential for tumor growth and angiogenesis whereas others found no significant role for tumor-derived TF in these processes.

What is clear is that the role of TF in tumorigenesis is complex. The relative contribution of tumor-derived TF and host-related TF in tumor growth and angiogenesis may vary and be dependent both on context and also be tumor specific. When the oncogenic transformation induces TF in tumor cells, tumor-derived TF may assume a predominant role in tumor growth and angiogenesis. In these settings, the contribution of host-related TF to tumorigenesis could be minimal. When tumor cells lack TF or express low levels of TF, host-related TF, in cooperation with circulating hemostatic factors, may play a more significant and critical role in tumorigenesis. As Yu et al11 rightly pointed out, defining a universal role for TF in cancer may prove elusive. Nonetheless, a common theme emerges from all the studies carried out so far on the role of TF in cancer pathogenesis, which is that TF provides an attractive target to regulate tumor growth and/or block the progression of metastatic disease.

The study of Yu et al11 also reveals other novel observations, but unfortunately these are neither fully developed nor vigorously pursued. Low-levels of host TF were found to cause qualitative changes in blood vessel patterning (shift to smaller diameter blood vessels) in BIGF1 melanoma. However, this change in tumor vascular microarchitecture in low-TF mice had no effect on the rate of tumor formation. How host TF impacts blood vessel patterning and whether this has any consequences on tumorigenesis needs further investigation. The observation that low-TF mice contain larger spleens is intriguing. It is unclear whether the larger spleens observed in low-TF mice are limited to low-TF mice in SCID background or whether it is also apparent in other genetic backgrounds as well. If the larger spleen containing greater reserves of lymphatic cells is responsible for the observed partial protection of low-TF mice from the toxic side effects of cyclophosphamide, it indicates a novel role for TF in modulating hematopoietic toxicity of cyclophosphamide and probably other chemotherapeutics. It would be interesting to see whether this holds true on further investigation.

In summary, the impressive study conducted by Yu et al11 illustrates the context-dependent role of host TF in tumor formation, angiogenesis, and chemotherapy. The observation that TF could be “shared” between cancer and host cells via intercellular transfer of TF-containing microvesicles is very helpful in resolving some of the apparent inconsistencies in the literature on the role of tumor-derived TF in tumor growth and metastasis. Other interesting observations made in the study, ie, effect of host-TF in modulating the tumor microvasculature pattern and toxicity to anticancer chemotherapeutics, need a further validation.

Sources of Funding
The manuscript was supported by grants HL58869 (to L.V.M.R.) and HL65500 (to U.R.P.) from the National Heart, Lung, and Blood Institute.

Disclosures
None.

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doi: 10.1161/ATVBAHA.108.176149

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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