Abstract—Tissue factor (TF) is best known as the primary cellular initiator of blood coagulation. After vessel injury, the TF:FVIIa complex activates the coagulation protease cascade, which leads to fibrin deposition and activation of platelets. TF deficiency causes embryonic lethality in the mouse and there have been no reports of TF deficiency in humans. These results indicate that TF is essential for life, most likely because of its central role in hemostasis. In addition, aberrant TF expression within the vasculature initiates life-threatening thrombosis in various diseases, such as sepsis, atherosclerosis, and cancer. Finally, recent studies have revealed a nonhemostatic role of TF in the generation of coagulation proteases and subsequent activation of protease activated receptors (PARs) on vascular cells. This TF-dependent signaling contributes to a variety of biological processes, including inflammation, angiogenesis, metastasis, and cell migration. This review focuses on the roles of TF in hemostasis, thrombosis, and vascular development. (Arterioscler Thromb Vasc Biol. 2004;24:1015-1022.)

Key Words: tissue factor • coagulation proteases • PAR signaling

A general scheme of the clotting cascade is shown in Figure 1. After vascular injury, clotting is initiated by the binding of plasma FVII/FVIIa to tissue factor (TF) (also known as coagulation factor III or tissue thromboplastin). The TF:FVIIa complex of the extrinsic pathway initiates blood coagulation by activating both FX and FIX. The FVIIIa:FIXa complex of the intrinsic pathway provides an alternative route to generate FXa, which participates in the prothrombinase complex (FVa:FXa). This complex activates prothrombin to thrombin, which plays a central role in the coagulation protease cascade. It activates FXI, which is an alternative way to generate FIXa.1,2 Thrombin also activates FXIII, as well as various cofactors, cleaves fibrinogen, and stimulates platelets via cleavage of protease activated receptors (PARs). Platelets accelerate the activation of the coagulation cascade by binding FXI via the receptor glycoprotein Ib-IX-V and by providing a thrombogenic surface for the assembly of the prothrombinase complex (FVa:FXa).3–5

Recent in vitro studies have shown that the coagulation proteases FVIIa, FXa, and thrombin activate various PARs (Figure 2). The PAR family consists of 4 members, PAR-1 to PAR-4.6–7 The TF:FVIIa complex activates PAR-2 and FXa activates both PAR-1 and PAR-2.8–11 Thrombin activates PAR-1, PAR-3, and PAR-4.7 PAR-1, -2, and -4 are expressed by a variety of vascular cells, including endothelial cells.7 Interestingly, thrombin activation of human platelets is mediated by PAR-1 and PAR-4, whereas thrombin activation of mouse platelets is mediated by a PAR-3/4 complex.12,13

Taken together, these studies suggest that TF, in addition to its role in coagulation, may contribute to other biological processes by enhancing signaling in vascular cells via the generation of coagulation proteases and the activation of PARs (Figure 2). Recently, we showed that crosstalk between coagulation and inflammation in endotoxemia is mediated by PAR-1 and PAR-2.14

Role of TF in Thrombosis

Aberrant TF expression triggers intravascular thrombosis associated with various diseases, such as atherosclerosis, cancer, and sepsis (reviewed in14–17). Importantly, inhibition of TF:FVIIa activity reduced coagulation and decreased mortality in animal models of sepsis.18–20 In atherosclerosis, TF is expressed by macrophage-derived foam cells within atherosclerotic plaques.21 Moreover, TF levels were higher in atheroma from patients with unstable angina compared with stable angina.22 These results strongly suggest that high levels of TF exposed upon plaque rupture trigger thrombosis and myocardial infarction (Figure 3). Thus, the classical view of TF is that it is expressed locally within an atherosclerotic lesion. Inhibition of TF would be expected to reduce thrombosis associated with a variety of diseases.

