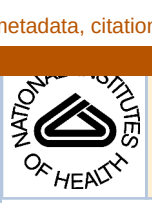
View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Carolina Digital Repository



NIH Public Access

Author Manuscript

Semin Thromb Hemost. Author manuscript; available in PMC 2010 April 1.

Published in final edited form as:

Semin Thromb Hemost. 2008 March ; 34(2): 182–186. doi:10.1055/s-2008-1079258.

Use of Mouse Models to Study the Role of Tissue Factor in Tumor Biology

Rafal Pawlinski, Ph.D.[1] and **Nigel Mackman, Ph.D.**[2]

[1] Department of Immunology, The Scripps Research Institute, La Jolla, California

[2] Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

Abstract

Tissue factor (TF) is the primary initiator of the coagulation cascade and plays an essential role in hemostasis. TF also contributes to many diseases, including cancer. The correlation between thrombosis and cancer has been recognized for more than a century. However, it is only in the past two decades that we have begun to understand the role of TF in tumor biology. TF expression is upregulated on both tumor and host cells in cancer patients as well as in the circulation. Clinical observations indicate a direct correlation between the levels of tumor cell TF expression and poor prognosis for cancer patients. The role of TF in tumor biology has been extensively studied using various mouse tumor models. It has been demonstrated that tumor cell TF contributes to tumor metastasis, growth, and angiogenesis. The role of host TF in tumor progression is less clear. Recently developed mouse models with altered levels of TF may be useful in further analysis of the role of host cell TF in cancer.

Keywords

Tissue factor; tumor; mouse models; coagulation

Tissue factor (TF) is a 47-kDa transmembrane receptor that binds plasma factor VII/VIIa (FVII/FVIIa).[1] This TF:FVIIa bimolecular complex initiates blood coagulation by activating both factor X (FX) and factor IX (FIX), which leads to the generation of thrombin, fibrin deposition, and platelet activation.[1] TF expression by perivascular cells provides a hemostatic barrier to limit hemorrhage after vessel injury.[2] In addition to its essential role in hemostasis, TF activates cell signaling.[3] The formation of the TF:FVIIa and TF:FVIIa:FXa complexes leads to cleavage of protease-activated receptors (PARs) at the cell surface. Specifically, TF:FVIIa activates PAR-2, whereas TF:FVIIa:FXa can activate both PAR-1 and PAR-2,[3] which both lead to the recruitment of G proteins and the activation of various intracellular signaling pathways. For example, it has been shown that the TF:FVIIa–PAR-2 pathway induces expression of the proangiogenic cytokine IL-8 in tumor cells[4] and also contributes to retinal neoangiogenesis.[5] In addition, the TF cytoplasmic domain can regulate the p38 mitogen-activated kinase and extracellular signal-regulated kinase1/2 and the rac pathways,[6] as well as suppress integrin-mediated migration of cells.[7]

Address for correspondence and reprint requests: Nigel Mackman, Ph.D., Division of Hematology/Oncology, Department of Medicine, University of North Carolina, 917 Mary Ellen Jones Bldg, 98 Manning Drive, CB#7035, Chapel Hill, NC 27599 (nigel_mackman@med.unc.edu).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Increased intravascular TF expression is observed in a variety of diseases including cancers.[2,8] TF is expressed by the tumor cells themselves and is induced in host cells, such as monocytes, macrophages, and endothelial cells.[8] This may contribute to the prothrombotic state that is associated with cancer.[9] TF is overexpressed in many types of human cancers, and clinical studies have shown a correlation between the levels of TF expression and poor prognosis.[10–13] Several studies using different mouse tumor models demonstrated that TF plays a key role in tumor biology. In this review, we will summarize the current knowledge regarding the role of TF in tumor growth, angiogenesis, and metastasis, focusing on the data obtained from mouse models. In addition, we will discuss the generation of new mouse lines, with modified TF expression, and how these mice could be used to further elucidate the role of TF in tumor biology.

