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Review

Tissue factor pathway inhibitor in atherosclerosis

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A R T I C L E I N F O

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A B S T R A C T

Tissue factor pathway inhibitor (TFPI) reduces the development of atherosclerosis by regulating tissue factor (TF) mediated coagulation pathway. In this review, we focus on recent findings on the inhibitory effects of TFPI on endothelial cell activation, vascular smooth muscle cell (VSMC) proliferation and migration, inflammatory cell recruitment and extracellular matrix which are associated with the development of atherosclerosis. Meanwhile, we are also concerned about the impact of TFPI levels and genetic polymorphisms on clinical atherogenesis. This article aims to explain the mechanism in inhibiting the development of atherosclerosis and clinical effects of TFPI, and provide new ideas for the clinical researches and mechanism studies of atherothrombosis.

1. Introduction

Atherosclerosis is the main cause of cardiovascular pathology, as well as morbidity and mortality worldwide. A large number of studies have shown that atherothrombosis is a chronic inflammatory disease, also an autoimmune disease, caused and maintained by the migration, proliferation and activation of immune cells [1,2]. Early, antigen presenting cells promote antigenic presentation in response to stimulating sources, including altered self-materials, thereby promoting adaptive immune responses [3]. T cells and macrophages activated by TLR (Toll-like receptor) ligands and scavenger receptors enter the endothelium, forming an inflammatory environment and promoting plaque formation [4–6]. Inflammatory cytokines accelerate and continue atherogenesis. Tissue factor (TF) is involved in the pathogenesis of atherosclerosis by promoting thrombus formation, inflammation, migration and proliferation of vascular smooth muscle cells (VSMCs) [7]. Tissue factor pathway inhibitor (TFPI) inhibits TF activity and reduces the development of atherosclerosis.

2. Structure and function of TFPI

TFPI is a protein produced by the alternative splicing event occurring at the 3′ and 5′ ends of the precursor of TFPI mRNA (precursor mRNA). Several spliced TFPI protein isoforms with different anticoagulant activities were generated after splicing including TFPI α and TFPI β expressed in all mammalian and TFPI δ produced in humans and TFPI γ produced in mice only [8]. The latter two isoforms have low levels of transcription in vivo. TFPI α is the first isolated form of TFPI containing three tandemly arranged Kunitz-type protease inhibitor domains, K1, K2 and K3, consisting of a negatively charged amino terminus and a positively charged carboxyl group End composition. TFPI β lacks K3 and instead has an alternative carboxy terminus that binds to glycosylphosphatidylinositol (GPI) anchoring [9].

The differences in the mRNA splicing patterns of TFPI α and TFPI β lead to the unique physiological characteristics of both. The TFPI α and TFPI β isoforms are differentially expressed in platelets and endothelial cells, respectively, and have different mechanisms associated with the cell surface. TFPIα attaches to the cell surface by attaching to unidentified GPI-linked proteins. While TFPI β binds directly to endothelial cells because it contains a C-terminal GPI anchoring sequence [10]. The positively charged C-terminus of TFPIα mediates the binding of TFPIα to the endothelial surface and increases the affinity of TFPIα for negatively charged glycosaminoglycans and thrombin on the EC surface, and FVII-activated proteases and lipoprotein receptor-related proteins [8,11]. That reduces TFPI plasma levels and accelerates the degradation and clearance of TFPI α. Plasma cholesterol is lowered through the

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interaction of its carboxyl terminus with lipoproteins and heparan sulfate proteoglycans [12]. The TFPI α alkaline C-terminal region was found to have almost the same amino acid sequence as the basic region of the factor V (FV) B domain. While, this acidic region of the B domain interacts with a basic region within the B domain in order to keep the FV in an inactive facilitator conformation [13]. The C-terminus of TFPIα binds to the acidic region of the B-domain of FV and inhibits FV activation by preventing cleavage of Arg1545 [14,15]. The K1, K2 domains of TFPI α and TFPI β inhibit TF-FVIIa complex activating factor X (FX) by interacting with the active site of activated factor X (FXa) and the active site of activated factor VII (FVIIa), respectively [16,17]. In fact, TFPI β has a better inhibitory effect on TF-FVIIa [18]. Some researchers found that TFPI β can effectively inhibit TF-FVIIa-mediated cell migration in vitro, and found in Chinese hamster model that it can effectively inhibit TF-mediated cell infiltration into lung tissue. Similarly, inhibition of TFPI β expression in breast cancer cells results in enhancing cell migration [16,18]. As a GPI-anchored protein, TFPI β is localized in the cell membrane microenvironment, called the caveolae, and studies have shown that direct inhibition of FXa by TFPI β is unaffected but enhances its anti-TF activity [19].

