Tissue Factor Expression, Angiogenesis, and Thrombosis in Pancreatic Cancer

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Abstract

Purpose: Hemostatic activation is common in pancreatic cancer and may be linked to angiogenesis and venous thromboembolism. We investigated expression of tissue factor (TF), the primary initiator of coagulation, in noninvasive and invasive pancreatic neoplasia. We correlated TF expression with vascular endothelial growth factor (VEGF) expression, microvessel density, and venous thromboembolism in resected pancreatic cancer.

Experimental Design: Tissue cores from a tri-institutional retrospective series of patients were used to build tissue microarrays. TF expression was graded semiquantitatively using immunohistochemistry in normal pancreas (n = 10), intraductal papillary mucinous neoplasms (n = 70), pancreatic intraepithelial neoplasia (n = 40), and resected or metastatic pancreatic adenocarcinomas (n = 130).

Results: TF expression was observed in a majority of noninvasive and invasive pancreatic neoplasia, including 77% of pancreatic intraepithelial neoplasias, 91% of intraductal papillary mucinous neoplasms, and 89% of pancreatic cancers, but not in normal pancreas. Sixty-six of 122 resected pancreatic cancers (54%) were found to have high TF expression (defined as grade ≥2, the median score). Carcinomas with high TF expression were more likely to also express VEGF (80% versus 27% with low TF expression, P < 0.0001) and had a higher median MVD (8 versus 5 per tissue core with low TF expression, P = 0.01). Pancreatic cancer patients with high TF expression had a venous thromboembolism rate of 26.3% compared with 4.5% in patients with low TF expression (P = 0.04).

Conclusions: TF expression occurs early in pancreatic neoplastic transformation and is associated with VEGF expression, increased microvessel density, and possibly clinical venous thromboembolism in pancreatic cancer. Prospective studies evaluating the role of TF in pancreatic cancer outcomes are warranted.

Pancreatic cancer is responsible for over 200,000 deaths per year worldwide and is the fourth leading cause of cancer death in the United States (1, 2). One of the major complications of pancreatic cancer is venous thromboembolism, an association first described by Sproul in 1938 (3). Reported incidence rates of venous thromboembolism in pancreatic cancer range from 17% to as high as 57% (4). The mechanisms underlying this association of venous thromboembolism with pancreatic cancer and its biological implications are incompletely understood.

Emerging data suggest that the hemostatic system regulates angiogenesis (5). It is therefore possible that hemostatic activation in pancreatic cancer contributes not only to clinical thrombosis but also to tumor angiogenesis. The link between hemostasis and angiogenesis is illustrated by the physiologic roles of tissue factor (TF; ref. 6), a 47-kDa transmembrane protein that is the principal physiologic initiator of coagulation. TF binds and activates factor VIIa, the TF-VIIa complex, then activates factor X, leading eventually to the generation of thrombin required for physiologic hemostasis. In addition to its role in hemostasis, TF may also contribute to angiogenesis by up-regulating vascular endothelial growth factor (VEGF) and down-regulating the angiogenesis inhibitor thrombospondin, a mechanism independent of coagulation activation (7).

TF is normally absent from quiescent endothelium and is expressed in smooth muscle cells surrounding blood vessels. However, in malignant tissue, TF is present on neoplastic cells as well as endothelial cells (8). TF expression is induced early in
colorectal cancer cells that possess mutations in KRAS and TP53 genes (9). TF expression has been shown to be associated with increased angiogenesis in various solid neoplasms, including hepatocellular, colorectal, and prostate cancers (10–12), as well as in hematologic malignancies (13). Although it has been proposed that TF may function as an effector of the angiogenic phenotype in neoplastic cells, this remains to be firmly established. TF seems to be important for tumor growth and metastasis as well (8, 14, 15).

The role of TF in pancreatic cancer is of particular interest. TF is expressed in pancreatic cancer cells and correlates with poor histologic grade and worsened prognosis (16, 17). However, the association of TF with angiogenesis in pancreatic cancer or with venous thromboembolism, a frequent clinical event in this disease, has not been previously studied. There are also no data regarding TF expression in pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN), two recognized noninvasive precursors to invasive pancreatic cancer.

