Tissue factor (TF) has long been known as a key initiator of the coagulation cascade. Over the last decade, our understanding of the molecular regulation of TF expression in vascular cells has profoundly improved; moreover, TF has been recognized to be involved in the pathogenesis of cardiovascular diseases. Therefore, therapeutic strategies are being developed to specifically interfere with TF and its effectors.

We will review the molecular regulation of TF expression emphasizing the role of TF in cardiovascular diseases as well as the resulting implications for the treatment of atherosclerosis and acute coronary syndromes.

**Molecular Mechanisms of Tissue Factor Expression**

Tissue factor, formerly known as thromboplastin, is a 47-kDa protein expressed in both vascular and nonvascular cells. The TF gene is located on chromosome 1 and consists of 6 exons. One main transcript as well as at least one alternatively spliced form have been described. In the vessel wall, TF is constitutively expressed in subendothelial cells such as vascular smooth muscle cells leading to rapid initiation of coagulation when the vessel is damaged. In contrast, endothelial cells and monocytes do not express TF under physiological conditions; as a consequence, there is no appreciable contact of cellular TF with the circulating blood. In response to various stimuli, however, TF expression and activity can be induced in these cells as well.

The coagulation cascade is initiated as soon as TF comes into contact with circulating activated factor VII (VIIa), resulting in the TF-FVIIa complex (Figure 1). Alternatively, TF can bind inactive factor VII and form the TF-FVII complex, which is converted to TF-FVIIa by FVIIa or already formed TF-FVIIa. The TF-VIIa complex activates factor IX, which in turn activates factor X; alternatively, factor X is directly converted to factor Xa by TF-FVIIa. In complex with factor Va and calcium, Factor Xa catalyzes the conversion of prothrombin to thrombin, thereby leading to fibrin formation, platelet activation, and, ultimately, generation of a thrombus. Several of these activated proteases, including factor IXa, factor Xa, thrombin, and the TF-VIIa complex itself, can convert factor VII to VIIa in an auto-feedback loop.

In addition to its well-established role in coagulation, TF participates in other cellular processes. It is involved in migration and proliferation of vascular smooth muscle cells. Furthermore, the development of embryonic blood vessels is critically dependent on TF because mice lacking TF die beyond embryonic day 8.5 secondary to abnormal circulation from yolk sac to embryo. TF has also been observed to promote tumor neovascularization and metastasis.

Over the last years, our knowledge of the molecular mechanisms regulating TF expression as well as its biological
action in vascular cells has greatly advanced and is delineated in this section.

**Endothelial Cells**

Endothelial TF is induced by cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β, or CD40 ligand, by biogenic amines such as serotonin or histamine, and by mediators such as thrombin, oxidized LDL, or vascular endothelial growth factor (Figure 2). Despite their diversity, most of these mediators share similar signal transduction pathways regulating TF induction. The MAP kinases p38, p44/42 (ERK), and c-jun terminal NH₂-kinase (JNK) are involved in TNF-α–induced, histamine-induced, and thrombin-induced TF expression, whereas the effect of vascular endothelial growth factor (VEGF) is only mediated by p38 and ERK. TNF-α and VEGF are known to induce TF expression through activation of protein kinase C as well. These signal transduction molecules stimulate the TF promoter by activating transcription factors such as AP-1, nuclear factor (NF)-κB, and EGR-1, ultimately resulting in upregulation of TF mRNA. Regulation of the TF promoter is reviewed in detail elsewhere.

Unlike MAP kinases or protein kinase C, the PI3-kinase pathway negatively regulates endothelial TF expression; as a consequence, inhibition of PI3-kinase or its downstream mediators increases TF expression in response to TNF-α, histamine, thrombin, and VEGF. The mechanism of the enhanced endothelial TF expression on PI3-kinase inhibition has not yet been elucidated in detail. Downstream targets of PI3-kinase such as the mammalian target of rapamycin are known to be involved in the regulation of protein translation, which may at least in part account for their effect on TF expression. In one study, VEGF-induced p38 activation was enhanced when PI3-kinase was blocked by wortmannin; hence, cross-talk to MAP kinases may explain the inhibitory role of the PI3-kinase pathway on VEGF-induced TF expression. In contrast, such cross-talk is not observed in response to thrombin, indicating that the molecular events underlying the effect of PI3-kinase on endothelial TF expression differ with the particular stimulus involved.