Recent studies suggest that an additional source of TF, known as blood-borne TF or plasma TF, may also contribute to thrombosis. In healthy subjects, TF antigen is present in plasma at a mean level of 149 to 172 pg/mL.23,24 Importantly, several studies have shown that levels of blood-borne TF are
Increased in various disease states, such as atherosclerosis, sepsis, diabetes, and sickle cell disease. Some studies show a correlation between the levels of blood-borne TF and acute myocardial infarction. Nemerson et al demonstrated that blood-borne TF in human blood supported clot formation in vitro. In addition, inhibition of TF in a rabbit model of venous thrombosis reduced thrombus propagation. We have shown that hematopoietic cell-derived, TF-positive microparticles also contributed to laser injury-induced thrombosis in the microvasculature of the cremaster muscle (Chou J, et al, submitted for publication). In contrast, hematopoietic cell-derived TF did not contribute to thrombosis induced by carotid artery injury in the mouse (Day S, et al, submitted for publication). Differences in these studies may be caused by differences in the models, type of injury, and the vascular bed.

One controversial issue is the form of blood-borne TF. Many studies have shown that hematopoietic cell-derived, TF-positive microparticles also contributed to laser injury-induced thrombosis in the microvasculature of the cremaster muscle (Chou J, et al, submitted for publication). In contrast, hematopoietic cell-derived TF did not contribute to thrombosis induced by carotid artery injury in the mouse (Day S, et al, submitted for publication). Differences in these studies may be caused by differences in the models, type of injury, and the vascular bed.

Figure 1. The coagulation protease cascade. Formation of the TF:FVIIa complex initiates clotting by activating FX and FIX. Alternatively, FXI can activate FIXa. The prothrombinase complex (FVa:FXa) activates prothrombin (PT). Thrombin activates various proteases and cofactors. Thrombin cleavage of fibrinogen to soluble monomers (SFM), which are cross-linked by FXIIIa, and activation of protease-activated receptors (PARs) on platelets leads to the formation of a clot.

Figure 2. TF, coagulation proteases, coagulation, and PAR signaling. TF-dependent generation of coagulation proteases activates multiple pathways involved in coagulation and signaling. Different coagulation proteases activate various PARs on platelets and endothelial cells. In the mouse, thrombin activation of platelets is mediated via a PAR-3/4 complex.

Figure 3. Role of TF in thrombus formation after rupture of an atherosclerotic plaque. TF expressed by foam cells (orange) and in the necrotic core (yellow) of the plaque would be exposed to clotting factors in the blood and initiate clotting after plaque rupture. In addition, blood-borne TF may contribute to thrombus propagation. TF is constitutively expressed by adventitial cells (blue), EC, endothelial cells; SMC, smooth muscle cells.

TF Deficiency Is Associated With Embryonic Death

In 1996, 3 groups independently knocked-out the murine TF gene. All groups reported a high rate (≈90%) of lethality of TF−/− embryos at approximately embryonic day (E10.5). Two groups proposed that the death of TF−/− embryos was caused by a hemostatic defect that resulted in fatal embryonic bleeding. In contrast, we noted a disorganization of the yolk sac vasculature and proposed that TF may play an additional nonhemostatic role in blood vessel development.

The controversy regarding the phenotype of TF−/− embryos was further complicated by the observation that all FVII−/−

016 Arterioscler Thromb Vasc Biol. June 2004
embryos survived embryonic development. It was suggested that TF may contribute to vascular development independently of FVII by enhancing signaling, adhesion, or chemotaxis. However, subsequent studies have shown that FVII−/− embryos generated in low-FVII mothers exhibit defects in the yolk sac vasculature and die at E10.5 in a similar manner to TF−/− embryos (E. Rosen, personal communication). These data suggest that the transfer of very low levels of maternal FVII into FVII−/− embryos rescues the defect in the yolk sac vasculature at E10.5 and permits the survival of FVII−/− embryos.

We used a transgenic approach to analyze the role of FVII binding to TF in the yolk sac vasculature. We found that transgenes expressing low levels of either wild-type human TF or human TF lacking the cytoplasmic domain rescued the embryonic lethality of TF−/− embryos. Similarly, embryos expressing wild-type levels of murine TF lacking the cytoplasmic domain developed normally. In contrast, a transgene expressing low levels of human TF with a mutated extracellular domain that reduced FVII/FVIIa binding failed to rescue TF−/− embryos. These results indicated that the TF extracellular domain, but not the cytoplasmic domain, was required for hemostatic protection and/or structural maintenance of the yolk sac vasculature.