We, therefore, chose to study the expression of TF in resected noninvasive precursor lesions and invasive pancreatic cancer. We now report that the induction of TF is an early event in the development of pancreatic cancer and that the level of TF expression correlates with increased angiogenesis, as determined by the expression of VEGF, an important proangiogenic cytokine (18), and high intratumoral microvessel density, a reliable marker for angiogenesis in various solid neoplasms (19). We also find that increased TF expression in pancreatic cancer specimens may correlate with subsequent symptomatic venous thromboembolism.

### Materials and Methods

**Patient characteristics.** Formalin-fixed, paraffin-embedded tumor tissue was collected retrospectively from (a) 40 patients with PanINs at Johns Hopkins University, (b) 70 patients with resected IPMNs at Johns Hopkins University (n = 64) and University of Rochester (n = 6), (c) 138 patients who underwent pancreatic resection for pancreatic ductal adenocarcinoma at University of Rochester (n = 79) and Fredmerit Memorial Lutheran Hospital/Medical College of Wisconsin (n = 59) between January 1994 and February 2002, and (d) 8 patients with metastatic pancreatic cancer that were enrolled on a clinical study at the University of Rochester. Distal bile duct, ampullary, and duodenal adenocarcinomas as well as other pancreatic neoplasms and patients who received preoperative therapy were excluded from this study. All pathology reports were reviewed, and tumor-node-metastasis stage and grade were assigned using the American Joint Committee on Cancer criteria (20). Surgical margins were considered positive if infiltrating adenocarcinoma was present at the uncinate process, retroperitoneal soft tissue, or final pancreatic neck margin. Twelve adenocarcinomas were uninterpretable for one or more of the immunohistochemical stains and were excluded. Four pancreatic cancer patients died within 30 days of surgery from perioperative complications and were excluded from survival analysis. Patients for whom follow-up regarding venous thromboembolism events was not available (n = 84), those with a prior history of venous thromboembolism or on chronic anticoagulation (n = 5), were excluded from analysis for venous thromboembolism outcomes.

Clinical information was obtained from a review of hospital and physician charts or from the respective hospital tumor registry. Patient follow-up was obtained through the review of hospital and physician records, direct patient contact, and the Social Security Death Index. This research protocol was reviewed and approved by Institutional Review Boards of the participating institutions.

### Construction of pancreatic tissue microarrays.

H&E-stained standard slides were reviewed from each section of pancreas, and a representative tumor region and the corresponding formalin-fixed paraffin tissue block were selected for use in the tissue microarray (21, 22). Two discrete histomorphologically representative regions were selected from each tissue block. Three 0.6-mm tissue cores were taken from each region using an automated custom-built tissue arrayer at the National Human Genome Research Institute and transferred to three individual recipient blocks at defined array coordinates (six cores per tumor). In addition, tissue cores were also selected from histologically normal pancreatic acini, pancreatic ducts, and duodenal mucosa for use as controls. Five-micrometer sections were cut from each recipient tissue microarray block using an adhesive-coated tape system (Instrumedics; ref. 21). Separate tissue microarrays were similarly prepared for PanINs and IPMNs at Johns Hopkins University.

**Immunohistochemistry.** Tissue sections from the pancreatic cancer tissue microarray were deparaffinized, rehydrated through graded alcohols, and washed with TBS. Expression of TF, VEGF, and CD31 was determined using the streptavidin-biotin-peroxidase complex method as reported previously, with antigen retrieval (22, 23). Antibodies used for immunostaining included an immunopurified polyclonal IgG (anti-sTF; 0.5 mg/mL) against residues 1 to 218 of the extracellular domain of human TF (24), rabbit polyclonal antibody to VEGF (1:50 dilution; Zymed Laboratories), and monoclonal anti-CD31 (1:120 dilution; Neomarkers, Inc.). The secondary antibody for CD31 was biotinylated rabbit anti-mouse antibody (1:200 dilution; DAKO). Labeling for TF and VEGF was completed using DAKO Rabbit Envision Plus kit (DAKO). The sections were counterstained with a modified Mayer hematoxylin followed by 10 dips in 3% ammonia water.

