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Thrombogenesis and thrombotic disorders based on 'two-path unifying theory of hemostasis': philosophical, physiological, and phenotypical interpretation

Jae C. Chang

Hemostasis, endowed to human to protect lives, is a process of logical blood clotting system to prevent blood loss in vascular injury. However, the notion that deadly thrombosis occurs as a result of normal hemostasis in intravascular injury could encounter with conceptual skepticism because the term 'thrombosis' automatically conjures up as serious disease. According to 'two-path unifying theory', normal hemostasis is initiated only by vascular injury through activated unusually large von Willebrand factor (ULVWF) path and/or activated tissue factor (TF) path. When these two equally important paths are unified in normal hemostasis, clotting at external bodily injury site is initiated for wound healing, but in intravascular injury 'blood clots' is formed to produce a disease called 'thrombosis'. As microthrombi from ULVWF path and fibrin clots from TF path become unified, macrothrombus would be formed via thrombogenesis. However, if ULVWF path and TF path cannot be unified due to lone ULVWF path activation, partial hemostasis produces only microthrombi seen in endotheliopathy-associated vascular microthrombotic disease. In real life, in-vivo fibrin clot cannot be formed alone via normal hemostasis because bleeding vascular injury always activates both ULVWF and TF paths. Without vascular injury, microthrombi due to activated ULVWF path occur in ADAMTS13 deficiency in thrombotic thrombocytopenic purpura, and fibrin clots due to activated TF path occur in acute promyelocytic leukemia. These two conditions can be called pathologic hemostasis. Three thrombogenic pathways produce three thrombotic disorders, which include macrothrombosis, microthrombosis and true DIC through macrothrombogenesis, microthrombogenesis and fibrinogenesis in both physiologic and pathological hemostasis. *Blood Coagul Fibrinolysis* **29:585–595 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

The fundamental concept of hemostasis and thrombosis is a very difficult one to embrace because the term hemostasis carries two paradoxically different connotations in clinical medicine; first, it is an essential process protecting human lives in the bleeding patient resulting from the external bodily injury, and second, it is also the process harming human lives by forming blood clots in intravascular injury or disease. The former would allow wound healing, but the latter could produce the serious thrombotic disease of three different kinds [1]. It is an irony that nature endowed human with one mechanism that can heal a life-threatening wound and also could cause deadly thrombotic disorder. A reflection on hemostasis paradox supports this author's long conviction that it may be nature's warning to human for a good reason.

Thrombosis is estimated to be the most common disease in human, and often more lethal than cancer at the onset of the disease. Additionally, so many patients die of thrombosis without knowing that they have it. This happens not only in stroke and myocardial infarction, but also in sepsis, trauma, hospitalization and complications of surgery, transplant, pregnancy, and medical treatment, including side effects of drugs.

Thrombosis and thrombogenesis

The concept of thrombosis can be understood as a condition that occurs as a result of intravascular injury, leading to blood clots. It is logical to accept the injury site such as particular organ or blood vessel determines the phenotype of thrombosis. Thus, the common approach has been that the application of the treatment should be directed to resolve 'blood clots' and also prevent it, but be tailored according to the need of the involved organ or blood vessel in an individual patient.

The mechanism of thrombogenesis is still an incompletely understood hemostatic process despite of extensive research efforts of many dedicated coagulation scientists and clinicians. Because thrombosis is commonly encountered in clinical medicine, the clinician has applied the knowledge what has been known about thrombosis and coagulation in patient care without

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Table 1 Classification of thrombotic disorders based on 'two-path unifying theory' of hemostasis