What Is the Phenotype of Embryos Deficient in Other Clotting Factors and Platelets?

Partial embryonic lethality (30%) was observed in FX−/− embryos at E11.5 to E12.5 with no histological defects in the yolk sac vasculature. However, maternal transfer of FX may partially rescue FX−/− embryos in a similar manner to the rescue of FVII/−/− embryos by maternal FVII. Approximately 50% of embryos deficient in FV at mid gestation, and many of these embryos exhibited defects in the yolk sac vasculature. Two independent groups reported that ~50% of prothrombin−/− embryos die by E11.5, with 1 group observing defects in the yolk sac vasculature. In contrast to the partial mid-gestational lethality observed in these mice, fibrinogen null (Fib−/−) embryos did not exhibit any embryonic lethality. In addition, mice deficient in the transcription factor, NF-E2, produced few platelets but embryos developed normally.

Does TF Play a Hemostatic and/or Nonhemostatic Role in the Maintenance of the Yolk Sac Vasculature?

Recently, it was shown that mice deficient in both fibrinogen and PAR-4, which abolishes thrombin-dependent platelet activation, exhibit no embryonic lethality. Similarly, mice deficient in both fibrinogen and platelets (Fib−/−/NF-E2−/−) survived embryonic development. Both these studies suggest that hemostasis may not be required for embryonic development. However, one must be cautious with this conclusion. Embryos and embryonic tissues may be exposed to minimal hemostatic challenge, which would require only very low levels of fibrinogen and platelets to maintain hemostasis. It is possible that a low level of hemostatic protection in Fib−/−/PAR-4−/− and Fib−/−/NF-E2−/− embryos is provided by low levels of thrombin-independent platelet activation or a low level of normal platelets. In contrast to embryonic development, birth exposes embryos to a severe hemostatic challenge, which would explain why Fib−/−/PAR-4−/− and Fib−/−/NF-E2−/− pups die soon after birth. If we propose that embryos and extra-embryonic tissue require some degree of hemostasis, then death of TF−/− embryos would be caused, in part, by a hemostatic defect.

The first suggestion that there may be a link between TF, coagulation proteases, and PARs during development of the yolk sac vasculature were the reports that ~50% of PAR-1−/− embryos die at E10.5. The phenotype of PAR-1−/− embryos resembled that of TF−/− embryos, as well as FV−/− and prothrombin−/− embryos. This suggested that TF-dependent generation of thrombin and activation of PAR-1 may contribute to development of the yolk sac vasculature. A subsequent study demonstrated that endothelial cell-specific PAR-1 expression rescued PAR-1−/− embryos from death, indicating that PAR-1 expression by endothelial cells was required for normal development of the yolk sac vasculature. Deficiencies in either PAR-3 or PAR-4 did not affect embryonic development but abolished normal thrombin responses in mouse platelets. Similarly, PAR-2−/− embryos on a mixed genetic background develop normally.

Why does TF deficiency result in 90% embryonic lethality at E10.5, whereas deficiencies in FV, prothrombin, or PAR-1 all lead to a 50% embryonic lethality? One idea is that TF-dependent generation of coagulation proteases may be required for both hemostasis and PAR signaling. Importantly, it is highly unlikely that TF−/− embryos can be rescued by maternal transfer because TF is a transmembrane protein. The major signaling pathway that would be disrupted in TF−/− embryos is thrombin-PAR-1 signaling in endothelial cells. However, TF deficiency would also disrupt TF:FVII/−/FXa-PAR-1 signaling and thrombin-PAR-4 signaling (Figure 2). In contrast, loss of individual downstream proteins, such as prothrombin and PAR-1, would have a less dramatic effect on signaling in endothelial cells of the yolk sac (Figure 2). Importantly, when FV deficiency is combined with PAR-1 deficiency, there is a high rate of embryonic lethality (96%), which is similar to that observed with TF deficiency (90%). FV−/−/PAR-1−/− embryos may have a combined hemostatic and PAR-1 signaling defect in a similar manner to TF−/− embryos.

