Tissue factor in health and disease

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1. ABSTRACT

Tissue Factor (TF) is a crucial initiator of the extrinsic coagulation cascade. TF is expressed on cells which are normally sequestered from blood. However, upon injury TF is exposed to the blood resulting in activation of the coagulation cascade. TF dependent generation of coagulation proteases also initiates intracellular signaling through protease activated receptors. Pathologic TF expression is found in patients with a number of different diseases. This review will describe the roles of TF in health and disease as well as discuss approaches to reduce pathologic TF expression.

2. INTRODUCTION

Tissue factor (TF) is the primary activator of the coagulation protease cascade. It is essential for hemostasis. However, aberrant TF expression can promote thrombosis in different diseases. Finally, TF can influence cell signaling by generating coagulation proteases that activate protease activated receptors (PARs). This review will summarize our current knowledge on TF and its role in health and disease.

3. TISSUE FACTOR AND COAGULATION

TF is a 47kd transmembrane glycoprotein that contains 3 domains (a short intracellular domain, a transmembrane domain, and an extracellular domain)(1). It is normally sequestered from blood and high levels are only found on cells surrounding blood vessels (2, 3). Drake and colleagues proposed that TF formed a hemostatic envelope that activated blood coagulation upon blood vessel injury(2). More recently it was shown that factor VII (FVII) is bound to TF surrounding dermal blood vessels in the absence of injury (4), which would allow a more rapid response to injury. TF is also highly expressed in cells of several organs, such as the placenta, heart, lungs, and brain. The TF/FVIIa complex activates factor IX (FIX) and factor X (FX) which subsequently leads to the activation of thrombin culminating in fibrin deposition.

Low levels of TF are also found circulating in the blood in the form of microparticles/ microvesiscles. These are small membrane vesicles that are released from cells upon activation or cell death (5). During microparticle generation, the plasma membrane loses its normal structure and phosphatydlserine (PS) becomes exposed on the outer leaflet of the membrane. It has been proposed that PS may induce a conformational change in TF that increases the activity of the TF/FVIIa complex. The identification of TF on microparticles has sparked an interest in its role in thrombosis. Indeed, an early study showed that TF positive microparticles isolated from patients undergoing cardiac surgery are highly pro-coagulant (6). The roles of TF positive microparticles in various disease states such as sepsis, acute coronary syndrome and cancer will be discussed further below.

Another form of TF present in blood is generated by alternative splicing of TF pre-mRNA (7). This so called alternatively spliced TF (asTF) has no transmembrane domain and likely has little to no pro-coagulant activity. However, it does bind to various integrins and enhances angiogenesis (8). The role of asTF in different biological processes is reviewed by Srinivasan and Bogdanov in another article in this issue.

4. TISSUE FACTOR AND PROTEASE ACTIVATED RECEPTORS

TF is known to have functions beyond its procoagulant activity, in part, by inducing the generation of coagulation proteases. These proteases activate a family of receptors called protease activated receptors (PARs). PARs are seven transmembrane spanning G protein coupled receptors that act as sensors of the local environment. There are four receptors in the family, PAR1-4 and they are expressed throughout the vasculature (9, 10). PARs are activated by proteolytic cleavage of the extracellular amino terminus which results in binding of a tethered ligand onto the receptor. This leads to activation of intracellular signaling pathways and the induction of various genes, including chemokines and cytokines. As such, these receptors are thought to mediate the cross-talk between coagulation and inflammation. Thrombin activates PAR1, PAR3, and PAR4(10). While both FVIIa and FXa activate PAR2 in vitro (11-14). However, the affinity for this interaction is much lower than other proteases that also activate PAR2, such as trypsin and tryptase (15). Thus, the contribution of FVIIa and FXa to the activation of PAR2 in vivo is still unclear.