Lung parenchyma, an invasive ductal breast cancer with known VEGF positivity, and placental tissue with known CD31 positivity served as positive controls for TF, VEGF, and CD31, respectively. Negative controls were done by replacing the primary antibody by normal serum.

All sections were reviewed independently by pathologists blinded to all clinical and pathologic information (C.K.R. and Y.C.H.). TF expression was graded on a scale from 0 to 3. A grade of 0 represented no stain uptake by malignant cells. Neoplastic cells were considered positive when they revealed cytoplasmic or membrane staining of at least moderate intensity and were graded as follows: grade 1, 1% to 33% positive cells; grade 2, 34% to 66% positive cells; and grade 3, >66% cells positive. Normal ductal structures admixed in some tumor samples did not stain and served as internal negative controls. VEGF expression was considered positive when at least one of the pancreatic tissue cores contained cytoplasmatic VEGF staining of moderate or greater intensity in >5% of pancreatic cancer cells.

CD31 staining was used to determine intratumoral microvessel density as described previously (23). Large and small microvessels as well as single brown immunostained endothelial cells were included in the microvessel count as previously recommended in consensus guidelines (19, 25). An individual microvessel density was calculated from each pancreatic cancer tissue core in the microarray, and six cores were evaluated for each tumor. The microvessel density for each tumor was defined as the mean value from all interpretable cores.

**Statistical analysis.** The association between immunohistochemical expression of TF, VEGF, microvessel density, and individual clinical and pathologic variables (age, gender, race, tumor size, pathologic stage, pathologic grade, margin status, operative procedure, and microvessel density) was assessed using Fisher’s exact test or χ² (categorical variables) or Wilcoxon’s rank-sum test (continuous variables). The associations between individual clinical and pathologic variables (age, gender, race, T stage, N stage, pathologic stage, pathologic grade, margin status, operative procedure, microvessel density, and the expression of TF and VEGF) and survival were assessed using the Cox proportional hazards regression model. A stepwise variable selection procedure was used to build a Cox proportional hazards multiple regression model for time to death; a significance level of 0.20 was used to determine
whether a variable could be entered into or removed from the regression model. Associations were quantified using hazard ratios and their 95% confidence intervals. Survival time was determined as the time from resection to death. For survivors, survival times were censored on the last date that patients were known to be alive. Survival probabilities were estimated using the method of Kaplan and Meier. Log-rank tests were used to compare survival curves among the various subgroups of patients. All statistical tests were two-tailed.

Results

Patient characteristics. Forty patients with PanIN, 70 patients with IPMN, and 122 patients with infiltrating pancreatic adenocarcinoma were evaluable for immunohistochemistry. Mean age of the pancreatic adenocarcinoma population was 67 ± 11 years. Sixty-six (54%) patients were male, and 56 (46%) patients were female. A majority of patients (54%) had stage I or II cancers. Margins of resection were involved by tumor in 21% of patients. Data regarding adjuvant therapy were available for 109 patients; of these, 79% received some form of adjuvant therapy (usually, 5-fluorouracil–based chemoradiation).

Immunohistochemical analysis of TF expression. TF expression occurred primarily in neoplastic cells but not in adjacent normal ductal cells (Fig. 1). Thirty-one of 40 (77%) PanINs expressed TF. Of these, 18 (45%) had grade 1 expression, 9 (22.5%) had grade 2 expression, and 4 (10%) had grade 3 expression. Similarly, 64 of 70 IPMNs (91%) expressed TF. Of these, 27 (38.6%) had grade 1 expression, 26 (37.1%) had grade 2 expression, and 11 (15.7%) had grade 3 expression. Morphologically, ducts with higher degrees of dysplasia showed higher grades of TF expression. Among resected or metastatic pancreatic cancers, 116 of 130 (89%) evaluable specimens expressed TF. This was classified as high (grade 2 or 3) or low (grade 0 or 1), based on the median score for the entire sample. Seventy patients (54%) were found to have high TF expression, and 60 patients (46%) had low or no TF expression. Representative specimens of grade 1 and 3 TF expression in pancreatic cancer are shown in Supplementary Fig. S1.

