Recent Advances in the Understanding of Thrombosis

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Endothelial dysfunction and the resultant upregulation of adhesion molecules on inflammatory cells lead to the development of vascular diseases.[1–3] Inflammatory cells secrete cytokines/chemokines and growth factors, induce endothelial dysfunction, and promote the proliferation of vascular smooth muscle cells.[4] In turn, activated endothelial cells (ECs) and vascular smooth muscle cells secrete multiple factors, which activate platelets and the coagulation-fibrinolysis system.[5–7] These factors also affect the vascular cells themselves in an autocrine/paracrine manner.[8,9] During the secretion of vasoactive factors, excessive and continuous activation of the Rho-kinase system plays a crucial role in the production of reactive oxygen species.[10–12] Additionally, excessive reactive oxygen species production (oxidative stress) causes endothelial dysfunction,[13] enhances expression of adhesion molecules, and activates platelets and the coagulation system.[8,14–24] Together with the authors' previous works on cardiovascular diseases, many studies have recently provided evidence for the importance of platelets and the coagulation-fibrinolysis systems in the development of vascular diseases.[25,26] The objective of this review is to highlight novel research about thrombosis in the field of vascular medicine.

Venous Thromboembolism

Venous thromboembolism (VTE) consists of deep vein thrombosis and pulmonary thromboembolism.[27,28] Pulmonary thromboembolism is a life-threatening manifestation of venous thromboembolism with a high recurrence rate after cessation of anticoagulation therapy.[29] Deep vein thrombosis is often associated with pulmonary thromboembolism and hospitalized patients are at high risk of VTE.[29] There are several risk factors, including genetic conditions, obesity, drugs, pregnancy, aging, trauma, and malignancy.[30] In a mechanistic study, Stark et al[28] demonstrated that pancreatic cancer cell–derived microvesicles induce thrombosis in mice. Moreover, they demonstrated that the tumor-derived microparticles express TF (tissue factor). [28] Another study suggested a novel pathway through which microvesicles induce thrombosis.[31] Additionally, premenopausal women taking hormonal contraception are at high risk of VTE.[32] Predictors of VTE recurrence include advanced age, obesity, male sex, active cancer, proximal deep vein thrombosis, elevated D-dimer levels after cessation of anticoagulation, antiphospholipid syndrome, antithrombin, protein C or protein S deficiency, pregnancy, and <3-month duration of anticoagulant treatment.[29] Endothelial damage, stasis, and blood hypercoagulability are important in the development of venous thrombosis.[27] Proinflammatory cytokines/chemokines play a crucial role in endothelial activation, damage, and adhesion molecule expression, promoting thrombus formation.[33–35] The mechanisms for the development of venous or arterial thrombi are different.[36] In particular, the development of venous thrombi is mainly attributable to venous stasis.[37] Recently, Nosaka et al[36] demonstrated that the absence of TNF-Rp55 (tumor necrosis factor receptor p55) delayed the resolution of venous thrombosis. In a murine venous thrombus model, they demonstrated that the TNFα-TNF-Rp55 axis could have an antithrombotic role in venous thrombosis by enhancing fibrinolysis and collagenolysis. Anticoagulant therapy is mainly used to prevent pulmonary thromboembolism and also to prevent the growth of the deep vein thrombosis, but it increases the incidence of bleeding complications.[28,38] In contrast, Nosaka et al's[36] study implied that the TNFα-TNF-Rp55 axis might be a novel target for thrombus resolution. However, in a recent issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Lehmann et al[39] demonstrated that platelets drive thrombus propagation in a hematocrit and glycoprotein VI–dependent manner in an in vitro venous thrombosis model. Importantly, those authors developed an in vitro experimental system that leverages the conventional advantages of microfluidic models using several key advances.[39,40]