5. TISSUE FACTOR AND DEVELOPMENT

TF plays an essential role in development. For instance, inactivation of the TF gene in mice results in death of the majority of embryos at embryonic day 9.5-10.5 (16-18). Two explanations for this embryonic lethality have been proposed. One group suggested that embryos lacking TF died because of a failure in remodeling of the yolk sac vasculature, while others proposed that the lack of TF led to bleeding (16-18). To date, no humans have been found that lack TF. These observations underscore the importance of TF for an organism containing blood in a high pressure vascular system. As a result, the role of TF in hemostasis has been difficult to study. However, mice with greatly reduced levels of TF in all tissues or mice selectively lacking TF in different tissues have been generated (19, 20). For instance, Low TF mice were generated by rescuing embryos lacking mouse TF with a very low level of human TF (at ~1% of the mouse TF levels). Mice lacking TF in myeloid cells, megakaryocyte/platelets, vascular smooth muscle cells, and both endothelial and myeloid cells are all viable (21, 22). The generation of these mouse models has provided a unique opportunity to study the roles of TF in hemostasis, thrombosis, and signaling.

6. TISSUE FACTOR AND PREGNANCY

Hemostasis must be maintained by both the mother and the fetus during pregnancy. Indeed, the uterus and placenta are highly vascularized tissues with high levels of TF (23, 24). The role of TF expression during pregnancy was investigated by breeding Low TF female mice with wild type male mice. In this scenario a high rate of lethal post-partum hemorrhage was observed. In addition, blood pools were observed in the placentae of embryos with low levels of TF, although the embryos themselves survived. The role of TF in pregnancy has been recently reviewed (25). Taken together, these data indicate that TF is necessary for placental and uterine hemostasis. Interestingly, the absence of the intrinsic proteins factors VIII and IX is not associated with increased post-partum bleeding in mice (26). The role of TF in non-hemostatic PAR signaling during pregnancy is not well understood. It has been suggested that thrombin activation of PAR1 in endothelial cells is important in yolk sack vascular development (26, 27). In addition, low levels of TF rescued the embryonic lethality of thrombomodulin deficient embryos, which appeared to be due to reduced PAR2 and PAR4 signaling rather than reduced fibrin deposition (28).

7. TISSUE FACTOR AND BACTERIAL INFECTION

During systemic bacterial infections, the presence of bacterial products, such as bacterial lipopolysaccharide (LPS), and pro-inflammatory cytokines increases TF expression within the vasculature. Systemic bacterial induce disseminated infections can intravascular coagulation (DIC), which is associated with intravascular fibrin deposition, a consumptive coagulopathy and finally bleeding. LPS administration to humans induces TF expression in circulating monocytes and elevated levels of TF positive microparticles (29). Another study found that LPS induced TF mRNA expression in whole blood, which was presumably due to induction of the TF gene expression in monocytes (30). Baboons exposed to a lethal dose of E. coli exhibited increased TF expression on circulating monocytes and DIC (31). Importantly, experimental strategies that inhibit the TF/FVIIa complex reduced coagulation, inflammation and mortality (32-37). Low TF mice also exhibited reduced coagulation, inflammation, and mortality after LPS administration (38). Finally, mice lacking myeloid TF had reduced coagulation in an endotoxemia model (21). Together these data provide evidence for a role for TF in DIC as shown in Figure 1. Inhibition of TF during sepsis may provide an attractive intervention strategy for septic patients with DIC. Unfortunately, a phase III clinical trial using recombinant



Figure 1. Roles of Tissue Factor in vascular occlusion. TF is expressed in a thrombus on the foam cells and endothelial cells within an atherosclerotic plaque. Plaque rupture causes exposure of TF to the circulating blood and results in clot formation. In addition, circulating microparticles can also express TF and become involved in clot formation during arterial thrombosis. During venous thrombosis, circulating microparticle TF may cause clot formation in areas of low flow in the valve pockets. This clot often elongates along the vessel wall before breaking off to cause a blockage of blood flow in the lungs. During disseminated intravascular coagulation, TF expression by monocytes and cell within the vessel wall activate coagulation. This systemic increased coagulation causes multiple organ failure and death. During sickle cell disease, TF associated with monocytes and the vessel wall contributes to clot initiation and vasocolusive crisis in the microvasculature.

tissue factor pathway inhibitor, the natural inhibitor of the TF/FVIIa complex, failed to decrease mortality in septic patients (39).