2.1. The role of TFPI on endothelial cell activation

Activation of endothelial cells (EC) results in leukocyte-EC interactions and leukocyte infiltration in atherosclerosis (Fig. 1). Vascular EC injury by lipids is the first event in the development of atherosclerosis. In response to injury, vascular endothelium is activated, with expression of adhesion molecules and release of chemokines such as chemokine (C–C motif) ligand 2(CCL2) which causes recruitment of lipid-laden monocytes into the subendothelium to create an inflammatory environment and promote atherosclerosis. It is well known that thrombin, a multifunctional plasma serine protease generated by the actions of tissue factor (TF) on circulating coagulation zymogens, modulates atherosclerotic lesions by stimulating a variety of cellular effects including through activation of EC in early and late atherosclerosis [20–23]. Thrombin activates EC to express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), and to release CCL2, which facilitates the recruitment of inflammatory cells into the vessel wall [24,25], accelerating VSMC migration and proliferation, and inducing the production of various pro-inflammatory markers [21,26,27]. Thrombin signals through PAR-1 to mediate these proatherogenic effects [28]. Various therapeutic agents that directly inhibit thrombin have been developed in recent years. Abundant evidences show that pharmacological inhibition of thrombin reduces progression of atherosclerosis by regulating endothelial barrier function and monocyte migration [22]. TFPI, which inactivates TF, factor (F)VIIa and FXa and reversibly inhibits thrombin generation [29–31], suppresses VCAM-1, TNF-α, CCL2 and MMP expression, and reduces the development of atherosclerosis [32,33]. In addition, TFPI inhibits endothelial cell activation through directly binding to very low-density lipoprotein receptor (VLDLR) [34,35].

2.2. The role of TFPI on macrophage function

Macrophages, as important inflammatory cells, play a crucial role in the development of atherosclerosis (Fig. 2). Activated macrophages phagocytose lipids to form foam cells which initiate the formation of atherosclerosis lesions while secreting a large number of chemokines (MCP-1, etc.), adhesion molecules (ICAM-1, etc.) and pro-inflammatory factors, promoting more inflammatory cells gathering. That accelerates the pathological process of atherosclerosis. In vivo, polarized macrophages can be divided mainly into two categories, namely M1 macrophages and M2 macrophages. The former has an effect of promoting inflammation, and the latter has effects of inhibiting inflammation and promoting tissue repair [36]. In M2 macrophages, cholesterol crystals (CC) induce an endoplasmic reticulum (ER) stress pathway-dependent pro-inflammatory response [37].TFPI protects against ER stress-induced inflammation by attenuating the upregulation of pro-inflammatory factors and downregulation of anti-inflammatory cytokines in M2 macrophages. In addition, a number of studies have found that TFPI significantly inhibits the inflammatory response and may have an inhibitory effect on atherosclerotic inflammatory response and stable atherosclerotic plaque [38,39]. TFPI alleviates atherosclerosis by regulating macrophage differentiation, inhibiting proliferation and foam cell formation [40]. Recombinant TFPI plays a protective role against atherosclerosis by enhancing macrophage apoptosis via upregulation of Fas/FasL [41].