Chronic Thromboembolic Pulmonary Hypertension

Although chronic thromboembolic pulmonary hypertension (CTEPH) and acute pulmonary embolism share some clinical manifestations, a limited proportion of patients with CTEPH have a history of acute pulmonary embolism.[41] Moreover, the risk factors of the development of CTEPH are different from the traditional risk factors of acute pulmonary embolism. Endothelial dysfunction seems to be involved in the pathogenesis of CTEPH.[42] Additionally, patients with CTEPH show distal pulmonary artery remodeling, which is similar to pulmonary arterial hypertension.[43] Recently, we demonstrated that the TAFI (thrombin-activatable fibrinolysis inhibitor) is a novel biomarker for patients with CTEPH.[42,44] CTEPH is one type of pulmonary hypertension categorized as group IV by the World Health Organization.[45–48] During the past 10 years, balloon pulmonary angioplasty has significantly improved the prognosis of CTEPH patients.[49–52] However, the pathogenesis of CTEPH remains to be fully elucidated. Thus,

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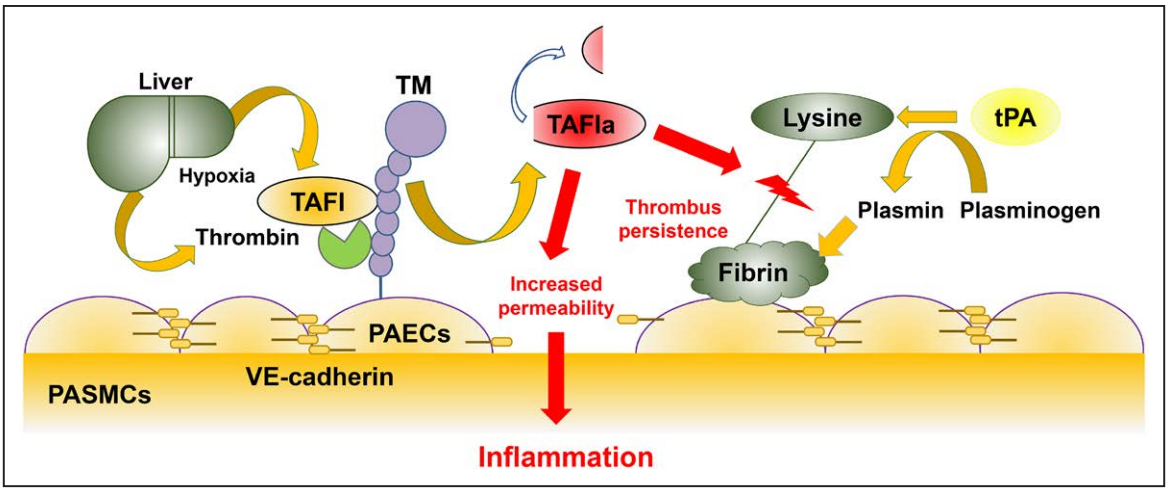

Figure. Increased plasma levels of activated TAFI (thrombin-activatable fibrinolysis inhibitor) and thrombosis in chronic thromboembolic pulmonary hypertension (CTEPH). The major findings of the present study: (1) plasma levels of TAFIa (activated TAFI) are markedly increased in CTEPH patients, (2) TAFI knockdown attenuates the development of hypoxia-induced pulmonary hypertension (PH), (3) TAFI overexpression promotes the development of hypoxia-induced PH and thrombus formation, (4) 3-dimensional computed tomography shows multiple obstruction of pulmonary arteries in TAFI-overexpressing mice, (5) the plasma from patients with CTEPH enhances pulmonary artery endothelial cell (PAEC) permeability and pulmonary artery smooth muscle cell (PASMC) proliferation, and (6) TAFIa inhibitor and PPARα (peroxisome proliferator-activated receptor-α) agonists reduces plasma TAFI and ameliorates the development of PH in mice and rats. TM indicates thrombomodulin; tPA, tissue-type plasminogen activator; and VE-cadherin, vascular endothelial cadherin.