TF also plays a role during lung injury induced by both local and systemic infection. Acute lung injury (ALI) in septic patients is characterized by non-cardiac pulmonary edema, inflammation, and fibrin deposition (40). During experimental sepsis in baboons, TF is expressed by both alveolar macrophages and alveolar epithelial cells, as well as on endothelial cells (31, 41). Interestingly, bronchoalveolar lavage fluid (BALF) from patients with peritonitis contained elevated levels of TF compared to patients with mechanical ventilation (42). These data solidify the notion that systemic infection can result in TF dependent activation of coagulation in the lungs.

Acute respiratory distress syndrome (ARDS) and pneumonia are also lung injuries found to be associated with activation of coagulation. TF expression has been found on alveolar macrophages and epithelial cells in the lungs of patients with ARDS (43). Also, patients with ARDS and pneumonia were found to have elevated TF activity in BALF (44). Interestingly, TF levels were found to be increased in BALF prior to diagnosis of ventilatorassociated pneumonia, suggesting that levels of TF could be used as a diagnostic tool for ventilator-associated pneumonia (45). In contrast to patients with ALI, fibrin deposition in patients with pneumonia was found to be localized to the primary infection site (46, 47). Importantly, blockade of TF activation decreased the procoagulant response, pulmonary fibrin deposition, and cytokine expression in various models of bacteria induced lung inflammation (47, 48). These data suggest that TF inhibition could be used to reduce lung injury. However, recombinant active site inactivated FVIIa(FVIIai) failed to reduce morbidity in patients with ALI/ARDS and was also associated with increased adverse bleeding events (49).

The role of PARs in endotoxemia and sepsis has been investigated by several different laboratories. Two studies found that the lack of either PAR1 or PAR2 did not reduce inflammation or mortality in endotoxemic mice (38, 50). In contrast, another study showed that PAR1 deficient mice exhibited reduced inflammation and increased survival compared with wild type littermates (51). The reason for these different results is unclear. Finally, inhibition of the different PARs with small cell permeable peptides called pepducins, revealed that PAR1 is detrimental to mice during the early phase of endotoxemia but later when acting through PAR2, it is beneficial (52).

The role of PAR1 and PAR2 in lung infection is also not well understood. One group found that PAR2 enhanced lung inflammation in a neuropeptide dependent manner (53). However, a later study by this group found no role for PAR2 in ALI (54). In contrast, we have found that mice lacking PAR2 have decreased chemokine expression compared with wild type littermate controls after intratracheal LPS installation (Williams and Mackman, unpublished data). Therefore, more studies are needed to fully understand how PARs contribute to lung injury.

8. TISSUE FACTOR AND VIRAL INFECTIONS

Several studies have investigated the role of TF in viral infections. During Ebola virus infection a number of pathways are dysregulated, including coagulation and inflammation. DIC is one major characteristic of Ebola hemmorhagic fever. Recent studies have analyzed TF expression during Ebola infection. Geisbert and colleagues showed that TF expression was increased in peripheral blood mononuclear cells in macaques infected with Ebola (55). Also, increased numbers of TF positive microparticles were found in plasma. The same group found that blockade of TF activity prolonged the survival of Ebola infected macaques and decreased levels of fibrin deposition and pro-inflammatory cytokine production (56).