Diseases/disorders	Macrothrombosis	Vascular microthrombotic disease (VMTD)		Consumption coagulopathy
Commonly associated other names	Localized thrombosis	TTP-like syndrome: False DIC: EA-VMTD; EA-DIT	TTP AA-VMTD; GA-VMTD	True DIC APL hemorrhagic disorder
Pathology				
Thrombosis form	Macrothrombus	Microthrombi	Microthrombi	Fibrin clots
Thrombus character	Platelet-ULVWF & Fibrin mesh complex	Platelet-ULVWF complex	Platelet-ULVWF complex	Fibrin meshes
Pathogenesis				
Hemostasis	Normal hemostasis	Normal hemostasis	Pathologic hemostasis	Pathologic hemostasis
Injury/pathology	Intravascular injury	Intravascular endotheliopathy	ADAMTS13 deficiency	APL
Hemostatic event	Combined endothelial and EVT injury	Endothelial injury	N/A	N/A
Involved path	Combined ULVWF and TF paths	Lone ULVWF path	Aberrant ULVWF path	Aberrant TF path
Genesis mechanism	Macrothrombogenesis (Combined microthrombo-fibrinogenesis)	Microthrombogenesis (at endothelial membrane)	Microthrombogenesis (in microcirculation)	Fibrinogenesis (in circulation)
Clinical features				
Thrombotic disorder	Macrothrombotic disease	Vascular microthrombosis	Microvascular thrombosis	Friable fibrin clots
Localization	Localized	Disseminated/focal/localized	Disseminated	Diffuse
Manifestation	Thrombotic	Thrombotic	Thrombotic	Hemorrhagic
Phenotypes	Localized thrombosis/ischemia	MODS (any organ); SIRS Thrombocytopenia MAHA	CNS dysfunction; HUS Thrombocytopenia MAHA	Hemorrhagic disorder Thrombocytopenia due to APL
Examples	Vascular phenotype designation (e.g., cerebral artery thrombosis) Organ phenotype designation (e.g., stroke; MI; PE) Ischemic phenotype designation (e.g., cerebral infarction; MI; gangrene) Expressive phenotype designation (e.g., CVA; STEMI; steal syndrome; PDIS; gangrene)	Acquired disseminated EA-VMTD (e.g., critical illnesses) Hereditary focal VMTD (e.g., HERNS) Neonatal localized VMTD (e.g., Kasabach-Merritt syndrome) Acquired focal VMTD (e.g., Susac syndrome; TIA; angina) Acquired localized VMTD (e.g., Heyde's syndrome)	Hereditary TTP Acquired immune TTP	

AA-VMTD, antibody-associated VMTD; APL, acute promyelocytic leukemia; CNS, central nervous system; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DIT, disseminated intravascular microthrombosis; DVT, deep vein thrombosis; EA-VMTD, endotheliopathy-associated VMTD; EVT, extravascular tissue; GA-VMTD, gene mutation-associated VMTD; HIT-TS, heparin-induced thrombocytopenia with thrombosis syndrome; MAHA, microangiopathic hemolytic anemia; MI, myocardial infarction; MODS, multiorgan dysfunction syndrome; PDIS, peripheral digit ischemic syndrome; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction; TF, tissue factor; TIA, transient ischemic attack; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor; VMTD, Vascular microthrombotic disease. Please note HT-TS is not the result of hemostatic disorder but immune-associated platelet thrombosis syndrome; NA, not applicable.

serious consideration of thrombogenesis. The clinician has inferred the notion of thrombosis from the point of view of its clinical expression. Thrombosis could display a clinical spectrum of various organ dysfunctions from central nervous system diseases (e.g., stroke syndrome, cerebrovascular accident) down to cardiac diseases (e.g., angina, myocardial infarction) and to peripheral vascular disease [e.g., deep vein thrombosis (DVT), ischemia or gangrene of the extremity] as shown in Table 1.

However, it has been a challenge to explain why certain phenotypes of thrombosis vary differently in their size, localization, and clinical expression, often with serious clinical ramification, altering prognosis and therapeutic approaches. For example, the clinical and pathologic features of disseminated microthrombosis in sepsis are very different from DVT and arterial thrombosis, or even from acute myocardial infarction and stroke. Many serious thrombotic disorders have been denoted with specific emphasis on vascular system such as cerebral artery thrombosis, coronary artery disease, hepatic vein thrombosis, renal artery thrombosis, disseminated intravascular coagulation (DIC), vascular microthrombotic disease (VMTD) [2–4], and others. In addition, clinicians have creatively used the terms with expressive phenotypes such as ST-elevation myocardial infarction (STEMI) [5], inferior vena cava (IVC) filter thrombosis syndrome [6], consumptive coagulopathy, posttransplant thrombosis, thrombophilia, sinus thrombosis, vascular access steal syndrome [7], microvascular thrombosis, vascular microthrombosis [2–4], immunothrombosis [8–10], and others. Many of these thrombotic disorders are partially understood at best and others are shrouded in secrecy for their pathogenesis to date. Is it reasonable to suspect some of these designations could have contributed to the shortcomings in the understanding of thrombogenesis and true character of 'blood clots' itself?

Beyond our comprehension that thrombosis is the result of 'blood clots' and 'blood clots' develops as a result of tissue factor (TF)-initiated coagulation process, it has been an enigma how the same pathophysiological mechanism via the same hemostasis produces distinctly different thrombotic disorders in the character of 'blood clots' and clinical phenotype *in vivo*. This author's contention is our search for the true nature of the thrombotic disease should go back to the hemostatic fundamentals for better understanding of hemostasis, thrombosis, and coagulation.

Recent acquisition of the knowledge on microthrombogenesis and a newly proposed hemostatic theory could resolve the puzzles of thrombogenesis and provide the identity of different thrombotic disorders [1,2–4,11,12]. Two independent theories, of which one is formulated from the logical nature of normal hemostasis [1] and the other is synthesized from the element of molecular response caused by endotheliopathy and microthrombogenesis [2–4,11,12], are derived from the studies of known blood coagulation mechanism and VMTD. The first is 'two-path unifying theory of hemostasis' [1] and the second is 'two-activation theory of the endothelium' [2–4,11,12]. Their application in analysis of the thrombotic disorders could untangle the complexity of pathophysiological mechanism of thrombogenesis [1].