we have tried to elucidate the pathogenesis of this disorder. Importantly, plasma levels of TAFI (also known as carboxypeptidase B2, coded by *CPB2*) are significantly elevated in CTEPH patients.[42,44] Additionally, we found that the minor allele *CPB2* is present in those patients.[44] TAFI is a glycoprotein that is cleaved and activated by the interaction with thrombin and thrombomodulin in vascular beds. The TAFIa (activated TAFI) reduces plasmin activity and inhibits fibrinolysis (Figure). We found that the plasma levels of TAFI are positively correlated with the clot lysis time in CTEPH patients.[44] Thus, we hypothesized that TAFI is directly involved in the pathogenesis of thrombus formation in pulmonary arteries, promoting the development of CTEPH. To test this hypothesis, we used 3 genetically modified mice models for TAFI, including systemic knockout, systemic overexpressing, and liver-specific overexpressing mice, in combination with a bone marrow transplantation technique.[42] Importantly, TAFI levels are markedly increased not only in the plasma but also in the pulmonary arteries of CTEPH patients. Plasma TAFI was locally activated by thrombomodulin in pulmonary vascular beds, inhibiting fibrinolysis and promoting both thrombus formation and pulmonary hypertension in mice (Figure). Thus, we performed an in silico screening using the Life Science Knowledge Bank database and found several TAFIa inhibitors that ameliorated the development of pulmonary hypertension in mice.[42] Among them, we found that PPARα (peroxisome proliferator-activated receptor-α) agonists significantly reduced liver TAFI synthesis and ameliorated pulmonary hypertension in mice and rats.[42] Thus, TAFIa could be a novel and promising therapeutic target in CTEPH.

Roles of Platelets in Arterial Thrombosis

Arterial thrombosis is the underlying cause of heart attacks and strokes, which are the leading cause of morbidity and mortality worldwide.[53–55] Platelets play a crucial role in the development of arterial thrombosis at the sites of atherosclerotic plaque rupture.[56] Binding of ADP and thromboxane A_2 to their receptors ($P2Y_1$ and $P2Y_{12}$, and thromboxane receptor, respectively) induce aggregation of platelets.[57,58] In clinical settings, antiplatelet agents, such as clopidogrel, prasugrel, ticagrelor, and acetylsalicylic acid, are used to exert antithrombotic effects.[59–61] Based on this background, Ni et al[62] sought to elucidate the effect of different doses of acetylsalicylic acid on the antithrombotic activity of clopidogrel in a mouse model of arterial thrombosis. Those researchers provided in vivo evidence that acetylsalicylic acid potentiates the antithrombotic effect of clopidogrel when it is given at doses that do not impair prostacyclin formation; if administered in doses that reduce prostacyclin formation, acetylsalicylic acid attenuated the antithrombotic effect of clopidogrel.

Platelets accumulate at the site of vascular injury and are involved in many physiological and pathophysiological processes, including hemostasis and thrombosis.[63,64] Recently, Abdelgawwad et al[65] demonstrated that the transfusion of recombinant ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats 13)-loaded platelets are a potential therapeutic method for arterial thrombosis, particularly in association with congenital and acquired immune-mediated thrombotic thrombocytopenic purpura.[66] Those authors concluded that the transfusion of recombinant ADAMTS13-loaded platelets could be developed as a potential novel therapeutic strategy for arterial thrombosis. Next, Ral GTPases are important drivers of cell proliferation and metastasis in multiple human cancers and regulate cell adhesion and membrane trafficking, including exocytosis.[63,64] Recently, Wersäll et al[67] demonstrated that these genes have overlapping and largely redundant roles in regulating P-selectin externalization, suggesting a role in the regulation of α-granule secretion. This may allow the development of targeted therapies for diseases of platelet-mediated inflammation. However, in a recent issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Gotru et al[68] demonstrated that TRPM7 (transient