Human immunodeficiency virus (HIV) is associated with increased risk for thrombosis. Levels of the pro-inflammatory cytokine interleukin-6 and the fibrinolytic product D-Dimer correlated with circulating HIV levels. It was also found that TF expression on circulating monocytes was increased in chronically HIV infected individuals (57). Herpes simplex virus 1 (HSV-1) infection of human umbilical vascular endothelial cells leads to increased TF, which likely contributes to the procoagulant state associated with this infection (58). In addition, patients in early phases of Dengue hemorrhagic fever had elevated levels of TF compared to patients with a milder form of infection (59). While more investigation of the relationship between TF and viral infection is clearly warranted, taken together these data suggest that blockade of TF activity may improve outcomes for patients with many different viral infections.

9. TISSUE FACTOR AND CARDIOVASCULAR DISEASE

Atherosclerosis is the accumulation of fatty lipids along the vessel wall of large and medium-sized arteries. Several risk factors can accelerate the formation of atherosclerosis include smoking, obesity, high cholesterol, diabetes, and hyperlipidemia. Atherosclerotic lesions, known as plaques, are comprised of lipids, cells, calcium, and components of extracellular matrix. High levels of TF are present in atherosclerotic plaques (2, 60). Thus, it has been proposed that upon plaque rupture, TF within the plaque contributes to the activation of coagulation and thrombotic occlusion of the vessel. TF within the plaque has been found on foam cells, macrophages and vascular smooth muscle cells, as well as in the form of MPs (2, 60, 61).

Studies have shown that oxidized low-density lipoprotein (LDL) and acetyl LDL induce TF expression in monoctye/macrophages, whereas only oxidized LDL induced TF expression in endothelial cells (62-68). Interestingly, atherosclerotic plaques with high levels of lipids in macrophages also have high levels of TF (69). Moreover, TF protein and activity was also increased in foamy macrophages and smooth muscle cells in atherosclerotic lesions rabbits fed a high fat diet (70). Proatherosclerotic cytokines and growth factors within the plaque may also induce TF expression. For example, TNF α , platelet-derived growth factor, or thrombin all induced TF expression in smooth muscle cells (71, 72). In addition, TNF α and vascular endothelial growth factor (VEGF) induce TF expression in endothelial cells (72, 73). Taken together, these data suggest that oxidized lipids, cytokines, and growth factors induce TF expression by cells within plaques.

An early study showed that a 50% reduction in tissue factor pathway inhibitor in all cells increased atherosclerosis in the apolioprotein E (ApoE) deficient model (74). Moreover, overexperssion of tissue factor pathway inhibitor by smooth muscle cells reduced atherosclerosis in mice (75). In contrast, Tilley and colleagues found that TF heterozygotes in the same model did not affect atherosclerosis (76). In addition, reducing TF expression in hematopoietic cells did not reduce atherosclerosis in low density lipoprotein receptor (LDLR) deficient mice (76). Interestingly, we found that a reduction of TF expression in smooth muscle cells was associated with reduced cell migration, and Low TF mice had reduced intimal hyperplasia following femoral artery injury (77). Also, recombinant FVIIai administration prior to femoral balloon artery angioplasty decreased vascular neointimal lesion formation and thrombosis in a baboon model (78). In addition, TFPI heterozygotic mice showed enhanced neointimal hyperplasia during vascular remodeling (79). These results suggest that additional studies are needed to analyze the role of TF expression by smooth muscle cells during vascular remodeling and atherosclerosis.

Another important facet of cardiovascular disease is acute coronary syndrome. Several recent publications have investigated the role of TF in acute coronary syndrome. Three groups found an increase in plasma TF levels in patients with acute coronary syndrome compared to those with stable disease (80-82). One of these groups also found, in patients with acute coronary syndrome, that plasma TF levels were also predictive of mortality (81). Certain single nucleotide polymorphisms in the TF gene are also associated cardiovascular death but not with disease state (83). In addition, patients with acute coronary syndrome had higher levels of TF positive monocyte/platelet aggregates than those with stable disease or healthy controls (84). Our group has found that hyperlipidemia in mice, monkeys and man is associated with increased monocyte TF expression, MP TF activity and activation of coagulation ((85)unpublished data). Given that cardiovascular disease can be associated with acute coronary syndrome and atherosclerosis, it may be possible to control adverse events associated with cardiovascular disease by inhibiting TF. Indeed, inhibition of TF using antibody or recombinant FVIIai

reduced injury after myocardial infarction in rabbits and mice (86-88).