TF expression and clinicopathologic characteristics in resected pancreatic cancer. High expression of TF was associated with several adverse clinical and pathologic characteristics in patients with resected pancreatic cancer (Table 1). Carcinomas with high TF expression were larger (3.1 versus 2.8 cm, \( P = 0.04 \)), more likely to be poorly differentiated (45% versus 28%, \( P = 0.07 \)), and more likely to have positive resection margins (30% versus 11%, \( P = 0.0085 \)). Patients with high TF expression were also more likely to be older (\( P = 0.05 \)). However, stage distribution was similar among the high and low TF-expressing carcinomas and a similar proportion of patients in both populations received adjuvant therapy.

TF expression and angiogenesis in resected pancreatic cancer. We correlated the expression of TF with subsequent development of symptomatic venous thromboembolism in a subgroup of 41 patients with resected or metastatic disease for whom follow-up regarding venous thromboembolism was available (Fig. 2). Of these, six patients subsequently developed objectively confirmed venous thromboembolism, including four patients with lower extremity DVT, one patient with an upper extremity DVT, and one patient with both a lower extremity DVT and a pulmonary embolism. Venous thromboembolism was more common (\( P = 0.04 \)) among patients with high TF-expressing carcinomas (5 of 19, 26.3%) than among those with low TF-expressing carcinomas (1 of 22, 4.5%).

Survival analysis. At the time of data analysis, resected patients had been followed for a median of 16 months (range, 51 days to 93 months). Five-year actuarial survival for patients with resected pancreatic cancer was 15%. Median survival in patients with low TF-expressing carcinomas was higher at 17.9 months compared with 12.6 months in those with high TF-expressing carcinomas, but this difference was not statistically significant (hazard ratio, 2.06; 95% confidence interval, 0.74-5.7; \( P = 0.16 \)). Multiple regression analysis was done using a Cox proportional hazards model to determine variables independently predictive of survival in patients with resected pancreatic cancer. Nodal stage, gender, histologic grade, margin status, the use of adjuvant therapy, TF and VEGF expression, and microvessel density were included in the stepwise model selection process. The absence of lymph node metastases (hazard ratio, 0.55; 95% confidence interval, 0.36-0.85; \( P = 0.007 \)) and the use of adjuvant therapy (hazard ratio, 0.46; 95% confidence interval, 0.28-0.78; \( P = 0.004 \)) were the only variables associated with a decreased risk of death in resected pancreatic cancer in this multivariate analysis.

Discussion

We characterized the expression of TF across a spectrum of normal pancreas, noninvasive precursor lesions, and invasive pancreatic cancer using immunohistochemistry. Normal pancreas did not express TF. In contrast, TF expression was observed with varying intensity in a large majority of both noninvasive and invasive pancreatic neoplasms. TF expression in resected pancreatic cancers correlated with expression of VEGF and increased microvessel density, suggesting a linkage with angiogenesis. Finally, in a subgroup of the study population, higher grades of TF expression in pancreatic cancer correlated with subsequent venous thromboembolism, suggesting an important role for TF in the pathogenesis of cancer-associated thrombosis.

PanINs are microscopic noninvasive intraductal neoplasms that harbor many of the genetic alterations observed in invasive pancreatic cancer (26). PanINs are believed to be precursors to invasive pancreatic cancer. IPMNs are morphologically distinct noninvasive macroscopic neoplasms that are also thought to be precursors to invasive pancreatic cancer, with ~30% of cases observed in association with invasive cancer (27). In our analysis, 77% of PanINs and 91% of IPMNs expressed TF, and ducts with higher grades of dysplasia showed higher grades of TF expression. This suggests that TF expression is an important early event in malignant transformation of the pancreas.
Elegant *in vitro* and *in vivo* animal studies conducted by Yu et al. show that in human colorectal cancer cells, TF expression is controlled by activation of the KRAS oncogene and inactivation of the TP53 tumor suppressor gene (9), common events in pancreatic cancer pathogenesis (28). It is possible, therefore, that TF expression in pancreatic cancer is also regulated by mutations in KRAS and TP53. Further studies to investigate the regulation of TF expression in PanINs, IPMNs, and pancreatic adenocarcinoma are necessary.