MOUSE TUMOR MODELS

Subcutaneous xenograft mouse models have been used for almost 40 years.[14,15] Because this model is relatively easy to establish, it has become very popular for use to study the role of different proteins in tumor biology. Human tumor cells cultured in vitro are injected into subcutaneous tissue of immunodeficient mice, which prevents the rejection of foreign cells. Severe combined immunodeficient (SCID) mice lack the ability to make T and B lymphocytes, whereas mutation in nude mice results in the reduction in the number of T cells.[16,17] However, there are several limitations with the xenograft model. These include the artificial nature of tumor cell lines passaged in culture for many generations, species differences between tumor and stromal cells, the subcutaneous location of the xenograft, and the lack of an adaptive immune response in the host. Some of these concerns can be overcome by using immunocompetent allograft models. However, given the heterogenous nature of cancers, the relevance of studying mouse tumors can be questioned. For some types of cancers, subcutaneous injection of tumor cells can be replaced with more relevant orthotopic injection, such as injection of breast cancer cells into the mammary pad of the mice. More recently, genetically engineered mouse (GEM) tumor models have been developed. In these models, tumor development is driven by expression of oncogenes or loss of tumor suppressors. The first generation of these GEM models used transgenic and standard gene targeting (knock-in or knockout) technology. More recently, conditional strategies have been used to generate mice with controlled gene expression in both a tissue- and a time-dependent manner. Although GEM models have their own limitations, their main advantage is the ability to drive tumor development with defined genetic changes in syngeneic tumor-host compartments. More detailed information about the pros and cons of different mouse cancer models can be found in recent reviews focusing on this subject.[18–20]

ROLE OF TF IN TUMOR GROWTH AND TUMOR ANGIOGENESIS

During the past 15 years, several studies have provided evidence that supports the importance of TF in tumor growth. Zhang and colleagues were the first to show a contribution of TF to tumor growth and angiogenesis in mice. Mouse fibrosarcoma cells overexpressing TF developed larger tumors compared with control cells.[21] Tumor size correlated with the amount of vascular endothelial cell growth factor (VEGF) secreted by the cells and the vascular density within tumors, suggesting that TF expression contributes to tumor growth by promoting angiogenesis.[21] Similar results have been observed in studies using human pancreatic adenocarcinoma, melanoma, and colorectal carcinoma cell lines.[22–24] One study indicated that the TF cytoplasmic domain regulates VEGF production and angiogenesis.[22] Blocking TF:FVIIa activity with either tissue factor pathway inhibitor (TFPI) or nematode anticoagulant protein NAPc2 inhibited the growth of mouse Lewis lung carcinoma in mice, whereas NAP5, a specific inhibitor of FXa, did not show any antitumor effects.[25] Based on these results, it has been proposed that the TF:FVIIa complex contributes to tumor growth by activating PAR-2,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

independent of downstream coagulation proteases FXa and thrombin.[25] However, a possible contribution of TF to tumor growth via FXa and thrombin generation has been demonstrated by Anderson and colleagues. In their experiments, a humanized anti-TF antibody CNTO 859, which acts primarily as a competitive inhibitor of FX binding to the TF:FVIIa complex preventing the generation of FXa, dramatically reduced tumor growth in an orthotopic breast cancer model.[26] Recently, it has been demonstrated that TF-dependent signaling contributes to tumor growth. An antibody (10H100) that selectively blocks TF:FVIIa signaling significantly reduced tumor growth.[27] In addition, an inhibitory anti–PAR-2 but not an inhibitory anti–PAR-1 antibody reduced tumor growth.[27] These results suggest that selective blockade of TF:FVIIa–PAR-2 signaling without interfering with TF:FVIIa procoagulant function may provide a novel strategy to reduce tumor growth in cancer patients without impairing hemostasis.