2.3. The role of TFPI on VSMC proliferation and migration

A prominent feature of atherosclerosis is the proliferation and migration of smooth muscle cells (Fig. 3). In recent years, angiopoietin (AMOT) has been found to be critical for regulating the Hippo signaling pathway [42]. Phosphorylation of the YES-associated protein (YAP), a key component of the Hippo signaling pathway, is involved in cell proliferation and migration [43]. Studies have confirmed that TFPI deficiency in $ApoE^{-/-}$ mouse vascular smooth muscle cells can accelerate the proliferation and migration of VSMC by decreasing the phosphorylation levels of AMOT and YAP, up-regulating the expression of proliferation and migration genes involved (CTGF, SLUG), thereby accelerating the development of atherosclerosis [44]. Fu et al. demonstrated that TFPI gene transfer induced VSMC apoptosis and affected its proliferation by inhibiting phosphorylation of the JAK-2/STAT-3 signaling pathway [45]. Later, they further suggested that TFPI inhibited TNF-α-induced VSMC proliferation by inhibiting the expression of MCP-3 and CCR2 and blocking phosphorylation of ERK 1/2 and PI3K/AKT signaling pathways [46]. Furthermore, TFPI inhibits proliferation and migration of VSMC by inhibiting MMP-2 and MMP-9 activities and inhibiting FAK phosphorylation which is a non-receptor protein tyrosine kinases that coordinate integrin and growth factor signaling cascades involved in VSMCs matrix invasion and migration [47].

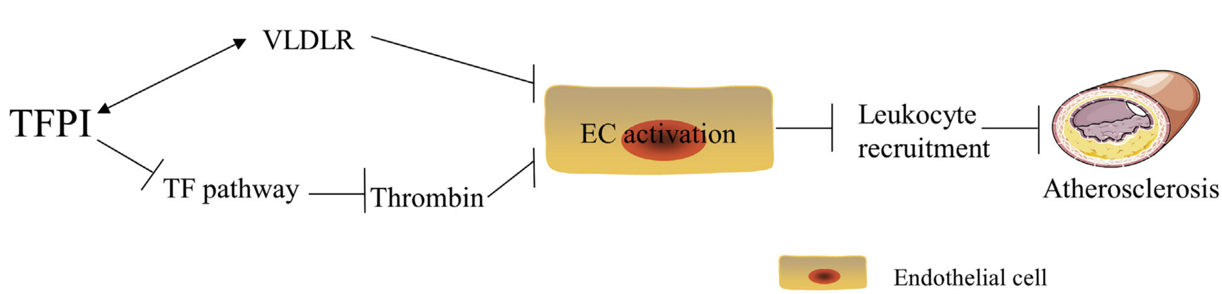

Fig. 1. Potential anti-atherosclerosis effects of TFPI in EC. TFPI can inhibit endothelial cell activation not only by binding to VLDLR but also by reducing thrombin production, which inhibits the development of atherogenesis. TFPI: tissue factor pathway inhibitor; TF pathway: tissue factor pathway; EC: endothelial cell; VLDLR: very low-density lipoprotein receptor.

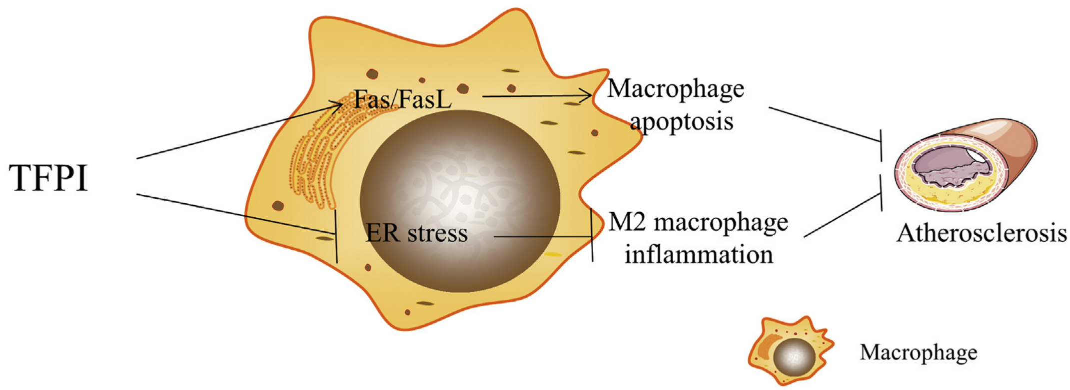

Fig. 2. Potential anti-atherosclerosis effects of TFPI in macrophage. TFPI exerts an inhibitive role against atherogenesis via enhancing macrophage apoptosis when Fas/FasL is upregulated. Similarly, TFPI may to suppress ER stress in M2 macrophages to reduce inflammation, followed by inhibition of atherothrombosis. ER stress: endoplasmic reticulum stress.