10. TISSUE FACTOR AND THROMBOSIS

Many different animal models have been used to study the role of TF in thrombosis. Some of these models use arterial injury to examine a role for TF in thrombosis. In these models, TF is exposed to blood after vessel damage, as shown at the top of Figure 1. One study demonstrated that Low TF mice had reduced thrombosis in a carotid artery injury model (89). In this model bone marrow transplantation indicated that the vessel wall provided the major source of TF that initiated thrombosis. Correspondingly, mice lacking TF in smooth muscle cells also showed reduced carotid arterial thrombosis (22). Moreover, inhibition of the TF/FVlla complex reduced thrombosis in pigs and rabbits (90-92). Recently the TF/FVIIa inhibitor recombinant nematode anti-coagulant protein c2 (NAPc2) was shown to reduce thrombosis in humans (93, 94). These data suggest that inhibition of TF/FVlla could provide a novel approach for prevention of thrombotic events.

Venous thromboembolism (VTE) is triggered by variety of factors, including stasis, endothelial cell activation, and/or changes in the blood itself. In fact, increased TF mRNA in thrombi and leukocytes has been shown to be associated increased risk for VTE (95, 96). In a mouse model of inferior vena cava ligation (IVC), thrombosis was significantly decreased in Low TF mice (89). Again, bone marrow transplantation demonstrated that vessel wall TF initiated thrombosis. However, it should be noted that this model is not ideal because there is significant damage to the vessel wall during the ligation. A recent study showed that ligation of the IVC in rats led to denudation of the endothelium. In addition, TF protein expression was observed in the infiltrating monoctves and endothelial cells at the site of injury (97). Patients with VTE also have increased TF mRNA expression in leukocytes (96). A diagram of venous thrombosis is found in Figure 1.

Circulating TF in the form of TF positive microparticles may also play a role in VTE. This may be particularly important in cancer patients. Indeed, VTE is a leading cause of death in cancer patients and TF expression has been described in glioma, colorectal cancer, ovarian cancer, non-small cell lung cancer, as well as renal cell cancer (98). Several studies using human tumors grown in mouse models have detected tumor-derived human TF in the blood (99, 100). Importantly, chemotherapy further increases the risk of VTE (101), and TF activity is increased in cells treated with chemotherapeutic agents (102). As such, several groups have analyzed levels of microparticle TF in cancer patients. One group found increased levels of microparticle TF activity in patients with pancreatic cancer, breast cancer, and early prostate cancer (103, 104). Another group found increased TF positive microparticles in colorectal cancer patients (105). In addition, cancer patients with VTE were found to have elevated levels of microparticle TF compared to cancer patients without VTE (106, 107). Our group found that

in a small cohort of 11 pancreatic cancer patients, 2 patients with the highest microparticle TF protein and activity levels subsequently developed VTE (108). These data indicate there is an association between increased microparticle TF and the risk of VTE in cancer patients. Nevertheless, further studies are needed to confirm these exciting early results.

11. TISSUE FACTOR AND CANCER

TF also plays a role in tumor metastasis. Indeed, inhibition of TF has been shown to reduce metastasis in a pulmonary metastasis mouse model (109-111). It is thought that tumor cells may be coated with fibrin and this coating allows for circulating tumors cells to be trapped in the microvasculature. Support for this hypothesis includes a study showing that mice deficient in fibrinogen had decreased tumor metastasis (112). In addition, in a mouse model, tumor associated TF was shown to play a role in fibrinogen mediated evasion of natural killer cell killing, which was associated with an increase in metastasis (113). Also, TF expression is associated with increased tumor cell invasion *in vitro* and *in vivo* (111, 114).