In contrast, there are some studies indicating that TF is not required for tumor growth. First, mouse teratomas and teratocarcinomas derived from $TF^{+/+}$, $TF^{+/-}$, and $TF^{-/-}$ embryos generated similar-sized tumors in immunodeficient SCID mice.[28] Another publication demonstrated that increasing TF expression in human melanoma cells did not increase VEGF expression or promote growth and vascularization of tumors.[29] Most recently, it was shown that expression of either wild-type TF or a truncated form of TF lacking the cytoplasmic domain in $TF^{-/-}$ fibroblastoma cells did not affect tumor growth.[30] Taking together, these studies indicate that TF plays an important role in tumor growth and tumor-related angiogenesis in many but not all tumors, which probably reflects the heterogeneity of tumor cells.

ROLE OF TF IN TUMOR METASTASIS

Tumor metastasis is a multistep process that consists of intravasation of tumor cells from the primary tumor into the circulation, survival in the circulation, arrest and extravasation from the microcirculation, and finally tumor growth at a distal site. SCID or nude mice injected intravenously with human tumor cells are widely used as experimental metastasis models. Metastatic cells have been found to express higher levels of TF compared with nonmetastatic cells, suggesting that TF may play a direct role in tumor cell metastasis.[31] Mueller and colleagues showed that inhibition of TF on two human melanoma cell lines significantly reduced lung metastasis in SCID mice.[31] Because the antibody used to block TF (5G9) specifically recognized only human TF, it could be concluded that tumor cell–derived TF is sufficient to support metastasis. A subsequent study showed that downregulation of TF expression by delivery of a small interfering RNA in human melanoma LOX-L cells reduced pulmonary metastasis in nude mice.[32] Most recently, Ngo and colleagues demonstrated that a humanized anti-TF monoclonal antibody (CNTO 859) efficiently inhibited experimental lung metastasis of human breast carcinoma cells in SCID mice.[26] Both proteolytic activity of the TF:FVIIa complex and the phosphorylation of TF cytoplasmic domain is required for full metastatic properties of the tumor cells in SCID mice.[33] The importance of TF cytoplasmic domain in metastasis was independently confirmed by Bromberg and colleagues.[29]

Tumor metastasis also has been studied using immunocompetent mice injected with mouse tumor cells. Consistent with the data obtained from the mouse xenograft model using immunodeficient mice, blocking TF activity on mouse melanoma cells B16F10 with anti-mouse TF antibody or reducing TF expression in these cells using a small interfering RNA significantly reduced lung metatstasis.[34,35] In addition, TFPI also significantly reduced experimental lung metastasis of B16F10 cells.[36] Furthermore, C57Bl/6-derived fibrosarcoma cells that were genetically incapable of TF expression showed no metastatic potential compared with the high metastatic abilities of fibrosarcoma cells expressing TF.[30]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Data obtained from both immunodeficient and immunocompetent mouse models strongly suggest that tumor cell TF contributes to tumor dissemination via a mechanism involving thrombin generation. T his conclusion is supported by multiple observations demonstrating that thrombin-mediated proteolysis, as well as fibrinogen- and PAR-mediated platelet activation, play roles in tumor metastasis.[30,37–39] However, the importance of the TF cytoplasmic domain in metastasis depends on the models. In contrast with the contribution of the cytoplasmic domain of TF to metastasis in xenograft models using immunodeficient mice, a recent publication by Palumbo and colleagues showed that TF expressed by mouse-derived fibrosarcoma cells supports metastasis through mechanisms independent of the cytoplasmic domain of TF but dependent on circulating hemostatic factors and platelet activation.[30] The authors proposed that multiple experimental differences between their and previous experiments may explain the discrepancy.

ROLE OF TUMOR-DERIVED VERSUS HOST-DERIVED TF IN TUMOR PROGRESSION

In contrast WITH the abundant literature focusing on the role of tumor cell–derived TF, the role of TF expressed by host cells in tumor progression has not been explored extensively. This is probably due to the fact that the absence of TF leads to intrauterine lethality[40] and that until recently there were no inhibitory anti-mouse TF antibodies.[34] It has been proposed that TF expressed on the tumor cells or endothelial cells, in patients with invasive breast cancer, can regulate tumor angiogenesis.[41] One study demonstrated that blocking the host TF with anti-mouse TF antibody had no effect on the growth of human mammary carcinomas in immunodeficient mice.[42] However, in the same model, combined therapy of anti-mouse and anti-human TF antibodies inhibited tumor growth more efficiently than by using only an anti-human TF antibody treatment.[42] These results would suggest that the host TF plays some role in tumor growth.