Reappraisal of hemostasis and thrombosis

Retrospective

The primary role of hemostasis is the formation of blood clots to stop bleeding via coagulation, contributing to the healing of the wound. However, it has also been understood that thrombosis is produced from blood clots as a result of hemostasis in the intravascular space [9,13]. Traditionally, this concept has implied that, since thrombosis is the product of coagulation, thrombogenesis has to be initiated by the exposure to TF [16–22]. This dogmatic concept has been universally mandated such that intravascular expression of TF via one or more of many theoretical mechanisms [14–19] has to be available to activate FVII to FVIIa, leading to subsequent coagulation cascade to form 'blood clots' (thrombi).

In retrospect, this very dogma that TF must be available for thrombogenesis has created confusion and misinterpretation about the nature of thrombogenesis and coagulation process as well as the character of various forms of thrombi. In clinical medicine, the thrombotic disorder has been generally termed according to clinical phenotypes such as stroke, myocardial ischemia and infarction, pulmonary embolism, DVT, arterial thrombosis, and individual organ-designated thrombotic syndromes. This pragmatic approach has served fairly well for the clinician in managing the patient through the central role of TF-induced activation of coagulation, and has promoted the usage of various anticoagulant regimens based on different phenotypes and severity of the thrombotic disorder.

However, when encountered by different kinds of thrombopathies and coagulopathies such as thrombotic thrombocytopenic purpura (TTP), TTP-like syndrome, hemolytic uremic syndrome, 'DIC', sepsis-induced 'DIC', consumptive coagulopathy, microthrombosis, and thrombo-hemorrhagic syndrome, TF-based dogmatic conception alone was found to be inadequate or not applicable in the clinical and pathologic interpretation of these groups of the thrombotic disorder. Thus, intensive research efforts have been directed to identify specific molecular pathogenesis of the thrombosis to elucidate the activation of coagulation system such as in response to inflammation [19,20], immune activation [8,9,21], endothelial injury [3,4,11,12], complement activation [2–4], and with participation of microparticles [22], soluble TF [23], glycocalyx role [24], FXII contribution [25], NETosis [8,9,21], leukocyte adhesion [26] and TF transfer [18], as well as decryption of encrypted TF [16] and even with reexamination of Virchow's triad theory [27,28], and others. So far, no solid lead has been captured yet in identifying the mechanism of thrombogenesis in spite of dedicated efforts of coagulation scientists and clinicians.