The extent of TF protein induction in vascular cells does not always correlate well with TF activity. One possible explanation is the concomitant secretion of tissue factor pathway inhibitor (TFPI), the endogenous inhibitor of TF. Another possible reason is the distribution of TF into several cellular compartments. Biologically active TF is indeed located at the cell surface, whereas intracellular TF constitutes a pool that is only released on cell damage. A combination of TNF-α and VEGF favors cell surface over intracellu-
Vascular Smooth Muscle Cells

In normal arteries, low levels of TF are found in the medial layer. Similarly, vascular smooth muscle cells in culture express low basal levels of TF. Mediators such as TNF-α, CD40 ligand, histamine, thrombin, endotoxin, and PDGF-BB as well as aggregated LDL and lysophosphatidic acid induce TF expression in vascular smooth muscle cells. In general, the extent of inducibility in response to these mediators appears to be lower than that observed in endothelial cells or monocytes. Relatively few studies have investigated the molecular mechanisms regulating TF expression in vascular smooth muscle cells. Similar to endothelial cells, an involvement of MAP kinases and PI3-kinase has been observed. In human vascular smooth muscle cells, p38 and PI3-kinase mediate thrombin-induced TF expression. In rat vascular smooth muscle cells, ERK is involved in TF expression to lysophosphatidic acid and PDGF-BB, whereas p38 and PI3-kinase do not play a role. Hence, the effect of MAP kinases and the PI3 kinase pathway appears to depend on the particular stimulus and/or the species involved.

Similar to endothelial cells, induction of vascular smooth muscle cell TF expression is only to some extent reflected in an increased TF activity. Consistent with this observation, vascular smooth muscle cell TF is found in three cellular pools, namely as surface TF, encrypted TF, and intracellular TF.

Monocytes and Macrophages

Monocytes, like endothelial cells, show very little to no basal expression of TF. Its expression can, however, be induced by inflammatory stimuli such as C-reactive protein or CD40 ligand. PDGF-BB, angiotensin II, and oxidized LDL have also been observed to induce TF in monocytes; yet one of the most extensively studied stimuli in this cell type is endotoxin. p38, ERK, and JNK are all involved in lipopolysaccharide-induced monocyte TF expression leading to nuclear translocation of the transcription factors EGR-1, c-Fos/c-Jun, and c-Rel/p65. Ultimately, binding of these transcription factors to the EGR-1, AP-1, and NF-κB sites of the TF promoter mediates the endotoxin-induced increase in TF mRNA transcription. Similar to endothelial cells, the PI3 kinase pathway exerts an inhibitory influence on TF induction in this cell type, and at least part of this action occurs through cross-talk with MAP kinases.

Type 1 (TH1) but not type 2 helper T cells (TH2) secrete mainly proinflammatory mediators such as TNF-α and interferon (IFN)-γ, which are involved in macrophage activation. Cytokines derived from TH1 cells as well as cell-to-cell contact with TH1 cells induces TF expression in monocytes. Transformation of monocyte-derived macrophages into foam cells results in increased TF expression as well. In contrast, TH2-derived mediators such as IL-4, IL-10, and IL-13 prevent TH1-induced TF expression. Thus, consistent with their role in macrophage activation and atherogenesis, proinflammatory stimuli released from TH1 cells upregulate TF expression, whereas cytokines derived from TH2 cells inhibit this effect.

Blood-Borne Tissue Factor

Tissue factor is not only present in vascular cells or leukocytes but can also be detected in the bloodstream, referred to as circulating or blood-borne TF. This form of TF is mainly associated with microparticles originating from endothelial cells, vascular smooth muscle cells, leukocytes, or platelets. In addition, TF containing microparticles are released from atherosclerotic plaques. Monocytes and platelets are known to exchange microparticle-bound TF. Because megakaryocytes, the bone marrow sedentary precursors of platelets, do not express TF, it is likely that this exchange represents a mechanism through which platelets are loaded with TF. In addition to carrying microparticle-derived TF, activated platelets induce tissue factor expression in human endothelial and smooth muscle cells, presumably by releasing soluble mediators such as serotonin and PDGF. Aggregating platelets thus induce a positive feedback loop that enhances local TF concentrations through two mechanisms and may be important for thrombus formation and/or propagation.