In the past few years, our laboratory has generated several mouse models with altered TF expression. Those models include low TF mice that express very low levels of human TF (1% of wild-type TF levels) in the absence of mouse TF.[43] In collaboration with Janusz Rak, we used low TF mice to study the role of host TF in tumor growth. Mouse tumor cell lines were highly tumorigenic in both wild-type and low-TF mice. However, injection of TF-deficient cells into low-TF mice resulted in almost complete inhibition of tumor growth.[8]

A second line of mice that we have generated contained a TF gene flanked by loxP site—so-called TF floxed mice.[44] These mice can be bred with mice expressing the Cre recombinase in different cell types to determine the role of TF derived from different host cells in tumor biology. We further investigated the role of host TF expressed by different cell types in tumor growth and metastasis using TF floxed/LysMCre (specific deletion of TF in mature neutrophils and monocytes/macrophages) and TF floxed/Tie-2Cre mice (endothelial cell and hematopoietic cell specific deletion). The reduction of TF expression in macrophages isolated from both TF floxed/LysMCre and TF floxed/Tie-2Cre mice was ~95% (Pawlinski and Mackman, unpublished data). Our preliminary results indicate that neither LysMCre-driven nor Tie-2Cre-driven deletion of TF had an effect on tumor growth caused by subcutaneous injection of mouse Lewis lung carcinoma cells (Zhang, Pawlinski, Mackman, and Liu, unpublished data). We also did not see significant differences between these two mouse strains and littermate controls in a lung metastasis model using mouse Lewis lung carcinoma cells (Zhang, Pawlinski, Mackman, and Liu, unpublished data). More detailed studies, involving different mouse tumor cell lines, are necessary to fully elucidate the role of host TF in tumor biology.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In addition to investigating the role of host TF in tumor biology using allograft approach, TF floxed mice expressing appropriate Cre recombinase can be crossed with various GEM mouse tumor models allowing in vivo manipulation of TF expression in specific tumor or stroma cells. Alternatively, a similar breeding strategy can be used to generate primary mouse tumor cell lines containing the TF floxed allele. After in vitro transfection with a vector expressing the Cre recombinase, tumor cell lines lacking TF can be established and used in allograft tumor models. Both mouse models with altered levels of TF, as well as recently developed mouse strains expressing normal levels of human TF,[44,45] may be very useful to further explore the role of host versus tumor cell TF in tumor biology. In addition, these new mouse models can be used to study the role of TF in cancer-associated thrombosis.

Acknowledgments

We would like to acknowledge Dr. Rak and Dr. Liu for the collaborative studies and the National Institutes of Health for the funding for this study.