receptor potential cation channel, subfamily M, member 7) kinase controls calcium responses in arterial thrombosis and stroke in mice. Additionally, Schwertz et al[69] provided the first evidence that platelets possess LINE-1 (long interspersed nuclear element-1)-encoded eRT (endogenous reverse transcriptase) activity. The authors also demonstrated that platelet eRT activity regulates platelet hyperreactivity and thrombosis.[69] However, regulated secretion is an essential part of platelet function in hemostasis and thrombosis processes. Classically, platelets contain 3 types of secretory granules: α-granules, dense granules, and lysosomes. Several regulators of the fusion machinery in secretory granule exocytosis have been identified in platelets. Recently, Adam et al[70] demonstrated that kinesin-1 is a new actor involved in platelet secretion and thrombus stability. Their study provided in vitro and in vivo evidence showing that the Kif5b (kinesin-1 heavy-chain isoform) is a new element in the mechanisms of α-granule and dense granule secretion.[70] Adam et al[70] further demonstrated that, independent of platelet activation, kinesin-1 links microtubules to α-granules and dense granules via the molecular machinery composed of granule-associated Rab27 protein and Slp4 adaptor protein.

Roles of the von Willebrand Factor in Arterial Thrombosis

Thrombosis is a localized clotting of blood that disturbs arterial or venous circulation, which is induced by alterations in the vascular wall, blood content, and blood flow.[71] When subendothelial matrix proteins are exposed by arterial injury, the vWF (von Willebrand factor) plays a crucial role in hemostasis via adhesion and spreading of platelets.[37,72–76] vWF is a large multidomain adhesive glycoprotein that is synthesized by ECs and megakaryocytes and is stored in the endothelial Weibel-Palade bodies or platelet α-granules. vWF binds to platelet glycoproteins Ibα and αIIbβ3, and subendothelial collagens, which induces platelet aggregation. Platelets interact with collagen through glycoprotein VI and α2β1, leading to platelet activation, spreading, and secretion, which in turn leads to thrombus formation.[64] The molecular mechanisms linking glycoprotein Ib/vWF interaction to platelet activation remain to be fully characterized. In a recent issue in *Arteriosclerosis, Thrombosis, and Vascular Biology*, Laurent et al[64] demonstrated the importance of downstream signaling of integrin αIIbβ3 to permit stationary adhesion contact. Using both a genetic approach and pharmacological inhibitors, the investigators provided new mechanistic insights into the role of phosphoinositide 3-kinase α in platelet activation and arterial thrombosis.[64]

Roles of ECs and TF in the Coagulation Cascade

The coagulation cascade is triggered by the binding of coagulation factor VII to the TF or by the contact system activation via factor XII, followed by a common pathway that leads to fibrin formation.[71] TF activates the extrinsic coagulation system and triggers both arterial and venous thrombosis. ECs form a barrier that protects blood clotting factors from exposure to subendothelial prothrombotic extracellular matrix components. Additionally, ECs secrete vasoactive factors that modulate platelet function, coagulation, fibrinolysis, and vascular function, which affect thrombotic formation.[71] Many factors, including nitric oxide, prostacyclin, vWF, and thrombomodulin, play crucial roles in the regulation of EC function and thrombosis formation. Thus, ECs have a pivotal role in modulating thrombosis and are an important target against thrombosis.[71] Superficial erosion of arterial plaques often causes thrombosis and induces acute coronary syndromes. On the surface of plaque rupture, platelets rapidly deposit at the site of subendothelial exposure. Additionally, thrombin is generated by the coagulation cascade that is triggered by exposed subendothelial TF. However, there are no therapies targeting superficial erosion. In a recent issue in *Arteriosclerosis, Thrombosis, and Vascular Biology*, Folco et al[77] demonstrated that NETs (neutrophil extracellular traps) can amplify and propagate local processes that lead to endothelial injury by eliciting EC activation and increased adhesivity; moreover, NETs induce TF expression and accelerate plasma clotting by ECs. Thus, they demonstrated a novel mechanism by which NETs can aggravate thrombosis at the sites of superficial erosion of atherosclerotic plaques.[77] The TF pathway activates coagulation, which triggers platelet activation and induces acute coronary syndromes. Although dual antiplatelet therapy is effective in secondary prevention, combining antiplatelet therapy with low-dose aspirin and oral coagulation FXa (factor Xa) antagonist rivaroxaban has a synergistic benefit over monotherapy.[78] However, thrombin functions as a key driver of clotting by promoting platelet activation via PAR1 (protease-activated receptor-1) and PAR4 and by cleaving fibrinogen for fibrin polymerization.[79] Blood clotting on a procoagulant surface under flow involves complex reactions among the activating platelets and coagulating factors. In a recent study, Zhu et al[79] measured the intrathrombus fibrin concentrations and revealed that fresh fibrinogen substrate can continuously enter the clot and is converted to fibrin monomer and incorporated into fibrin.