Recently, an alternatively spliced form of TF has been discovered, which is soluble, circulates in the blood, and exhibits procoagulant activity. Cytokines stimulate its expression in and release from endothelial cells. Alternatively spliced TF is not bound to microparticles and appears to represent a distinct form of circulating TF; as such, it may have an important role in thrombus propagation. Indeed, soluble TF may be particularly important in this context, as vessel wall-associated TF, being separated from the bloodstream by the freshly formed thrombus, may be prevented from contributing to thrombus growth.

These studies on blood-borne TF imply that activation of coagulation, contrary to traditional belief, may be initiated and propagated without contact of the blood to the extravascular space. The importance of blood-borne versus vessel wall-associated TF is currently a subject of debate. One study described that TF from leukocyte-derived microparticles importantly contributes to thrombus propagation in an animal model of thrombosis, whereas another one identified vessel wall–derived TF as the primary mediator driving thrombus formation after vascular injury. It is also controversial whether physiological concentrations of circulating TF can exhibit clot-forming activity in vivo.
relative contribution of soluble TF, microparticle-bound TF, and vessel wall–associated TF to initiation and propagation of thrombosis requires further study.

Tissue Factor in Cardiovascular Diseases
Tissue factor has been implicated in the pathogenesis of several cardiovascular disorders. The following section summarizes its involvement in cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking; its role in atherosclerosis and acute coronary syndromes is discussed as well.

Cardiovascular Risk Factors
Tissue factor plasma antigen is elevated in hypertensive subjects as compared with normotensive control subjects and can be lowered by different classes of antihypertensive drugs. Of particular interest is the observation that angiotensin II induces TF expression in monocytes, endothelial cells, and vascular smooth muscle cells through the angiotensin II type I receptor (AT-I). Consistently, both ACE inhibitors and AT-I receptor blockers reduce TF plasma activity in hypertensive patients. ACE inhibitors also reduce endotoxin-induced TF expression in monocytes, suggesting a pleiotropic effect of this class of drugs.

High glucose concentrations increase thrombin-induced TF expression in human endothelial cells. Similarly, glucose intake upregulates TF expression in monocytes of healthy humans. Hyperglycemia leads to the formation of advanced glycation end-products (AGE), which induce TF expression in endothelial cells through the receptor for advanced glycation end-products (RAGE) and activation of NF-κB. Consistently, both diabetic ApoE−/− mice display increased vascular expression of RAGE and TF; moreover, blockade of RAGE suppresses TF levels in the aorta of these mice, which may have interesting implications for the pathogenesis and treatment of diabetic vasculopathy. In diabetic patients, increased TF plasma levels are measured even without overt coronary artery disease, and TF levels are reduced by improving glycemic control. In obese nondiabetic subjects, insulin reduces both monocyte TF expression and TF plasma levels, which occurs due to a reduced activation of the proinflammatory transcription factor EGR-1, suggesting that insulin exerts its beneficial effects not only through improving hyperglycemia. Oxidized LDL increases TF expression in endothelial cells, monocytes, and macrophages, whereas reconstituted HDL inhibits thrombin-induced endothelial TF expression. Consistent with these observations, patients with elevated LDL levels display raised TF plasma activity. HMG-CoA reductase inhibitors (statins), the most widely used drugs for the treatment of hypercholesterolemia, reduce TF expression in monocytes, endothelial cells, and vascular smooth muscle cells. In apoE knockout mice, simvastatin inhibits TF expression in advanced atherosclerotic lesions independent of plasma lipid levels. Hence, the reduction of TF expression by statins is at least in part related to the pleiotropic antiinflammatory effects of this class of drugs. Consistent with this interpretation, endotoxin-induced TF expression is blunted after administration of simvastatin to healthy humans. Fabric acid derivatives are another class of drugs used to treat patients with dyslipidemia. Through activation of the peroxisome proliferator-activated receptor–α (PPAR-α), these drugs reduce TF expression in human monocytes and macrophages, which may in part be responsible for their beneficial effect in patients with cardiovascular diseases.

Exposure of apoE knockout mice to cigarette smoke results in an increased TF expression in atherosclerotic plaques as compared with mice breathing filtered room air. Cigarette smoking is associated with increased TF plasma levels in humans as well; indeed, a strong correlation is observed between the number of cigarettes smoked and TF plasma levels. These data indicate that TF may be involved in the proatherosclerotic effect of cardiovascular risk factors. It cannot be ruled out, however, that some of the observed elevations in TF plasma levels occur secondary to TF release from already established atherosclerotic plaques.