Alternatively, the high rate of lethality of FV−/−/PAR-1−/− embryos may suggest that thrombin activation of other endothelial cell receptors is required for the development of the yolk sac vasculature. The most likely candidate is PAR-4. Indeed, a recent study using endothelial cells from either PAR-1−/−, PAR-4−/−, or double knock-out mice (PAR-1−/−/PAR-4−/−) indicated that PAR-1 was the major thrombin receptor in endothelial cells but that PAR-4 also contributed to thrombin-dependent signaling. If we apply this scenario to the development of the yolk sac vasculature, we could argue that loss of the major thrombin receptor, PAR-1, would result in a defect in yolk sac development, whereas loss of the minor thrombin receptor, PAR-4, may not affect the yolk sac. It is possible that the survival of 50% of PAR-1−/− embryos is caused, in part, by thrombin-PAR-4 signaling. The partial redundancy in thrombin-PAR-1 and thrombin-PAR-4 signaling in endothelial cells in the development of the yolk sac can be easily analyzed by deter-
miming the effect of a combined deficiency of PAR-1 and PAR-4. One can speculate that PAR-1<sup>−/−</sup>/PAR-4<sup>−/−</sup> embryos will exhibit a higher rate of embryonic lethality than PAR-1<sup>−/−</sup> embryos.

TF<sup>−/−</sup> embryos exhibit a selective defect in the yolk sac vasculature with no defects in vascular beds within the embryo. One possible explanation for this observation is that the yolk sac vasculature is exposed to a greater hemostatic challenge because of its rapid development and/or its location at the surface. In contrast, the embryo is protected in a fluid-filled sack and may require minimal hemostasis. Alternatively, other factors may compensate for TF deficiency in the embryonic vasculature that are not present in the yolk sac vasculature.

In summary, these results suggest that TF plays both hemostatic and nonhemostatic roles in the yolk sac vasculature. The high rate of lethality of TF<sup>−/−</sup> embryos may be caused by loss of both hemostatic and nonhemostatic pathways and an absence of maternal rescue of this transmembrane receptor. TF may play a nonhemostatic role in the maintenance of the yolk sac vasculature by generating thrombin, which is required for the activation of PAR-1 on endothelial cells. In addition, the TF:VIIa:PAR-1 and thrombin-PAR-4 pathways may also contribute to maintenance of the yolk sac vasculature. At present, it is not known how PAR-1 signaling in endothelial cells stabilizes the yolk sac vasculature and no defects have been reported in the vasculature of adult PAR-1<sup>−/−</sup> mice.65,66 Nevertheless, further studies are required to determine whether the TF-thrombin-PAR-1 pathway plays a role in maintaining vessel stability in some vascular beds in adult mice.

**Role of TF in Tissue-Specific Hemostasis**

TF exhibits a nonuniform tissue distribution with high levels in the brain, lung, and placenta, intermediate levels in the heart, kidney, intestine, uterus, and testes, and low levels in the spleen, thymus, skeletal muscle, and liver.72–76 Immuno-histochemical and in situ hybridization studies demonstrated that high levels of TF were expressed by astrocytes in the brain, alveolar cells in the lung, trophoblasts in the placenta, epithelial cells surrounding organs and at body surfaces, adventitial fibroblasts surrounding blood vessels, and cardiac myocytes in the heart.73,76–80 This cell type-specific distribution suggested that TF provides a “hemostatic envelope” to limit bleeding after vessel injury.76 The higher levels of TF in the brain, lung, placenta, heart, and uterus would provide additional hemostatic protection to these vital organs.76 Figure 4 shows a model of tissue-specific hemostasis in which the TF:VIIa complex of the extrinsic pathway prevents bleeding in a select group of tissues. In contrast, tissues that express low levels of TF, such as skeletal muscle and joints, rely on the VIIa:FIXa complex of the intrinsic pathway to prevent bleeding. Indeed, this model explains why hemophilia patients deficient in either FVIII or FIX frequently bleed into joints and soft tissues.81