References

1. Mackman N, Tilley RE, Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscler Thromb Vasc Biol 2007;27:1687–1693. [PubMed: 17556654]
2. Pawlinski R, Pedersen B, Erlich J, Mackman N. Role of tissue factor in haemostasis, thrombosis, angiogenesis and inflammation: lessons from low tissue factor mice. Thromb Haemost 2004;92:444–450. [PubMed: 15351839]
3. Ruf W. Tissue factor and PAR signaling in tumor progression. Thromb Res 2007;120(Suppl 2):S7–S12. [PubMed: 18023716]
4. Hjortoe GM, Petersen LC, Albrektsen T, et al. Tissue factor-factor VIIa-specific up-regulation of IL-8 expression in MDA-MB-231 cells is mediated by PAR-2 and results in increased cell migration. Blood 2004;103:3029–3037. [PubMed: 15070680]
5. Belting M, Dorrell MI, Sandgren S, et al. Regulation of angiogenesis by tissue factor cytoplasmic domain signaling. Nat Med 2004;10:502–509. [PubMed: 15098027]
6. Ahamed J, Niessen F, Kurokawa T, et al. Regulation of macrophage procoagulant responses by the tissue factor cytoplasmic domain in endotoxemia. Blood 2007;109:5251–5259. [PubMed: 17332247]
7. Dorfleutner A, Hintermann E, Tarui T, Takada Y, Ruf W. Cross-talk of integrin alpha3beta1 and tissue factor in cell migration. Mol Biol Cell 2004;15:4416–4425. [PubMed: 15254262]
8. Milsom C, Yu J, May L, et al. The role of tumor-and host-related tissue factor pools in oncogene-driven tumor progression. Thromb Res 2007;120(Suppl 2):S82–S91. [PubMed: 18023719]
9. Rickles FR. Mechanisms of cancer-induced thrombosis in cancer. Pathophysiol Haemost Thromb 2006;35:103–110. [PubMed: 16855354]
10. Shigemori C, Wada H, Matsumoto K, et al. Tissue factor expression and metastatic potential of colorectal cancer. Thromb Haemost 1998;80:894–898. [PubMed: 9869156]
11. Ueno T, Toi M, Koike M, Nakamura S, Tominaga T. Tissue factor expression in breast cancer tissues: its correlation with prognosis and plasma concentration. Br J Cancer 2000;83:164–170. [PubMed: 10901365]
12. Poon RT, Lau CP, Ho JW, et al. Tissue factor expression correlates with tumor angiogenesis and invasiveness in human hepatocellular carcinoma. Clin Cancer Res 2003;9:5339–5345. [PubMed: 14614019]
13. Akashi T, Furuya Y, Ohta S, Fuse H. Tissue factor expression and prognosis in patients with metastatic prostate cancer. Urology 2003;62:1078–1082. [PubMed: 14665359]
14. Giovanella BC, Yim SO, Stehlin JS, Williams LJ Jr. Development of invasive tumors in the “nude” mouse after injection of cultured human melanoma cells. J Natl Cancer Inst 1972;48:1531–1533. [PubMed: 5030962]
15. Shimosato Y, Kameya T, Nagai K, et al. Transplantation of human tumors in nude mice. J Natl Cancer Inst 1976;56:1251–1260. [PubMed: 186624]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