Atherosclerosis
Monocytes infiltrate the intimal layer and then transform into macrophages and foam cells, which represents a hallmark of the inflammatory nature of atherosclerosis. In this inflammatory environment, cytokines such as TNF-α and interleukins are released and induce expression of TF. During the early stages of atherogenesis, enhanced TF expression is observed in monocytes; at later stages, TF expression is also detected in foam cells, endothelial cells, and smooth muscle cells. TF is present in the necrotic core of plaques as well, predominantly associated with microparticles derived from perishing foam cells, macrophages, or lymphocytes. Such microparticles indeed contain the major part of the TF activity in atherosclerotic plaques. Consistent with these observations, TF expression is closely associated with apoptosis of macrophages in lipid-rich plaques, which adds to the evidence that not only inflammation but also apoptosis can determine plaque thrombogenicity.

Increasing size of atherosclerotic plaques can lead to vascular stenosis, which is associated with enhanced shear forces promoting endothelial TF expression. In most instances, however, it is not the degree of luminal narrowing, but rather the composition of the plaque which determines the clinical course of events. Lipid-rich plaques with a thin cap, a large lipid core, extensive macrophage infiltration, and abundant TF expression are more prone to rupture than collagen-rich, fibrous plaques. Rupture of an atherosclerotic plaque exposes its highly procoagulant content to the circulating blood; thereby, TF-laden macrophages as well as TF-containing microparticles originating from the necrotic core initiate thrombus formation and related complications such as acute myocardial infarction (Figure 3).

Besides activation of the coagulation cascade, TF is involved in other pathogenetic events occurring during the formation of atherosclerotic lesions. TF is the receptor for factor VIIa and as such mediates responses such as migration and proliferation of vascular smooth muscle cells. These processes are importantly involved in vascular remodeling, because vascular smooth muscle cells migrate into and proliferate within the neointima of injured vessels. The effect
of the TF/FVIIa complex on migration and proliferation of vascular smooth muscle cells is critically dependent on the cytoplasmic domain of TF, as vascular remodeling in response to injury is reduced in mice lacking this domain. Recruitment of microvessels into atherosclerotic plaques can lead to plaque progression by contributing to plaque destabilization and rupture. As TF is involved in angiogenesis, it may also play a role in plaque neovascularization and thereby promote plaque destabilization. Thus, evidence is emerging that TF may not only be involved in atherogenesis by eliciting thrombosis but also by direct actions on vascular remodeling and plaque progression or instability.

Acute Coronary Syndrome and Percutaneous Coronary Intervention

Increased levels of TF antigen and activity are detected in atherectomy specimens from patients with unstable angina or myocardial infarction as compared with those with stable angina. In acute coronary syndromes, plasma concentrations of inflammatory cytokines such as TNF-α and interleukins are indeed increased at the site of coronary artery occlusion to such an extent that TF is induced in vascular cells. Hence, vascular cells as well as circulating leukocytes and aggregating platelets may be a source of the elevated levels of circulating TF measured in patients with acute coronary syndrome. As plaque rupture leads to exposure of highly procoagulant plaque content to the circulation, it may also contribute to the elevated TF plasma levels. Consistent with this interpretation, patients with unstable angina show higher TF plasma levels than those with stable angina, and elevated TF plasma levels may even predict future cardiovascular events in patients with unstable angina. Because a substantial number of patients with acute myocardial infarction have coronary artery thrombi on top of a superficial erosion, increased TF plasma levels in these patients may also originate from endothelial erosions of atherosclerotic lesions. Interestingly, several polymorphisms of the TF gene are known, and recent data suggest that certain genetic variations in the TF gene as well as the TF promoter may be associated with a worse outcome in patients with acute coronary syndrome, possibly through increased monocyte TF expression.

Selective cyclooxygenase-2 inhibitors (coxibs), rofecoxib in particular, have come under scrutiny as they are suspected of causing thrombotic complications in patients with cardiovascular diseases. This effect is believed to depend on inhibition of prostacyclin formation. Large-scale epidemiological studies have indeed suggested that rofecoxib intake is associated with an increased risk of myocardial infarction. This association, however, is not observed with celecoxib, which may be related to inhibition of TF expression by this coxib in endothelial cells. Given the importance of TF in the pathogenesis of acute coronary syndromes, this effect may account for the different occurrence of thrombotic complications between coxibs observed in epidemiological studies.