TF expression in tumor cells also increases tumor size and vascularity (115). Importantly, TF expression also increased expression of VEGF, a known inducer of angiogenesis. Conversely, a reduction in TF expression also reduced tumor growth (99). TF expression by host cells may also influence tumor angiogenesis. For example, one study found that tumors grown in Low TF mice had smaller blood vessels but the overall tumor growth was not affected by the lower levels of host TF (116).

The role of TF in tumor growth is not well understood. Inhibition of the TF/FVIIa complex reduced growth of melanomas in mice, and blockade of TF in immunodeficient mice decreased growth, vascularization, and VEGF expression of human tumor cells (117, 118). In addition, tumor growth was reduced in PAR2 deficient mice (119). The use of an antibody to TF/FVIIa complex that inhibits TF dependent signaling but not TF procoagulant activity also reduced tumor growth in wild type mice (120). Therefore, while it is likely that TF/FVIIa dependent activation of PAR2 plays a role in the growth of some tumors, but it is not clear if this pathway is important in all types of cancer.

12. TISSUE FACTOR AND ANTI-PHOSPHOLIPID ANTIBODY SYNDROME

Anti-phospholipid antibody syndrome is characterized by increased levels of anti-phospholipids and a hypercoagulable state. This syndrome is often found in patients with systemic lupus erythematosus, which is also characterized by an increase in many different autoantibodies. While one could imagine that antibodies to phospholipids may actually decrease availability of the surface needed to initiate coagulation, in fact the majority of these antibodies actually target phospholipid binding proteins and are associated with increased thrombotic risk (121). Passive transfer of anti-phospholipid antibodies has been shown to induce thrombosis in animal models (122, 123). The mechanism for this increased thrombosis is not yet understood, but several groups have found elevated TF expression in monocytes from patients with anti-phospholipid antibody syndrome (124-126). In support of this, *in vitro* studies have demonstrated induction of TF expression by anti-phospholipid antibodies in monocytes and endothelial cells (127, 128). TF activity was also found to be increased in carotid arteries and peritoneal cells of mice injected with anti-phospholipid antibodies (129).

A role for complement in anti-phospholipid antibody induced TF expression has been recently reviewed (130). Ritis and colleagues showed that complement C5a induced TF expression in neutrophils (131). However it should be noted that expression of TF by neutrophils is controversial and may be due to monocyte contamination and/or binding of TF positive microparticles by neutrophils(132). Nonetheless, complement induction of TF expression in neutrophils and subsequent neutrophil activation were found to play a role in fetal loss in a mouse model of anti-phospholipid antibody syndrome (133, 134). This is especially relevant as a common complication for women with anti-phospholipid antibody syndrome is an inability to carry a pregnancy to term. These data suggest that investigation into blockade of TF expression and/or activity could be a viable strategy for pathologic complications in anti-phospholipid antibody syndrome patients. In fact, recently it was demonstrated that statins decreased TF and PAR2 expression in neutrophils and prevent pregnancy loss in a mouse model of antiphospholipid antibody syndrome (135).

13. TISSUE FACTOR AND SICKLE CELL DISEASE

Sickle cell disease is associated with activation of coagulation. As shown at the bottom of Figure 1, it is thought that TF on monocytes and on the vessel wall contribute to coagulation in this disease. Recent studies found an elevated number of TF positive microparticles from monocytes and endothelial cells in blood from patients with sickle cell disease, compared to controls In addition, patients had elevated levels of TF (136). positive microparticles and markers of coagulation. Patients with sickle cell disease have also been found to have elevated levels of whole blood TF and circulating TF positive endothelial cells (137, 138). Nevertheless, there was no difference in plasma TF levels between those patients with steady state disease or those in pain crisis (137). More recently, mouse models of sickle cell disease have been developed and will be helpful in delineating the role of TF in this disease (139, 140). Clearly, more studies are required to understand the role of TF in this complex disease.