The high prevalence of TF expression in both noninvasive and invasive pancreatic neoplasms observed in our study suggests a potential role for TF in tumorigenesis, possibly through regulation of angiogenesis. Recent evidence suggests that TF-mediated signaling may play an important role in the regulation of angiogenesis (reviewed in ref. 29). Gene silencing of TF by small interfering RNAs in animal studies results in a 3-fold reduction in angiogenesis and increased levels of the antiangiogenic molecules thrombospondin-1 and thrombospondin-2 without affecting the mitogenic properties of neoplastic cells themselves (9). TF activation of the coagulation cascade results in the generation of thrombin, which in turn activates protease-activated receptor signaling leading to a variety of proangiogenic effects (6). In our study, we found that TF expression strongly correlated with both VEGF expression and increased microvessel density. We have previously published on the significance of DPC4 as an antiangiogenic molecule in resected pancreatic cancer (23). However, we found no correlation between TF expression and DPC4 expression (data not shown). Overall, our data are consistent with prior reports suggesting that the up-regulation of VEGF by TF is an important mechanism by which TF regulates angiogenesis (7, 9). However, our study could only establish a correlation and cannot directly evaluate the underlying mechanisms. Of note, recent reports suggest that VEGF may...
also serve as an autocrine factor for tumor cells and enhance tumor cell migration and invasion (30, 31). We indeed observed an association of TF with adverse clinicopathologic characteristics, consistent with prior reports (16, 17), although the association with worsened survival did not achieve statistical significance.

Pancreatic cancer has one of the highest rates of venous thromboembolism of all solid neoplasms (4). The mechanism underlying this association is incompletely understood, but TF expression by tumor cells may be partly responsible. In a case report, pancreatic cancer complicated by disseminated intravascular coagulation was associated with increased production of TF (32). In our analysis, higher grades of TF expression in tumor cells were associated with a nearly 4-fold increase in venous thromboembolism. It is possible that TF from tumor cells is shed into the circulation, thereby contributing to systemic thrombogenicity. Levels of plasma TF have been noted to be elevated in cancer patients, and experimental studies suggest that circulating TF may contribute to thrombus formation (33, 34). However, given the limited number of patients in our study for whom data regarding venous thromboembolism were available, confirmatory prospective studies are needed.

### Table 1. Clinical and pathologic characteristics of 122 patients with resected pancreatic cancer evaluated for TF expression