**Phenotype of Adult Mice Deficient in Different Clotting Factors**

Mice deficient in fibrinogen and FXIII exhibit fewer fatal hemorrhages, presumably due to platelet-dependent hemostasis.61,82,83 Consistent with this notion, Fib<sup>−/−</sup> mice deficient in either platelets (NF-E2) or thrombin activation of platelets (PAR-4<sup>−/−</sup>) die of hemorrhage in the first 48 to 72 hours of life.63,84 The mouse models of hemophilia A (FVIII<sup>−/−</sup>) and hemophilia B (FIX<sup>−/−</sup>) exhibit very rare spontaneous bleeding, which is a milder phenotype than human hemophilic subjects.85–88 Finally, mice deficient in FXI do not bleed during normal activity.89 In contrast, mice deficient in TF, VII, FX, FV, and prothrombin that survive embryonic development die in the perinatal period because of spontaneous hemorrhages resulting from impaired hemostasis.50–52,57,59,60,90 The perinatal death of mice deficient in clotting factors precludes studies of TF and coagulation proteases in hemostatic and nonhemostatic processes in adult mice.

**Phenotype of Low-TF Mice**

We generated low-TF mice by rescuing murine TF<sup>−/−</sup> embryos using a transgene (hTF).54 The human TF promoter in the transgene directed low levels (1% of wild-type TF levels) of human TF expression in a cell type-specific pattern that was similar to that of murine TF. Recently, Rosen et al generated mice that express low levels of murine FVII.91 Interestingly, the phenotypes of low-TF and low-FVII mice are very similar, suggesting that TF does not possess any FVII-independent activity. Defects in low-TF and low-FVII mice include fatal hemorrhages in the brain, lung, intestine, and uterus54,91,92 (E. Rosen, unpublished data), which is consistent with the notion that TF:VIIa-mediated coagulation varies between tissues.76

**Role of TF in the Uterus**

Pregnancy requires efficient hemostasis in the uterine wall during implantation and postpartum after the placenta has detached from the uterine wall. Indeed, high levels of TF are expressed in epithelial cells in the uterine wall, presumably to protect the mother from excessive bleeding during pregnancy92 (Figure 5). We examined the role of TF in uterine hemostasis by breeding low-TF female mice with wild-type male mice. Fatal postpartum hemorrhage was observed in 14% of the low-TF females,93 indicating that TF is required for postpartum hemostasis (Table). We did not observe any
hemostatic problems during implantation, which suggests that there are sufficient levels of TF in low-TF mice for this process. Importantly, low-FVII female mice also exhibit fatal hemorrhages during pregnancy in a similar manner to those observed with low TF female mice (E. Rosen, personal communication). Thus, the TF:FVIIa complex appears to play an important role in uterine hemostasis.

In complete contrast to the role of the TF:FVIIa complex in uterine hemostasis, female mice deficient in the hemophilia factors, FVIII and FIX, have normal pregnancies and postpartum hemostasis. In addition, FXI<sup>−/−</sup> females have normal pregnancies. These data indicate that the TF:FVIIa complex of the extrinsic pathway plays the dominant role in maintaining hemostasis in the uterus during pregnancy and postpartum independently of the FVIIIa:FIXa complex of the intrinsic pathway (Figure 4).

Female mice deficient in fibrinogen die of fatal hemorrhages at E10 because of defects during implantation. Maternal fibrinogen appears to play a dual role during implantation. It is required to maintain hemostasis and it also stabilizes the attachment of the placenta to the decidua (Figure 5). Similarly, 50% of female mice deficient in FXIII die during gestation, presumably because of impaired hemostasis. These observations are consistent with the fact that women with congenital deficiencies in FVII, fibrinogen, and FXIII exhibit spontaneous abortion, abruption, and postpartum hemorrhage.

**Role of TF in the Placenta**

The placenta is a highly vascularized organ that develops rapidly during pregnancy. It contains high levels of TF, presumably to maintain hemostasis throughout gestation. Figure 5 shows a diagram of the placenta. We examined the role of embryonically derived TF in the placenta by breeding low-TF female mice with either low-TF or wild-type male mice. Low-TF females carrying mTF<sup>−/−</sup> embryos had normal pregnancies, whereas low-TF female mice carrying low-TF embryos had a high rate (42%) of fatal late gestation hemorrhages (Table). Analysis of placentas of low TF embryos at E13.5 revealed large blood pools within the labyrinthine layer of the placenta. The presence of blood pools was dependent on the genotype of the embryo and independent of the genotype of the mother because blood pools were also observed in placentas of low TF embryos in mTF<sup>−/−</sup> mothers, but not in placentas of mTF<sup>−/−</sup> embryos in low TF mothers (Table). These blood pools appear to be formed by a