14. TISSUE FACTOR AND DIABETES

Patients with type II diabetes have an increased risk for death due to thrombotic complications (141). The literature on TF and diabetes has recently been reviewed by Bogdonov and Osterud (142). Increased circulating plasma TF activity was observed in patients with type II diabetes, and those with elevated insulin and glucose have even higher levels of TF activity (143). Oxidative stress in patients with type II diabetes has also been implicated in the induction of TF within the vasculature (144). In addition, peripheral blood mononuclear cells from patients with type II diabetes with vascular complications had elevated TF levels (145). Interestingly, another study found circulating TF induced thrombus formation in vitro correlated to glycemic control in patients with type II diabetes (146), suggesting a potential role for TF expressing circulating microparticles. Indeed, well controlled type II diabetes patients also had increased numbers of TF positive microparticles compared to controls (147). Taken together, these data suggest a role for TF in thrombosis in patients with type II diabetes.

15. TISSUE FACTOR AND OTHER NON-INFECTIOUS DISEASES

Increased TF expression has also been observed in a number of other non-infectious disease states. Increased circulating TF activity was found in patients with chronic obstructive pulmonary disease (148). An association between increased plasma TF expression and increased disease state was also observed in patients with liver disease (149). Patients with inflammatory bowel disease (IBD) have a 3-4 fold higher risk of thromboembolic events compared to the normal population (150). A recent study analyzed the levels of TF protein in plasma of IBD patients and found detectable levels of TF in 34% of IBD patients tested whereas no TF was detected in healthy controls (151). In addition, thrombin-anti-thrombin (TAT) levels were higher in a subset of IBD patients with higher plasma TF and FXIa levels compared to patients with low levels of plasma TF and FXIa. Similarly, blockade of TF decreased TAT, thrombus formation, and intestinal injury in a mouse model of colitis (152). Patients with acute Graft versus Host Disease after allogeneic hematopoietic stem cell transplantation were also found to have elevated levels of circulating TF protein. However, TF levels diminished after recovery but remained significantly higher than at baseline (153). Given the role TF has in coagulation and inflammation, many groups are continuing to investigate the relationship between TF and multiple disease states, especially in cases where an increased thrombosis risk is evident.

16. STRATEGIES TO TISSUE FACTOR

Inhibition of TF is an attractive method for prevention of hypercoaguable states and perhaps hyperinflammatory states. There are several different approaches that have been used to inhibit inducible TF expression or TF activity. These include recombinant proteins discussed previously such as TFPI, FVIIai, and NAPc2, as well as drugs such as statins. Since TF is required for normal hemostasis, but is upregulated in monocytes and possibly other cells during many disease states, it would be ideal to inhibit this inducible, pathologic TF. Statins have been shown to reduce inducible TF expression by monocytes and macrophages both *in vitro* and *in vivo* (154-156). Statins are able to prevent activation of NF- κ B and Rho/Rho kinase(154, 157, 158) which are known to be involved in upregulation of TF expression (159-161). Recently, our group found that simvastatin reduced monoctye TF expression and MP TF activity in hypercholesteremic monkeys (unpublished data). Thus, it is promising that statins may be used as an inhibitor of inducible TF expression that would prevent excessive pathologic TF expression while leaving protective hemostatic TF intact.

17. CONCLUSION

This review summarizes the roles of TF in health and disease. TF is clearly important for normal hemostasis, pregnancy, and development. However, TF also plays a pathogenic role in many diseases including, bacterial and viral infections, atherosclerosis, thrombosis, cancer, antiphospholipid antibody syndrome, sickle cell disease, and type II diabetes, among others. The development of TF inhibitors as novel drugs for the treatment of these diseases is an attractive possibility. However, the risk of bleeding complications due to TF inhibition must be considered. Ideally one would like to inhibit the expression of the inducible TF and preserve the constitutively expressed hemostatic TF. One potential therapy may be statins, which have been shown to be effective at inhibiting TF induction in various systems.

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