Editorial

New Insights of the Tissue Factor Pathway Inhibitor in Patients with Hypercholesterolemia Treated with Statins

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It has been previously reported that statins reduce the risk of cardiovascular events through the reduction of the cholesterol level, the improvement of the endothelial function, the suppression of inflammation, plaque stabilization, the downregulation of tissue factor (TF) and plasminogen activator inhibitor-1 and the upregulation of thrombomodulin (TM)¹⁻³. Sekiya *et al.* reported that fluvastatin increases the endothelial tissue factor pathway inhibitor (TFPI) expression through the inhibition of mevalonate-, GGPP-, and Cdc42-dependent signaling pathways and the activation of the p38 MAPK, P13K and PKC pathways⁴. We herein discuss new evidence regarding the pleiotropic effect of statins for the upregulation of TFPI.

TFPI is the primary physiological regulator of TF-induced blood coagulation. There are two major isoforms of TFPI *in vivo*: TFPI α , which contains three Kunitz-type inhibitory domains (designated K1, K2, and K3) and is secreted by endothelial cells and platelets⁵ and TFPI β , which contains only the K1 and K2 domains and is attached to the endothelial surface via a glycosylphosphatidylinositol (GI) anchor. TFPI α and TFPI β , which inhibit the generation of TF-factor VIIa-dependent factor Xa (FXa) and free FXa, have been demonstrated to play pivotal roles in the biochemical and physiological mechanisms that underlie bleeding and clotting disorders⁵.

The immunodepletion of TFPI has been reported to increase the development of disseminated intravascular coagulation (DIC) in animal models⁶. TFPI^{+/-}

mice demonstrated a mild procoagulant state⁷ which was enhanced by TFPI heterozygosity with other procoagulant mutations, such as FV Leiden⁸ or partial TM deficiency⁷. Although TFPI deficiency has not yet been described clinically, the plasma TFPI α level is reported to be slightly low in the patients with thrombotic states⁹⁻¹¹. Oral estrogen therapy induces the reduction of total TFPI concentration and activity¹². Although TFPI α (free TFPI) does not bind with lipoproteins, total TFPI associates tightly with lipoproteins. TFPI α , which contributes approximately 10-30% of the total TFPI pool, is thought to be the more predominant form of the anticoagulant¹³. The plasma concentration of TFPI α rapidly increases two- to four-fold following heparin infusion¹⁴. The inhibition of the TFPI activity has been recently investigated as a treatment strategy for hemophilia and was demonstrated to improve hemostasis in several hemophilia animal models^{15, 16}.

Thus, the regulation of TFPI by statins may play an important role in the anticoagulant effects of the patients with hypercholesterolemia.

Competing Interests

The authors have no competing interests to declare in association with this study.

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Fig. 1. New insights of the tissue factor pathway inhibitor.

TF: tissue factor, TFPI: tissue factor pathway inhibitor, TM: thrombomodulin, PAI-I: plasminogen activator inhibitor-I, DIC: disseminated intravascular coagulation, and VTE: venous thromboembolism

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