16. Bosma GC, Custer RP, Bosma MJ. A severe combined immunodeficiency mutation in the mouse. Nature 1983;301:527–530. [PubMed: 6823332]
17. Nehls M, Pfeifer D, Schorpp M, Hedrich H, Boehm T. New member of the winged-helix protein family disrupted in mouse and rat nude mutations. Nature 1994;372:103–107. [PubMed: 7969402]
18. Kung AL. Practices and pitfalls of mouse cancer models in drug discovery. Adv Cancer Res 2007;96:191–212. [PubMed: 17161681]
19. Sharpless NE, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. Nature Reviews Drug Discov 2006;5:741–754.
20. Van Dyke T, Jacks T. Cancer modeling in the modern era: progress and challenges. Cell 2002;108:135–144. [PubMed: 11832204]
21. Zhang Y, Deng Y, Luther T, et al. Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice. J Clin Invest 1994;94:1320–1327. [PubMed: 7521887]
22. Abe K, Shoji M, Chen J, et al. Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor. Proc Natl Acad Sci U S A 1999;96:8663–8668. [PubMed: 10411932]
23. Kakkar AK, Chinswangwatanakul V, Lemoine NR, Tebbutt S, Williamson RC. Role of tissue factor expression on tumour cell invasion and growth of experimental pancreatic adenocarcinoma. Br J Surg 1999;86:890–894. [PubMed: 10417560]
24. Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. Blood 2005;105:1734–1741. [PubMed: 15494427]
25. Hembrough TA, Swartz GM, Papathanassiu A, et al. Tissue factor/factor VIIa inhibitors block angiogenesis and tumor growth through a nonhemostatic mechanism. Cancer Res 2003;63:2997–3000. [PubMed: 12782609]
26. Ngo CV, Picha K, McCabe F, et al. CNTO 859, a humanized anti-tissue factor monoclonal antibody, is a potent inhibitor of breast cancer metastasis and tumor growth in xenograft models. Int J Cancer 2007;120:1261–1267. [PubMed: 17192924]
27. Versteeg HH, Schaffner F, Kerver M, et al. Inhibition of tissue factor signaling suppresses tumor growth. Blood 2008;111:190–199. [PubMed: 17901245]
28. Toomey JR, Kratzer KE, Lasky NM, Broze GJ Jr. Effect of tissue factor deficiency on mouse and tumor development. Proc Natl Acad Sci U S A 1997;94:6922–6926. [PubMed: 9192667]
29. Bromberg ME, Sundaram R, Homer RJ, Garen A, Konigsberg WH. Role of tissue factor in metastasis: functions of the cytoplasmic and extracellular domains of the molecule. Thromb Haemost 1999;82:88–92. [PubMed: 10456459]
30. Palumbo JS, Talmage KE, Massari JV, et al. Tumor cell-associated tissue factor and circulating hemostatic factors cooperate to increase metastatic potential through natural killer cell-dependent and-independent mechanisms. Blood 2007;110:133–141. [PubMed: 17371949]
31. Mueller BM, Reisfeld RA, Edgington TS, Ruf W. Expression of tissue factor by melanoma cells promotes efficient hematogenous metastasis. Proc Natl Acad Sci U S A 1992;89:11832–11836. [PubMed: 1465406]
32. Wang X, Wang M, Amarzguioui M, et al. Downregulation of tissue factor by RNA interference in human melanoma LOX-L cells reduces pulmonary metastasis in nude mice. Int J Cancer 2004;112:994–1002. [PubMed: 15386437]
33. Mueller BM, Ruf W. Requirement for binding of catalytically active factor VIIa in tissue factor-dependent experimental metastasis. J Clin Invest 1998;101:1372–1378. [PubMed: 9525979]
34. Kirchhofer D, Moran P, Bullens S, Peale F, Bunting S. A monoclonal antibody that inhibits mouse tissue factor function. J Thromb Haemost 2005;3:1098–1099. [PubMed: 15869619]
35. Amarzguioui M, Peng Q, Wiiger MT, et al. Ex vivo and in vivo delivery of anti-tissue factor short interfering RNA inhibits mouse pulmonary metastasis of B16 melanoma cells. Clin Cancer Res 2006;12:4055–4061. [PubMed: 16818705]
36. Amirkhosravi A, Meyer T, Chang JY, et al. Tissue factor pathway inhibitor reduces experimental lung metastasis of B16 melanoma. Thromb Haemost 2002;87:930–936. [PubMed: 12083498]
37. Camerer E, Qazi AA, Duong DN, et al. Platelets, protease-activated receptors, and fibrinogen in hematogenous metastasis. Blood 2004;104:397–401. [PubMed: 15031212]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

38. Hu L, Lee M, Campbell W, Perez-Soler R, Karpatkin S. Role of endogenous thrombin in tumor implantation, seeding, and spontaneous metastasis. Blood 2004;104:2746–2751. [PubMed: 15265791]

39. Palumbo JS, Kombrinck KW, Drew AF, et al. Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 2000;96:3302–3309. [PubMed: 11071621]

40. Carmeliet P, Mackman N, Moons L, et al. Role of tissue factor in embryonic blood vessel development. Nature 1996;383:73–75. [PubMed: 8779717]

41. Contrino J, Hair G, Kreutzer DL, Rickles FR. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. Nat Med 1996;2:209–215. [PubMed: 8574967]

42. Ngo, CV.; Manning, CA.; McCabe, F., et al. Combination antibody therapy targeting both xenograft- and host-derived tissue factor leads to potent tumor inhibition. Presented at: The 96th Annual Meeting of the American Association for Cancer Research; April 16–20, 2005; Anaheim, CA.