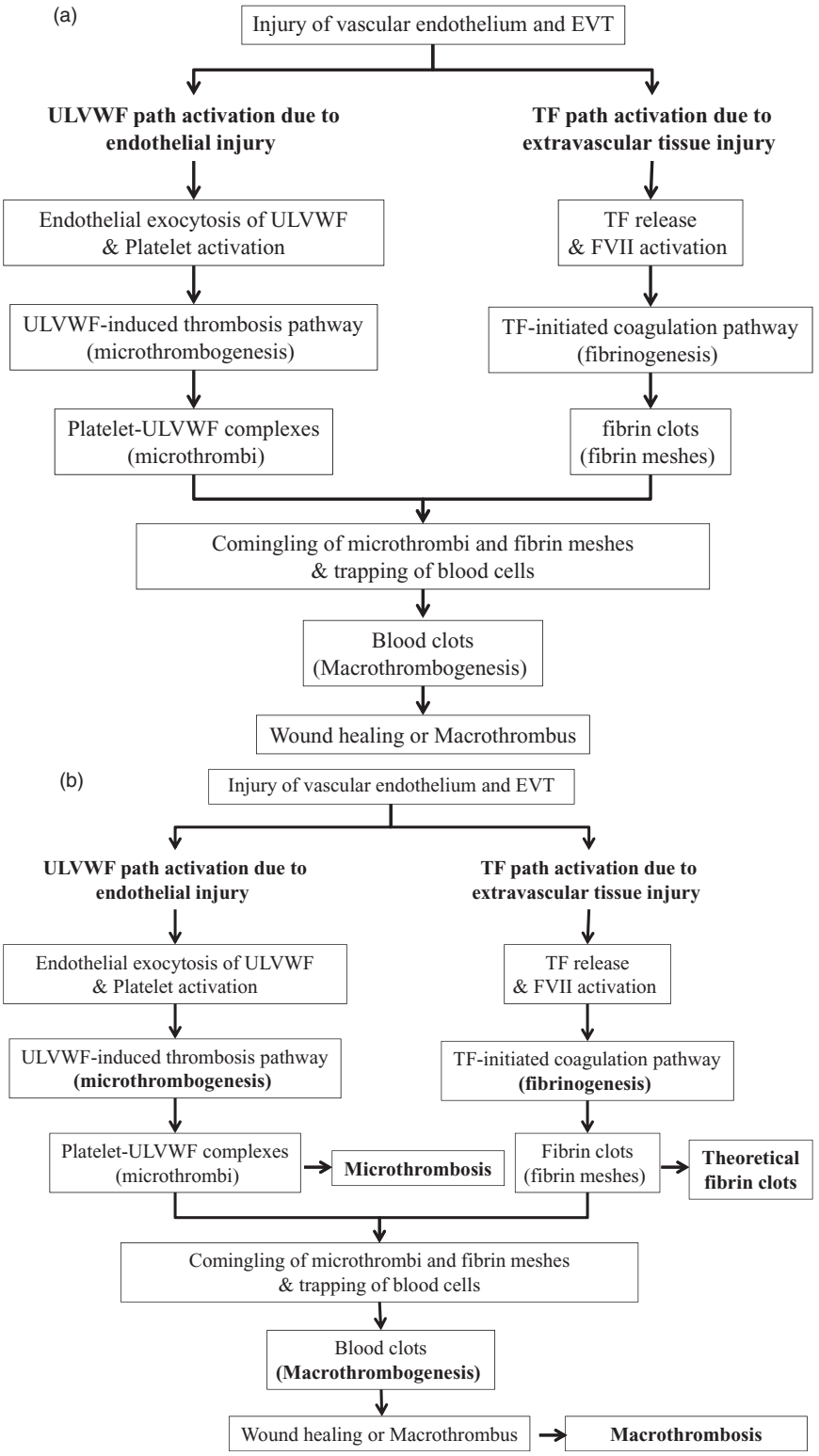
Almost all of these research efforts have been centered on the proposition supporting the central role of TF in every thrombotic disorder. Because of the lack of progression toward comprehensible thrombogenesis fixated on TF pathway, now some scientists are repositioning themselves to the nondogmatic direction in search of additional mechanisms of thrombogenesis [21,22,26,29]. Among these theories and hypotheses, cross-talk theory between inflammation and coagulation has gained its prominence. Most of disseminated thrombotic disorders, including false DIC [2,3] and TTP-like syndrome [2], have almost always coexisted with inflammation, especially in critically ill patients with diseases such as sepsis, trauma, and other critical illnesses [19,20,30–32]. These disseminated thrombotic disorders are theorized to be the result of uncontrolled activation of TF-initiated coagulation system developing through cross-talk mechanism between inflammation and coagulation. The theory has proposed thrombogenesis is a complex process mediated by various inflammatory cytokines and other bioactive molecules activating the coagulation system [32,33]. But, its mechanism is not been clearly demonstrated as yet.

Perspective

In inflammation and coagulation cross-talk theory, however, the critical component of vascular injury, in particular, the levels (depth) of damage has been mostly ignored [1]. How could thrombosis occur in 'DIC' of sepsis without vascular injury? How is it possible that enough TF becomes available for disseminated disease such as 'DIC' without vascular injury? What is the direct evidence of TF participation in inflammation? Above all, one very important question for 'DIC' is why microthrombosis develops in sepsis instead of disseminated macrothrombosis in intravascular space? The heart of the question is what is the difference between thrombus and microthrombi. This author believes the missing pieces are the 'vascular injury' and 'the levels (depth) of the damage' in interpretation of thrombogenesis. The oversight of these principles must have blocked the identity of the true pathogenesis of the thrombotic disorder as well as the character of intravascular thrombi.