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
<th>High TF expression (%)</th>
<th>Low TF expression (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>122</td>
<td>66 (54)</td>
<td>56 (46)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>67 ± 11</td>
<td>68 ± 11</td>
<td>65 ± 12</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (54)</td>
<td>34 (52)</td>
<td>32 (48)</td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>56 (46)</td>
<td>32 (57)</td>
<td>24 (43)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9 ± 1.0</td>
<td></td>
<td>3.1 ± 0.9</td>
<td>2.8 ± 1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 and T2</td>
<td>51 (44)</td>
<td>26 (41)</td>
<td>25 (46)</td>
<td>0.58</td>
</tr>
<tr>
<td>T3 and T4</td>
<td>66 (56)</td>
<td>37 (59)</td>
<td>29 (54)</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>66 (54)</td>
<td>35 (53)</td>
<td>31 (56)</td>
<td>0.71</td>
</tr>
<tr>
<td>N1</td>
<td>55 (46)</td>
<td>31 (47)</td>
<td>24 (44)</td>
<td></td>
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<td>Tumor stage</td>
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<tr>
<td>I and II</td>
<td>65 (54)</td>
<td>34 (52)</td>
<td>31 (56)</td>
<td>0.53</td>
</tr>
<tr>
<td>III and IV</td>
<td>56 (46)</td>
<td>32 (48)</td>
<td>24 (44)</td>
<td></td>
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<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Poor</td>
<td>44 (37)</td>
<td>29 (45)</td>
<td>15 (28)</td>
<td>0.07</td>
</tr>
<tr>
<td>Moderate</td>
<td>50 (42)</td>
<td>26 (43)</td>
<td>24 (44)</td>
<td></td>
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<tr>
<td>Well</td>
<td>24 (20)</td>
<td>9 (14)</td>
<td>15 (28)</td>
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<tr>
<td>Margin status</td>
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<tr>
<td>Negative</td>
<td>96 (79)</td>
<td>46 (70)</td>
<td>50 (89)</td>
<td>0.0085</td>
</tr>
<tr>
<td>Positive</td>
<td>26 (21)</td>
<td>20 (30)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Operative procedure</td>
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<td></td>
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<tr>
<td>Pancreatoduodenectomy</td>
<td>107 (88)</td>
<td>57 (88)</td>
<td>50 (89)</td>
<td>0.58</td>
</tr>
<tr>
<td>Total pancreatectomy</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
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<tr>
<td>Distal pancreatectomy</td>
<td>11 (9)</td>
<td>7 (11)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>86 (79)</td>
<td>43 (75)</td>
<td>43 (83)</td>
<td>0.35</td>
</tr>
<tr>
<td>No</td>
<td>23 (21)</td>
<td>14 (25)</td>
<td>9 (17)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Data are presented as n (%) or as mean ± SD.

### Table 2. Correlation of TF expression with the expression of other angiogenesis variables in resected pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>High TF expression</th>
<th>Low TF expression</th>
<th>P</th>
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<tbody>
<tr>
<td>VEGF expression</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive</td>
<td>53</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Microvessel density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 per tissue core</td>
<td>27</td>
<td>33</td>
<td>0.047</td>
</tr>
<tr>
<td>&gt;6 per tissue core</td>
<td>39</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
<td>6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Fig. 2. TF expression and symptomatic venous thromboembolism (VTE) in pancreatic cancer. Pancreatic cancer patients with low TF expression had a venous thromboembolism rate of 4.5%, and this was elevated 4-fold to 26.3% in patients with high TF expression (P = 0.04).
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studies are necessary. If confirmed in a prospective setting, our finding suggests that TF expression by neoplastic cells or levels of circulating TF could be used as predictive biomarkers for cancer-associated venous thromboembolism in this and other cancers.

Our study had limitations. Although efforts were made to enroll consecutive patients, the analysis was retrospective. In addition, the use of a tissue microarray could have underestimated the true frequency, particularly in patients with focal expression of TF. The use of automated analysis of tissue arrays is increasing in frequency and has several advantages, including a more objective analysis. However, our pathologists were blinded to specimen identification. Tissue specimen collection occurred at multiple sites, and there may have been variations in time of tissue procurement and fixation. However, VEGF stain intensity is only minimally affected by induced tissue ischemia when compared with other markers (35). In an analysis of over 100 hepatic tissue samples obtained from various sources, we have found consistent staining patterns for TF, suggesting a low hypoxic variability response for TF as well. Detailed follow-up regarding the presence of venous thromboembolism was available only for a subgroup of patients seen at a single institution and not for the entire study population, and in this regard, our data should be regarded as preliminary until confirmed prospectively in a larger sample.

A variety of TF-directed therapeutic agents are currently in various stages of drug development and have been shown to be safe, although there is a concern regarding bleeding risk. These include TF antagonists such as recombinant TF pathway inhibitor and anti-TF antibodies (36, 37). In addition, other drugs have been shown to indirectly affect TF expression, including vitamin D3, retinoids, and heparins (38–40). Some of these agents have shown antitumor and antiangiogenic effects in preclinical studies (41). TF represents an attractive and novel therapeutic target in pancreatic cancer, and anti-TF approaches deserve further study in this setting.

References


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