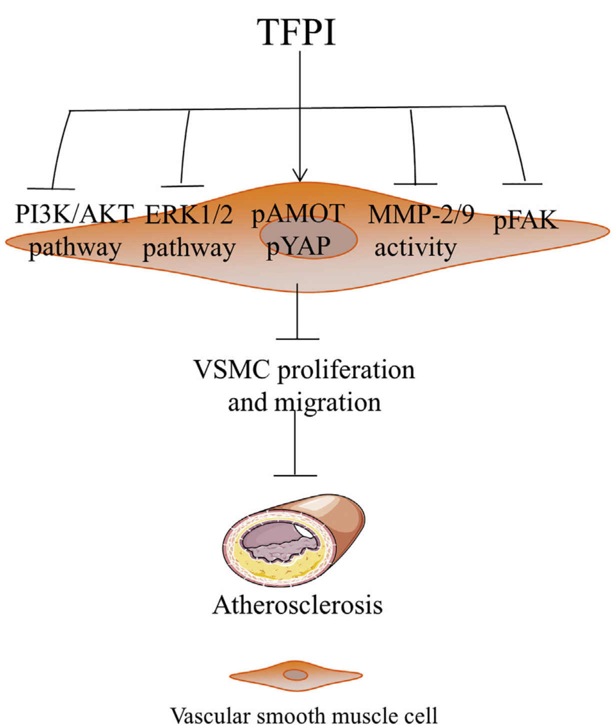

Fig. 3. Potential anti-atherosclerosis effects of TFPI in VSMC. The interference of TFPI on multiple signaling pathways or molecular activity can result in an inhibition of the migration and proliferation of VSMC, consequently exerting an anti-atherogenesis effect. VSMC: smooth muscle cell.

2.4. The role of TFPI on lipid metabolism

In the past two decades, multiple large trials have shown that most cholesterol-lowering statin drugs slow progression of, rather than reverse atherosclerosis [48,49]; that is apart from the slight regression shown with a high dose of the potent drug atorvastatin [50] and the moderate regression shown by the very potent rosuvastatin, in highrisk patients [51]. TFPI was originally named lipoprotein associated coagulation inhibitor due to its ability to bind to lipoproteins (Fig. 4). Circulating (soluble) TFPI predominately binds to lipoproteins in human plasma and is cleared by the complex binding low density lipoprotein (LDL) receptor related protein and heparin sulfate proteoglycans, in the process clearing lipoproteins bound to TFPI [12,52]. Importantly, the c-terminus of TFPI (TFPIct) is required for binding to lipoproteins [53,54] or to the VLDL receptor [55]. TFPIct has the ability to stimulate VLDL uptake, internalization, and degradation in vascular cells and embryonic fibroblasts [12]. Intravenous injection of TFPIct alone seems sufficient to significantly lower plasma cholesterol and reduce atherosclerotic plaque formation in Apo E deficient mice [12].

2.5. The role of TFPI on MMP activity

The destruction of the integrity of the fibrous cap of atherosclerotic plaque is mainly due to the degradation of proteins in fibrillar collagen, elastin and proteoglycan in ECM, which reduces the stability of atherosclerotic plaque [56]. Finally, it can cause plaque rupture, hemorrhage, and thrombosis. Tissue-type matrix metalloproteinase inhibitor (TIMP) and peroxisome proliferator-activated receptor-gamma (PPAR-γ) have inhibitory effects on MMP. The former is a natural inhibitor that has an inhibitory effect on MMP activity. The latter is a nuclear receptor, which can achieve anti-inflammatory effects by inhibiting the activity of pro-inflammatory transcription factors such as AP-1 and STAT, and can inhibit the expression of MMP to maintain plaque stability [57]. Many proteins have been found to contain amino acid sequences similar to the amino terminus of TIMP and may act as inhibitors of MMP. One of the regions in the TFPI molecular structure is similar to TIMP, and thus can directly inhibit the activity of MMP. Moreover, compared to TIMP's only inhibitory effect on collagenase, TFPI inhibits the role of proteases more generally and plays a more powerful role [58]. Zhao et al. have found that TFPI can inhibit the activity of MMP and reduce the degradation of ECM and inhibit the migration of VSMC [47]. But whether this inhibition is indirect or direct is controversial. Studies have shown that TFPI can inhibit the expression of MMP-2, 9 by promoting PPAR-γ phosphorylation, thereby reducing the degradation of ECM, which slows the occurrence of atherosclerotic lesions and increases the stability of plaque [57] (Fig. 4). In addition, some researchers have demonstrated that TFPI can indirectly inhibit the activation of plasmin and trypsin-mediated MMP, which is conducive to plaque stabilization.