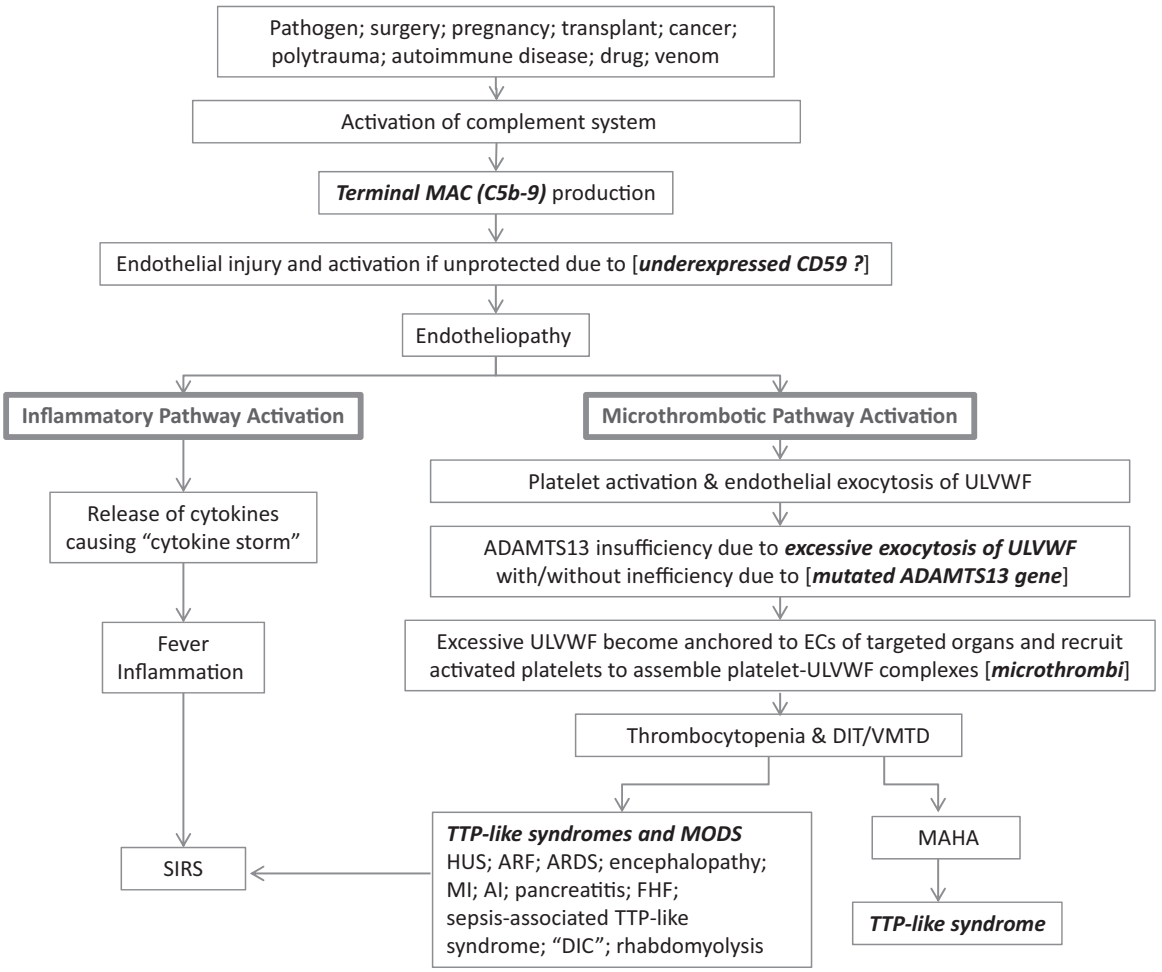
Because the cross-talk theory has been accepted and has become so popularized, it is common to see dogmatic

Fig. 1



(a) Normal hemostasis based on 'two-path unifying theory' (data from [1]). The concept of this theory is derived from the physiopathological logic of hemostasis described in five hemostatic principles and five essential components participating in hemostasis [1] and known works of many dedicated coagulation scientists. The figure is self-explanatory. (b) Normal hemostasis, leading to thrombosis based on 'two-path unifying theory'. Please see illustrated (b), showing three different thrombogeneses in 'two-path theory' (macrothrombogenesis, microthrombogenesis and fibrinogeneis) are annotated in bold face. Each pathogenesis occurs when unusually large von Willebrand factor (ULVWF) path, tissue factor (TF) path or combined paths are utilized depending upon the levels of damage in intravascular injury [endothelium and extravascular tissue (EVT)]. The characters of the thrombus(i) from different paths are very different and produce distinctly different clinical thrombotic disorders as shown in Table 1 and text.

Fig. 2



Molecular pathogenesis of unusually large von Willebrand factor (ULVWF) path in endotheliopathy-associated vascular microthrombotic disease (EA-VMTD) (data modified from [2]). Figure 2 elaborates 'two activation theory of the endothelium', which shows complement-induced endothelial molecular events, leading to endotheliopathy-associated disseminated intravascular microthrombosis (DIT)/ vascular microthrombotic disease (VMTD) (i.e., thrombotic thrombocytopenic purpura -like syndrome) and multiorgan dysfunction syndrome (MODS). The organ phenotype syndrome in MODS includes encephalopathy, acute respiratory distress syndrome (ARDS), fulminant hepatic failure (FHF), acute renal failure (ARF)/hemolytic uremic syndrome (HUS), myocardial infarction (MI), adrenal insufficiency (AI), pancreatitis, rhabdomyolysis, and others. For example, in sepsis complement activation is the initial critical event. Complement activation can occur through one of three different pathways (i.e., classical, alternate and lectin). In addition to lysis of pathogen by terminal product C5b-9, it could induce endotheliopathy to the innocent bystander ECs of the host. C5b-9-induced endotheliopathy is suspected to occur if the endothelium is 'unprotected' by CD59. Activated inflammatory pathway provokes inflammation in sepsis, but inflammation could be modest if organ involvement is limited. Activated microthrombotic pathway causes endotheliopathy-associated DIT if the excess of ULVWF develops following endothelial exocytosis as a result of relative insufficiency of ADAMTS13 with/without mild to moderate ADAMTS13 deficiency, which might be associated with heterozygous gene mutation or polymorphism of the gene. This theory explains all the phenotypes of EA-VMTD as illustrated in the Figure 2.

phrase 'cross-talk between inflammation and coagulation'. In addition to the arguments and questions that I have posed above, this cross-talk theory has not been successful in eliciting any convincing evidence that is applicable to clinical practice yet. Also, extensive clinical therapeutic trials utilized in the treatment based on this theory have failed to produce an effective therapeutic regimen [34,35].