Roles of PARs in Thrombosis

The 4 members of the PAR family (PAR1-4) are ubiquitously expressed in the vascular system and are activated by proteolytic cleavage of their N-terminal domains.[78] PAR1, PAR3, and PAR4 are preferentially cleaved by the serine protease thrombin, which is an essential enzyme in hemostasis and thrombosis.[80] PAR1 is classically activated by thrombin via proteolysis. The binding of thrombin to PAR1 can also result in transactivation of PAR2. This activation induces a major conformational change and transmembrane signaling to intracellular G proteins.[81] As a result, PAR1 signaling in the vascular wall plays a crucial role in the development of intimal hyperplasia, endothelial injury–induced restenosis, and the endothelial barrier function.[78] In contrast, thrombin is inactivated by ATIII (antithrombin III) and heparin, resulting in the formation of the TAT (thrombin-ATIII) complex.[78] In a recent issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Rana et al[81] demonstrated that MMP1 (matrix metalloprotease-1) can activate PAR1 via noncanonical signaling at a site distinct from thrombin. They showed that targeting the MMP1-PAR1 system with inhibitors of either MMP1 or

PAR1 significantly decreased the total atherosclerotic burden, macrophage infiltration, and plaque angiogenesis in mouse models of atherosclerosis.[81] Moreover, the plasma levels of MMP1, but not those of thrombin, were significantly correlated with the total coronary atherosclerotic burden in patients with coronary artery disease.[81] Rana et al[81] concluded that the PAR1 activator MMP1 promotes the development of atherosclerosis and that preventing PAR1 inflammatory signaling downstream of MMP1 may be effective for suppressing atherosclerotic plaque formation and progression.[81] In contrast, van den Eshof et al[82] demonstrated that thrombin-induced EC phosphoregulation is mediated exclusively by PAR1, that thrombin and thrombin-tethered ligand peptide induce similar phosphoregulation, and that only canonical PAR1 cleavage by thrombin generates a tethered ligand that potently induces early signaling.