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**Effect of Reduced Levels or Deficiency of Different Clotting Factors and Platelets on Pregnancy and Birth in Mice**

<table>
<thead>
<tr>
<th>Gene</th>
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<th>Placental Blood Pools</th>
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<td>Postpartum hem</td>
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*Defects in placental–decidual interface. gest indicates gestation; hem, hemostasis.
disruption of the contacts between layer I trophoblasts that subdivide maternal lacunae. At present, it is unclear if these blood pools in low-TF placentas are caused by a hemostatic defect or a nonhemostatic defect. Interestingly, blood pools were also observed in placentas of mothers with reduced numbers of platelets (NF-E2−/−), which suggests a hemostatic defect. Placental blood pools in low-TF mothers with compromised uterine hemostasis often ruptured into the uterine cavity, which explains the high rate of fatal late-gestational hemorrhage observed in breedings between low-TF male mice and low-TF female mice. However, blood pools in placentas of low-TF embryos only rarely caused fatal hemorrhages in mothers with high levels of uterine TF, ie, mTF+/− mothers. Therefore, expression of embryonic TF in the placental barrier appears to play a critical role in hemostasis in the placenta.

Importantly, low levels of TF rescue the placental defect in thrombomodulin−/− embryos, which may be caused by rebalancing PAR signaling in trophoblasts. However, a deficiency in thrombomodulin did not prevent the formation of blood pools in low-TF placentas. Placental hemorrhage has been also observed in placentas lacking leukemia inhibitory factor receptor, and leukemia inhibitory factor has been shown to regulate trophoblast protease generation. These results suggest that TF may also contribute to the maintenance of the placenta by regulating the generation of coagulation proteases and PAR signaling. Further studies are required to understand the role of TF in the placenta.

Role of TF in the Heart
TF is constitutively expressed in cardiac myocytes but not in skeletal myocytes. The likely function of TF in the heart is to provide additional hemostatic protection. Low-TF mice had very low levels of TF in their hearts compared with the level of TF in the hearts of wild-type mice, suggesting reduced TF expression in cardiac myocytes. Importantly, low-TF mice and low-FVII mice exhibited hemosiderin deposition and fibrosis in their hearts. We believe that the hemosiderin is derived from erythrocytes hemmorhaging into the myocardium and phagocyte digestion of the hematin. Indeed, we observed occasional hemorrhages in the hearts of low-TF mice. Taken together, these results suggest that low-TF and low-FVII mice have impaired heart hemostasis. More recently, we have found that overexpression of murine TF in the cardiac myocytes abolishes fibrosis in the hearts of low-TF mice (unpublished data). These results indicate that TF expression by cardiac myocytes plays a key role in the heart, most likely by providing additional hemostatic protection to this vital organ that may be prone to mechanical injury of the vessels. In contrast, FIX−/− mice have normal hearts. These results suggest that the TF:FVIIa complex, but not the FVIIIa:FIXa complex, plays a critical role in heart hemostasis (Figure 4). Nevertheless, we cannot exclude the possibility that cardiac myocyte TF plays additional roles in cell survival and/or maintenance of the heart vasculature.

Summary
The death of TF−/− embryos and the absence of TF-deficient humans indicate that TF is essential for life. TF plays a critical role in hemostasis in all tissues. However, TF expression within astrocytes in the brain, cardiac myocytes in the heart, and trophoblasts in the placenta appears to provide these tissues with additional hemostatic protection. Abrupt TF expression in the vessel wall and/or circulating cells initiates life-threatening thrombosis in various diseases. In addition, blood-borne TF may also contribute to the propagation of thrombi. Finally, TF plays a nonhemostatic role in many biological processes, such as vascular development. It appears that TF-dependent generation of thrombin is required for PAR-1 signaling in endothelial cells of the yolk sac vasculature. Future studies should determine how TF contributes to inflammation, tumor angiogenesis, metastasis, and cell migration.

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Role of Tissue Factor in Hemostasis, Thrombosis, and Vascular Development
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