Editorial

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

Hideo Wada1, Takuya Aota2, Yoshiki Yamashita2, Takeshi Matsumoto3 and Naoyuki Katayama2

1 Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Japan
2 Department of Hematology and Oncology, Mie University School of Medicine, Tsu, Japan
3 Blood Transfusion, Mie University Hospital, Tsu, Japan

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-I 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: TFPIα, which contains three Kunitz-type inhibitory domains (designated K1, K2, and K3) and is secreted by endothelial cells and platelets5) and TFPIβ, which contains only the K1 and K2 domains and is attached to the endothelial surface via a glycosylphosphatidylinositol (GI) anchor. TFPIα and TFPIβ, 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 TFPIα level is reported to be slightly low in the patients with thrombotic states9,10). Oral estrogen therapy induces the reduction of total TFPI concentration and activity11). Although TFPIα (free TFPI) does not bind with lipoproteins, total TFPI associates tightly with lipoproteins. TFPIα, 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 TFPIα rapidly increases two- to fourfold 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 models15, 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.

Acknowledgments

This work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan for Blood Coagulation Abnormalities and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1) Masamura K, Oida K, Kanehara H, Suzuki J, Horie S, Ishii H, Miyamori I: Pitavastatin-induced thrombomodu-
Cholesterol level ↓, improvement of endothelial function, suppression of inflammation, plaque stabilization, TF ↓, PAI-I ↓, TM ↑

Statin

TFPI ↑ ↔ Cardiovascular Events ↓

TFPI ↓ (mild prothrombotic state) + other thrombophilia

Treatment of Hemophilia

Thrombosis

- FVIII or FIX deficiency
- Prothrombotic state
- VTE
- Ischemic diseases
- DIC
- Estrogen therapy

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