Although the cross-talk theory between 'inflammation and coagulation' is not confirmed, there is a plenty of evidence of coexistence of inflammation and thrombosis in VMTD associated with sepsis and other critical illnesses [2–4,11,12]. That does not mean they do interact each other. Instead, inflammation and coagulation do exist as independent phenotypes [2–4] without cross-linking as shown in Figure 2. To date, the concept that thrombosis in VMTD develops through activated TF path has never been proven and has not been substantiated by any acceptable study. Now, it is becoming clear that microthrombotic disorder in sepsis and other clinical illnesses occurs only in activated unusually large von Willebrand factor (ULVWF)

path without activated TF path even though VMTD is a hemostatic disease [1–4,11,12]. According to 'two-activation theory of the endothelium' [1–4], in endotheliopathy, two different pathways (i.e., inflammatory and microthrombotic) are neither cross-linked nor interdependent. Inflammatory cytokines from activated inflammatory pathway promotes inflammation as seen in systemic inflammatory response syndrome (SIRS), but microthrombogenesis orchestrates multiple phenotypic syndromes such as consumptive thrombocytopenia in critically ill patients (TCIP), microangiopathic hemolytic anemia (MAHA), TTP-like syndrome, and multiorgan dysfunction syndrome (MODS) seen in endotheliopathy-associated VMTD (EA-VMTD) [1–4,11,12,36]. Indeed, EA-VMTD, which includes 'DIC', is a partially activated hemostatic disorder through lone activation of ULVWF path of normal hemostasis as shown in Figure 2.

For these reasons, the fundamental research of thrombogenesis and thrombosis should go back to the basics of hemostasis, which first logic starts with the axiom that 'normal hemostasis can be activated only by vascular injury'. This means thrombosis cannot occur without intravascular injury [1]. In addition, the research efforts should be redirected from the emphasis of organ or vascular localization phenotypes and TF dogma to the study of the nature of thrombogenesis and character of thrombus itself. It is because even though the mechanism of normal hemostasis is only one process, it must be also applied to every thrombotic disorder, but by accepting the proposition of variable thrombogenesis depending upon the levels of intravascular injury [1].

Basics in hemostasis

Terminology

Since the terminology in hemostasis and related disorders sometimes may contribute to the confusion and misunderstanding, it is best to start with exploration of acceptable definition for commonly used scientific and clinical terms in coagulation and with proper designation of vocabulary, specific in thrombogenesis as follows:

First, three different kinds of blood clots are recognized [1], which are:

(1) Microthrombi: blood clots made of 'platelet and ULVWF complexes' [1–4,11,12]
(2) Fibrin clots: blood clots made of 'complexes of fibrin meshes' [1]
(3) Macrothrombus: blood clot made of the 'unified complex of 'microthrombi and fibrin clots' [1]

Second, three different kinds of thrombogenesis are recognized via hemostasis:

(1) Macrothrombogenesis: blood clot forming process via unifying the products of microthrombogenesis (microthrombi) and fibrinogenesis (fibrin clots) [1]
(2) Microthrombogenesis: blood clot forming process via activated ULVWF path of normal hemostasis [1–4,11,12]
(3) Fibrinogenesis: blood clot forming process via activated TF path [1]

Third, there is the pertinent hemostatic lexicon, being used in clinical science of blood coagulation and thrombosis, which vocabulary includes:

(1) Hemostasis: blood clot forming process to stop bleeding in vascular injury due to external bodily or intravascular injury. Normal hemostasis produces thrombosis in intravascular injury via activated ULVWF path and/or TF path, but in the absence of vascular injury, pathologic hemostasis produces thrombosis in two diseases, which are TTP and acute promyelocytic leukemia (APL) via aberrant ULVWF path or aberrant TF path respectively [1].
(2) Coagulation: blood clot forming process in vascular injury through 'normal' hemostasis. It is initiated by bleeding as a result of external bodily injury or intravascular injury, and also it can be created in in-vitro laboratory tests (e.g., clotting time, prothrombin time and activated partial thromboplastin time), leading to fibrin clots. Two exceptions occurring without vascular injury are microthrombosis in TTP and fibrin clots in true DIC associated with APL, in which in-vivo coagulation occurs due to pathologic hemostasis through aberrant ULVWF path in TTP and aberrant TF path in APL [1].
(3) Thrombogenesis: blood clot forming process to produce specific thrombus, thrombi and blood clots through normal hemostasis. It is initiated by endothelial and/or EVT injury, leading to bleeding within the vascular lumen, or due to endotheliopathy as a result of intravascular injury of the blood vessel. This term may also be applied to the genesis of TTP and APL although they are not the result of vascular injury, but thrombogenesis occurs through pathologic hemostasis in the intravascular space [1].
(4) Thrombosis: blood clot-formed state within intravascular space as a result of thrombogenesis. Thus, it is recognized as disease (e.g., microvascular thrombosis, vascular microthrombosis, DVT, hepatic vein thrombosis, sinus thrombosis).
(5) Gangrene: tissue death caused by a lack of blood supply. It develops almost always due to thrombosis. Gangrene is irreversible but ischemia may be reversible.
(6) ULVWF: ultra large high molecular VWF multimers among the spectrum of VWF multimers, which are stored in Weibel-Palade bodies of the endothelium to be readily available in vascular injury. They form high strength bonds spontaneously with the platelet glycoprotein Ib-IX complex [37] and produce long microthrombi strings made of platelet and ULVWF complexes.

(7) Tissue factor: transmembrane receptor for FVII/VIIa. TF is constitutively expressed in the cells surrounding blood vessels. It is completely separated from the endothelium, which blocks this potent 'activator' interfacing with circulating ligand FVII and prevents inappropriate activation of the clotting cascade [38,39] in the absence of vascular injury.
(8) Endothelium: monolayer of endothelial cells, constituting the inner cellular lining of the blood vessels, including arteries, veins and capillaries. It releases ULVWF and inflammatory cytokines in response to endotheliopathy and triggers microthrombogenesis and inflammation among other molecular expressions. However, evidence is controversial that cytokines involve in thrombogenesis.
(9) EVT: tissue situated outside the blood vessel. It contains abundant amount of TF that becomes available in the situation of blood vessel injury breaching the endothelium.

Major components of hemostasis

It is well established that the following five components are the essential participant in normal hemostasis [1,40–44], perhaps with contribution of collagen and adhesive molecules:

(1) Endothelium
(2) ULVWF from the endothelium
(3) Platelets
(4) TF from the extravascular tissue EVT
(5) Coagulation factors

Hemostatic principles

No matter what the true nature of hemostasis may be, the same logic of normal hemostasis should be applicable in producing the same kind of 'blood clots' in external bodily injury and intravascular injury [1]. In thrombosis, however, different phenotypes of thrombus occur dependent upon the levels of damage in the intravascular injury. The unwavering hemostatic principles are as follows:

(1) Normal hemostasis can be activated only by vascular injury.
(2) Hemostasis must be activated through ULVWF path and/or TF path.
(3) Normal hemostasis is the same process in both hemorrhage and thrombosis.
(4) Normal hemostasis is the same process in both arterial thrombosis and venous thrombosis.
(5) The levels of vascular damage (endothelium and/or EVT) determine the phenotypes of hemorrhagic syndrome and generate different phenotypes of the thrombotic disorder.

One hemostatic exception is pathologic hemostasis where the thrombotic disorder occurs without vascular injury. This rare situation is known to occur only in two diseases: one is microthrombosis in TTP via activated 'aberrant' ULVWF path and the other is fibrin clots (i.e., DIC) in APL via activated 'aberrant' TF path [1] as shown in Tables 1 and 2. These pathophysiological mechanisms are explained in detail in previous publication [1].

Table 2 Pathogenic paths of thrombotic disorders

1. In intravascular injury → normal hemostasis
   - Complete hemostasis → simultaneously activated ULVWF and TF paths
     ↓
     Macrothrombogenesis
     ↓
     Macrothrombus
     ↓
     Macrothrombotic disease (e.g., DVT)
   - Incomplete hemostasis → lone activated ULVWF path
     ↓
     Microthrombogenesis
     ↓
     VMTD (e.g., TTP-like syndrome)

     → lone activated TF path (cannot occur)

2. In diseases without vascular injury → pathologic hemostasis
   - ADAMTS13 deficiency → aberrant ULVWF path activation
     ↓
     Microthrombogenesis
     ↓
     VMTD (e.g., TTP)
   - Acute promyelocytic leukemia → aberrant TF activation
     ↓
     Fibrinogenesis
     ↓
     Consumptive coagulopathy (e.g., APL)
3. In immune response to heparin-PF4 → heparin-PF4 antibody formation
     ↓
     Platelet aggregation
     ↓
     Platelet thrombosis (e.g., HIT-TS)

APL, acute promyelocytic leukemia; DVT, deep vein thrombosis; HIT-TS, heparin-induced thrombocytopenia with thrombosis syndrome; TF, tissue factor; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor.