As neither rofecoxib nor the experimental coxib NS-398 inhibit endothelial TF expression, the effect of celecoxib appears to occur independent of cyclooxygenase inhibition; instead, it is mediated by decreasing TNF-α–induced JNK phosphorylation. Because platelets represent a major source of TF, it is conceivable that antiplatelet drugs, which are used for treating acute coronary syndromes, reduce TF expression as well as TF plasma levels. Indeed, the ADP receptor antagonist clopidogrel reduces TF expression in the ischemic coronary artery in an animal model of acute myocardial infarction. Moreover, as interaction with platelets induces TF expression in monocytes, the GPIIb/IIIa antagonist abciximab suppresses monocyte TF expression and activity by reducing platelet-monocyte cross-talk; likewise, abciximab reduces monocyte TF expression in patients undergoing carotid angioplasty with stenting. Aspirin, however, inhibits endotoxin-induced tran-
scriptional activation of TF expression in monocytes and may thus reduce TF plasma activity by direct actions on the regulation of TF expression as well. In contrast to these agents, long-term treatment with the oral anticoagulant warfarin increases soluble TF levels, probably as the result of decreased TF consumption.

Percutaneous coronary intervention is the preferred treatment for patients presenting with acute myocardial infarction. It is unclear whether or not TF plasma levels are increased after percutaneous coronary intervention, as some groups found an increase whereas others did not. It is conceivable that plaque dissection caused by balloon dilation may lead to exposure of plaque content to the bloodstream and thereby increase TF plasma levels. In the reperfusion phase, oxygen-derived free radicals were observed to mediate TF induction, whereas continuous inflammatory alterations of the atherosclerotic coronary arteries may increase TF levels at later stages. If present, increased TF levels have a negative prognostic value with regard to the development of restenosis.

Drug-eluting stents are covered with pharmacological agents, which, once released into the coronary artery after stent deployment, inhibit vascular smooth muscle cell proliferation and thereby restenosis. In contrast to reduced restenosis rates, however, the frequency of stent thromboses has not decreased with drug-eluting stents as compared with bare metal stents. Rapamycin, which is used for stent coating, increases endothelial TF expression, suggesting a potential role for this drug in the development of subacute stent thrombosis. However, additional studies are needed to assess the implications of these findings in vivo. Platelet activation is a crucial event in the pathogenesis of thrombus formation. The use of platelet receptor antagonists such as clopidogrel has indeed reduced the incidence of stent thrombosis, whereas withdrawal of antiplatelet therapy favors thrombus formation. Therefore, it will be of great interest to study the dynamic interaction between rapamycin and platelet activation as well as the spatio-temporal pattern of TF expression in the arterial wall after deployment of drug-eluting stents.

**Therapeutic Implications**

Various agents have been developed to specifically interfere with the action of TF and the TF/FVIIa complex (Figure 4). In contrast to classic antithrombotic drugs, these agents target the first steps of coagulation while leaving the downstream effectors intact. In addition, these drugs can interfere with promigratory or proproliferative effects of TF. In this section, we will focus on recently developed drugs specifically targeting TF, whereas nonspecific inhibitors will not be discussed.

**Inhibition of TF Synthesis**

A hairpin ribozyme, which destroys TF mRNA, abrogated induction of TF protein expression and activity in vascular smooth muscle cells. Similarly, antisense oligonucleotides, hybridizing to their complementary target mRNA and thereby preventing translation, inhibited TF induction in monocytes. An alternative approach takes advantage of curcumin, a naturally occurring pigment suppressing the activation of the transcription factors Egr-1, AP-1, and NF-κB, and resulting in inhibition of TNF-α-induced endothelial TF induction.
Although novel and intriguing, the clinical applicability of these approaches has not yet been examined.

Direct Inhibition of TF Action

Different antibody preparations directed against the TF antigen (TF Ab) have been tested in vivo. In a rabbit carotid artery thrombosis model, a monoclonal anti–TF Ab inhibited thrombus formation and shortened tissue plasminogen activator lysis time. Similarly, administration of a monoclonal anti–TF Ab reduced infarct size in a rabbit coronary artery ligation model as the result of reduced chemokine expression and leukocyte infiltration. In humans, a polyclonal anti–TF Ab reduced thrombogenicity of disrupted atherosclerotic plaques by impairing platelet and fibrin deposition. In a recent dose-escalating trial, a chimeric monoclonal anti–TF Ab potently inhibited thrombin formation in patients with stable coronary artery disease.