2.6. The role of TFPI on thrombin production

Thrombin is a downstream product of TF-induced coagulation. In addition to its role in the coagulation pathway, it can also play a regulatory role in many processes, such as regulating vascular tone and permeability, promoting neovascularization, and accelerating VSMC migration and proliferation, recruiting monocytes to atherosclerotic lesions, inducing the production of various pro-inflammatory markers, and the like [21,26,27]. These effects accelerate the development of atherosclerosis. Thrombin inhibitors have been reported to increase plaque stability and reduce plaque area. TFPI, a potent inhibitor of TF-mediated thrombin generation, blocks TF-FVIIa complexes and inhibits FXa production in an FXa-dependent manner, which inhibits thrombin

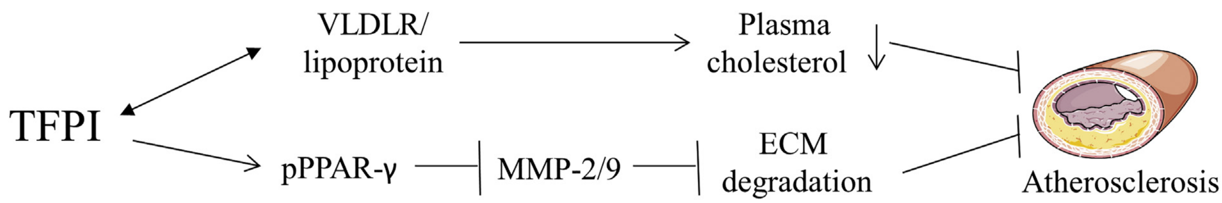

Fig. 4. Potential anti-atherosclerosis effects of TFPI in extracellular matrix degradation and lipid metabolism. The combination of TFPI and VLDLR/lipoprotein promotes a decrease in plasma cholesterol and attenuates the progression of atherothrombosis. TFPI inhibits the degradation of EMC to promote plaque stabilization and prevent the development of atherogenesis. PPAR-γ: phosphorylated peroxisome proliferator-activated receptor-gamma; ECM: extracellular matrix.

formation [38,59,60]. And it also inhibits protease-activated receptors (PARs) pathway which is needed by thrombin to induce a variety of vascular pro-inflammatory responses. Furthermore, although the C-terminus of TFPI binding to the acidic B domain of FVa inhibits the formation of thrombin by inhibiting the formation of prothrombinase [10], there is currently insufficient evidence to prove that TFPI can affect the development of atherosclerosis by this way.

2.7. Clinical studies on TFPI in atherosclerosis

Normally, TFPI is expressed in the microvascular endothelium [61]. However, TFPI mRNA and TFPI protein were detected in carotid and coronary arteries with atherothrombotic lesions [61,62]. Since then, some researchers have found that lacking TFPI exacerbates atherogenesis in ApoE$^{-/-}$ mice [57]; while overexpression of TFPI increases the stability of atherosclerotic plaque in ApoE$^{-/-}$ mice [38,63]. A number of clinical studies have shown that TFPI is associated with atherosclerosis [62,64–66]. Toshiyuki Sakata et al. analyzed the association of intimal-medial thickness (IMT), an indicator of atherothrombosis, with hemostatic markers in 522 non-cardiovascular adults enrolled in the Suita study [64]. In this study, free TFPI levels were found to be positively and independently correlated with the degree of IMT in men, not women, and demonstrated the potential of free TFPI as a useful marker of early atherothrombosis. In a multi-ethnic study of atherosclerosis, the researchers found that plasma total TFPI was positively associated with IMT in different genders and races [65]. While in others studies, researchers have found that TFPI expression was increased in atherosclerotic plaques of asymptomatic individuals and symptomatic patients [62]. TFPI levels were also positively correlated with carotid intima-media thickness (cIMT) in studies of advanced subclinical atherothrombosis in HIV-infected patients [66]. Some investigators conducted a prospective observational study of 50 patients with coronary artery disease (CAD) and 30 patients with normal coronary arteries [67]. It was revealed that the burden of atherogenesis is associated with increased TFPI activity.