PAR2-dependent signaling also plays a crucial role in enhanced inflammation in the pathogenesis of autoimmune conditions.[78,83] In a recent issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Jones et al[83] demonstrated that PAR2 deficiency is associated with attenuation of atherosclerosis and may reduce lesion progression by preventing monocyte infiltration. The authors confirmed the presence of PAR1 and PAR2 in both mouse and human atherosclerotic lesions.[83] Importantly, they found that PAR2 deficiency, but not PAR1 deficiency, is associated with decreased early- and late-stage atherosclerosis.[83] In contrast, the difference in PAR4 signaling by ethnicity is partially explained by a single-nucleotide variant in PAR4. Thus, Tourdot et al[59] sought to determine whether the difference in PAR4 signaling by this PAR4 variant was due to biased Gq signaling and whether the difference in PAR4 activity resulted in resistance to traditional antiplatelet intervention. Importantly, they demonstrated that the rate of $G\alpha_{13}$ activation after PAR4 stimulation was enhanced in membranes expressing the PAR4-Thr120 variant relative to those expressing the PAR4-Ala120 variant.[59] Additionally, activation of the $G\alpha_{13}$ effector RhoA occurred earlier and was elevated in PAR4-stimulated platelets from patients expressing the PAR4-Thr120 variant compared with those expressing the PAR4-Ala120 variant.[59] Moreover, RhoA-dependent platelet shape change was enhanced after PAR4 stimulation in platelets expressing the PAR4-Thr120 variant.[59] Tourdot et al[59] concluded that the signaling difference induced by the PAR4-120 variant results in an enhancement of both Gq and G_{13} activation and thrombus formation, resulting in potential resistance to traditional antiplatelet therapies targeting COX-1 (cyclooxygenase-1) and the $P2Y_{12}$ receptor. Additionally, Wilson et al[80] demonstrated that PAR4 antagonism with BMS-986120 inhibits human ex vivo thrombus formation. BMS-986120 is a novel first-in-class oral PAR4 antagonist with potent and selective antiplatelet effects. Wilson et al[80] concluded that BMS-986120 is a highly selective and reversible oral PAR4 antagonist that substantially reduces platelet-rich thrombus formation under conditions of high shear stress. Thus, PAR4 antagonism seems to have major potential as a therapeutic antiplatelet strategy. Thrombin not only acts as a coagulation protease but also as an extremely potent agonist activating human platelets via proteolytic cleavage of PAR1 and PAR4.[84] Moreover, thrombin-induced platelet aggregation in arterial thrombotic diseases is refractory to aspirin and $P2Y_{12}$ inhibitors.[85] PAR1 activation leads to rapid and transient signaling, whereas PAR4 activation leads to prolonged signaling, which is required for stable thrombus formation.[86] To date, the majority of studies have focused on PAR1, leading to the development of 2 PAR1-specific antagonists, vorapaxar and atopaxar. However, recent studies have started to shift toward the understanding of the contribution of PAR4 to platelet activation.[85] Indeed, it has been shown that PAR4-selective inhibition has significant antithrombotic effects with a low bleeding tendency.[87]

Endothelial Glycocalyx and Glycosaminoglycans

EG (endothelial glycocalyx) covers the apical surface of ECs.[88] EG is composed of proteoglycans, glycoproteins, glycolipids, and glycosaminoglycans, in particular, hyaluronan.[88] Hyaluronan creates a space between the blood and the endothelium that allows controlling the vascular permeability, adhesion of leukocytes and platelets, and endothelial response to blood flow. Glycosaminoglycans heparan sulfate, dermatan sulfate, and heparin are important anticoagulants that inhibit clot formation.[89] Many proteins have been reported to bind and neutralize these glycosaminoglycans promoting clot formation.[89] Glycosaminoglycans have multiple functions and influence several physiological processes, including the control of coagulation. Additionally, glycosaminoglycans affect lipid metabolism, inflammation, cell adhesion, migration, invasion, and differentiation.[88] When coagulation needs to be activated, glycosaminoglycans are neutralized to enable clot formation. In contrast, FGF (fibroblast growth factor) need to bind to endothelial heparin sulfate to function. Similar to FGF, chemokine and cytokine activities are closely related to their ability to bind endothelial glycosaminoglycans. Indeed, glycosaminoglycans can modulate the inflammatory response by binding cytokines and preventing them from binding to cell surface receptors. Cleavage of glycosaminoglycans releases cytokines and increases EC activation. It is known that platelet factor 4, an important glycosaminoglycan-neutralizing protein, neutralizes the negative charge of glycosaminoglycans at the surface of ECs.[90] This allows platelets to associate with ECs and then enhance thrombus formation.

Conclusions

Whereas many points remain to be clarified, recent basic research has elucidated the precise mechanisms for the development of thrombotic diseases. Based on this scientific progress, there are several ongoing clinical trials that may provide novel therapies for thrombotic diseases. Nowadays, translational research has become increasingly important. Based on the progress in basic research, it is expected that new therapeutic strategies will become available in the near future.

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Disclosures

None.

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