An alternative approach consists of a mutant form of TF, which binds to factor VIIa but exhibits reduced catalytic activity. In a rabbit model of arterial thrombosis, this protein displayed potent antithrombotic properties while causing less bleeding than heparin. Another mutated form of TF exhibited antithrombotic properties in a guinea pig model of recurrent arterial thrombosis.

Active-Site Inactivated Factor VIIa

Active-site inactivated factor VIIa (FVIIai) binds to TF but lacks catalytic activity; as such, it competes for TF with the physiologically occurring form of factor VIIa. Several animal studies examined the effect of FVIIai in vivo, demonstrating decreased recurrent arterial thrombosis, reduced infarct size, and improved reflow phenomenon; after administration of a single dose, the effect of FVIIai was long-lasting without affecting systemic hemostatic parameters. Application of a structurally different but functionally similar site-inactivated factor VIIa compound reduced restenosis in a femoral artery injury model, which may in part be due to the fact that TF as well as several downstream coagulation factors stimulate vascular smooth muscle cell migration and proliferation.

Recombinant Tissue Factor Pathway Inhibitor

Tissue factor activity is counterbalanced by its endogenous inhibitor, TFPI. TFPI interferes with activity of the TF/FVIIa complex by binding to the active site of FXa leading to formation of a quaternary complex with TF/FVIIa. Under physiological conditions, TFPI is mainly synthesized and released by endothelial cells. In animal models, recombinant TFPI (rTFPI) reduced fibrin deposition and neointimal thickening after balloon injury. In human atherosclerotic arteries, rTFPI diminished plaque thrombogenicity by inhibiting platelet and fibrin deposition.

Adenoviral gene transfer represents an alternative approach for application of a recombinant protein. Adenoviral overexpression of TFPI in injured arteries inhibited recurrent thrombosis induced by shear stress without affecting systemic coagulation parameters. Similarly, overexpression of TFPI reduced thrombogenicity as well as vascular remodeling of balloon-injured atherosclerotic arteries.

Based on these observations, clinical studies have investigated the safety and efficacy of rTFPI. Initial trials revealed promising results in various settings; a double-blinded, randomized, phase III trial in patients with severe sepsis and mild coagulopathy, however, failed to show a clinical benefit of rTFPI, whereas the frequency of severe adverse events with bleeding was increased. Further studies are needed to definitively assess the safety and efficacy of rTFPI as a therapeutic principle.

Nematode Anticoagulant Protein c2

Nematode anticoagulant protein c2 (NAPc2) is isolated from the saliva of the hookworm Ancylostoma caninum; it interferes with TF activity by binding to factor Xa or factor X before formation of a quaternary inhibitory complex with TF/FVIIa. Several studies in primates as well as first studies in humans revealed very promising results; in a phase II clinical trial, rNAPc2 indeed appeared safe and effective in preventing thrombin generation during coronary angioplasty in combination with aspirin, clopidogrel, and heparin.

Summary and Conclusions

Over the last years, major advances have been made in elucidating the molecular regulation of TF expression. Various cytokines, growth factors, and biogenic amines have been recognized to induce TF expression in endothelial cells, vascular smooth muscle cells, and monocytes. Signal transduction mechanisms specific for both the cell type and the stimulus involved regulate TF induction and cellular distribution. In addition to cellular TF, an important role of blood-borne TF is emerging; at present, however, the relative contribution of vessel wall–associated versus blood-borne TF to thrombus formation and/or propagation is debated.

Patients with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking have elevated plasma levels of TF, which may be involved in the proatherosclerotic effect of such risk factors. Moreover, TF expression is upregulated in the inflammatory environment of atherosclerotic plaques, and large amounts of TF are released during plaque rupture, leading to thrombus formation and elevated TF plasma levels in patients with unstable angina and acute coronary syndromes. As TF simulates vascular smooth muscle cell migration and proliferation, it may promote atherogenesis and restenosis not only by initiating thrombosis but also by direct actions on vascular remodeling and plaque progression.

Several promising therapeutic strategies have been developed for targeting the action of TF including antibodies against TF, site-inactivated factor VIIa, recombinant TFPI, and recombinant NAPc2. Despite recent setbacks with application of rTFPI, interfering with the TF pathway appears to be an attractive target for the treatment of cardiovascular diseases.

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None.

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