Based on the correlation between TFPI and atherosclerosis, researchers have conducted a series of studies on the effects of TFPI gene polymorphisms in atherosclerosis [68–70]. Single nucleotide polymorphisms (SNPs) were selected by HapMap data and dbSNP data [68]. Identification of potential functional polymorphisms according to the criteria, 9 SNPs of TFPI-2 (rs3763473, rs59805398, rs60215632, rs59999573, rs59740167, rs34489123, rs4517, rs4264 and rs4271) were retained in the study. Data and specimens of 470 patients with coronary atherothrombosis and 306 patients with normal coronary arteries were studied. After grouping with the Gensini score, the researchers analyzed adjusted data for age, gender, hyperlipidemia, and diabetes by multivariate regression analysis. The rs59805398 CC genotype and C allele have a significant impact on the risk of coronary atherosclerosis (odds ratio 2.88, 95% confidence interval [1.84–4.506]; odds ratio 1.99, 95% confidence interval [1.56–2.55]). Similarly, the rs34489123 AA genotype and the A allele have a important influence on the risk of coronary atherogenesis (odds ratio 2.76, 95% confidence interval [1.26–6.07]; odds ratio 1.85, 95% confidence interval [1.38–2.49]). It was thus found that the two genomes (rs59805398 and rs34489123) are associated with coronary atherogenesis in the Chinese population and can be used to assess the risk of coronary atherosclerosis. In a study of 610 patients with coronary atherosclerosis and 1223 healthy controls, the A allele of rs34489123 and the G allele of rs4264 of TFPI-2 gene were found to be associated with an increased risk of coronary atherosclerosis [69]. Using logistic regression to assess the relationship between 4 SNPs and coronary atherosclerosis, it was found that the risk of coronary atherosclerosis was significantly increased in the TFPI-2 gene in the A allele of rs34489123 and the G allele carrier of rs4264 (odds ratio 1.70, 95% confidence interval [1.20–2.31], odds ratio 1.62, 95% confidence interval [1.21–2.11]). In addition, some researchers studied 1271 patients with coronary atherogenesis and 1287 normal people in northern China, and found that two SNPs of TFPI (rs7586970 and rs6434222) affect the risk of coronary atherogenesis [70].

3. Summary and perspectives

TFPI is a class of anticoagulant serine protease inhibitors with a Kunitz-type domain , and is the only natural species known to regulate TF-mediated extrinsic coagulation pathways. TFPI achieves unique antithrombotic by forming a TF-FVIIa-TFPI-FXa quaternary complex with active molecules in the TF pathway, inhibiting activated FVIIa and FXa, and reducing thrombin generation [63]. In addition, TFPI inhibits the development of atherosclerosis by inhibiting the activity of endothelial cells, promoting apoptosis of macrophages at plaques, blocking the activity of MMP, inhibiting the proliferation and migration of VSMC, and inhibiting the secretion of pro-inflammatory factors [71]. Current research suggests that TFPI has anti-atherosclerotic and antithrombotic effects, and its genetic polymorphism is also associated with an increased risk of atherosclerosis. Because the development of atherosclerosis is a complex process, TFPI may have other mechanisms of action to exert anti-atherosclerosis, even to subside plaque by regulating cell migration and lipid reduction in plaques. In future clinical studies, attention should be paid to the effects of TFPI on atherosclerosis in different regions of the world, and the genetic polymorphisms of its various isoforms on atherosclerosis also the same. Meanwhile, clinical studies should confirm whether TFPI can be used as a biomarker to predict clinical atherogenesis and its prognosis.

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