43. Parry GC, Erlich JH, Carmeliet P, Luther T, Mackman N. Low levels of tissue factor are compatible with development and hemostasis in mice. J Clin Invest 1998;101:560–569. [PubMed: 9449688]

44. Pawlinski R, Tencati M, Holscher T, et al. Role of cardiac myocyte tissue factor in heart hemostasis. J Thromb Haemost 2007;5:1693–1700. [PubMed: 17663739]

45. Snyder LA, Rudnicki KA, Tawadros R, et al. Expression of human tissue factor under control of the mouse tissue factor promoter mediates normal hemostasis in knock-in mice. J Thromb Haemost 2008;6:306–314. [PubMed: 18005233]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

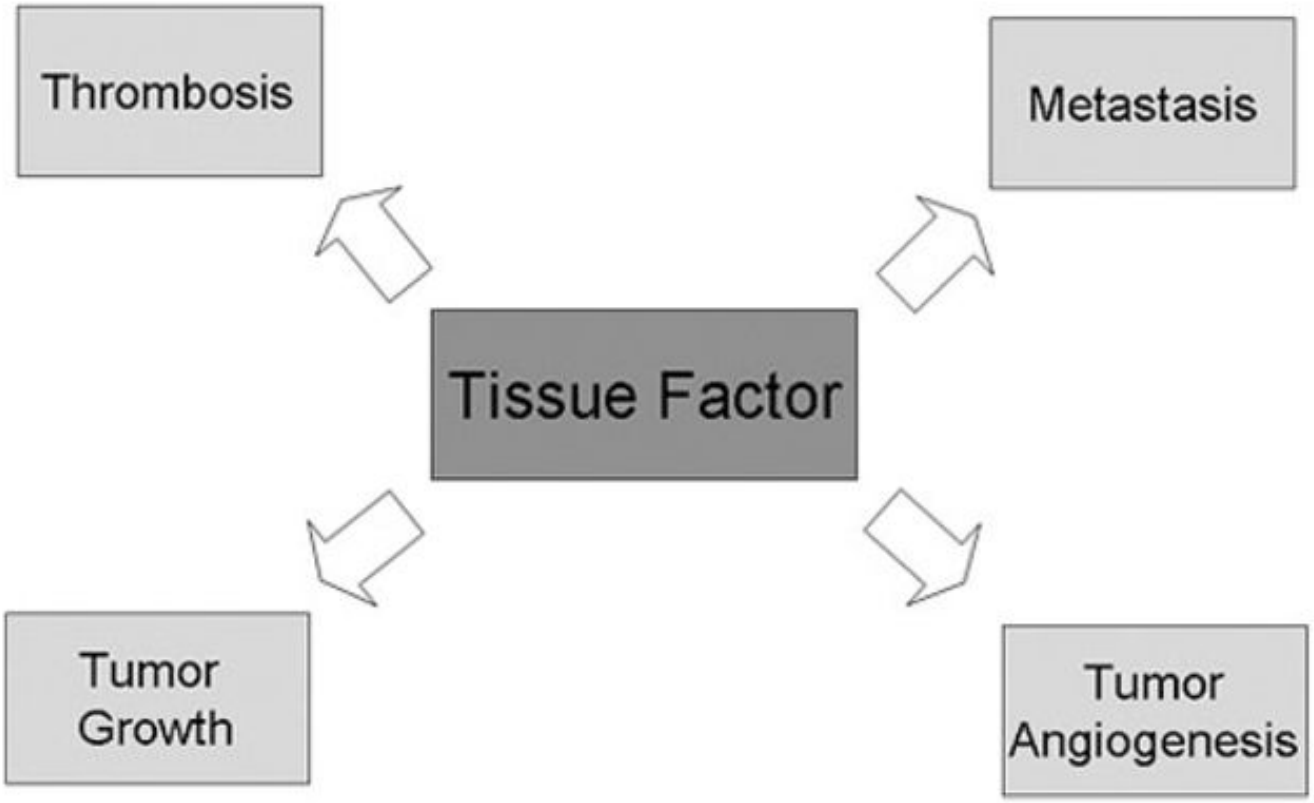


Figure 1.
Roles of TF in tumor biology.