Another nonhemostatic exception is platelet thrombosis in heparin-induced thrombocytopenia (HIT-TS). HIT-TS is not caused by hemostasis because there is no evidence it utilizes either ULVWF path and/or TF path. Following heparin administration, heparin-platelet factor 4 antibodies can be formed. The complex of heparin-platelet factor 4 antibodies activates platelets, leading to intravascular aggregation of platelets, and produces the multiple large platelet thrombi. This syndrome is true platelet thrombosis occurring in both venous and arterial systems, especially in lower extremities, which has been called 'white clot syndrome' [45,46].

Other than these three diseases that are known to date, every thrombotic disorder should obey the principle of normal hemostasis and 'two-path unifying theory', which is illustrated in Figure 1a and explained from the original article [1] as follows:

Mechanism of normal hemostasis based on 'two-path unifying theory'

In the advent of recognition of VMTD/disseminated intravascular microthrombosis (DIT) as a distinct disease entity, its identification of molecular pathogenesis [1–3,11,12,36], which knowledge is gained from the concept of microthrombogenesis [1–3], is shedding light upon the physiopathological mechanism of hemostasis and its role in various hemorrhagic syndromes and thrombotic disorders. This new paradigm, identifying the pathogenesis of different phenotypes of the thrombotic disorder, could impact positively in the prevention and treatment of many coagulation disorders.

To account for clinical phenotypes of the hemorrhagic diseases and thrombotic disorders, a novel 'two-path unifying theory of hemostasis' is proposed as illustrated in Figure 1a [1]. In the settings of intravascular injury and extravascular bodily injury, all five hemostatic components must be properly functional for normal hemostasis to produce healthy hemostatic plug. Physiological hemostasis should be achieved through the activation of two independent but simultaneously cooperating hemostatic paths.

First, ULVWF-induced microthrombotic path (ULVWF path) must be activated in vascular endothelial injury. Endothelial injury causes platelet activation and endothelial exocytosis of ULVWF from Weibel-Palade bodies and promotes sufficient release of these prothrombotic multimers [44,47–49]. ULVWF become anchored to the edge of damaged endothelial cells (ECs) with support of collagen as long elongated strings [44] and recruit platelets. Both components together form platelet-ULVWF complexes, which become 'microthrombi' strings that are tightly attached to endothelial membrane [44,47–49]. This process, forming microthrombi, is called microthrombogenesis [1–4,11,12].

Second, in normal hemostasis TF-initiated fibrinogenic path (TF path) also must be activated in bleeding vascular injury. If the injury, in addition to the endothelium, extends into the TF-rich EVT, TF is released into the local vascular injury site and activates FVII in circulation to FVIIa. According to 'cell-based model of coagulation' [39,50], TF-FVIIa complexes activate FX to FXa. FXa with FVa that is activated from FV forms FXa-FVa complex (prothrombinase). Prothrombinase activates prothrombin to make small priming amounts of thrombin, which is called initiation phase. This priming amount of thrombin promotes FVIIIa-FIXa complex (tenase) feedback. This complex converts FX to FXa and markedly increases thrombin generation in amplification phase. In final stage, thrombin will convert sufficient amount of fibrinogen to fibrin to make enough 'fibrin meshes' [40,51,52]. This process, forming fibrin meshes, can be called fibrinogenesis [1].

In ULVWF path, microthrombogenesis assembles 'microthrombi' strings. In TF path, via activated coagulation cascade fibrinogenesis molds 'fibrin meshes' Both microthrombi and fibrin meshes comingle at the site of endothelial injury and perhaps with help of adhesion molecules [53–56] become unified together and trap blood cells to produce interconnected 'blood clots'. These blood clots become healthy 'hemostatic plug' preventing unnecessary hemorrhage at external vascular injury site, but also become pathologic 'macrothrombus' in intravascular injury site as illustrated in Figure 1a and b. The macrothrombus forming process can be called macrothrombogenesis [1].

Mechanisms of thrombogenesis based on 'two-path unifying theory'

It is the hemostatic logic that every thrombosis, other than microthrombosis in TTP and fibrin clots occurring in true DIC associated with APL, develops only after the endothelial and/or EVT damage following vascular injury [hemostatic principle 1 and 5] and should take place via the ULVWF and/or TF path of normal hemostasis [hemostatic principle 2] shown in Figure 1. There is no exception. By applying the levels of vascular damage and the activated path of hemostasis based on 'two-path unifying theory', the thrombotic disorder can be classified according to the logical mechanism of the thrombogenesis. The different physiopathological mechanisms of thrombogenesis can be summarized as follows.

First, three different types of thrombogenesis can occur as illustrated in Figure 1b.

(1) Macrothrombogenesis
(2) Microthrombogenesis
(3) Fibrinogenesis

Macrothrombogenesis occurs due to localized normal hemostasis as a result of simultaneous activation of ULVWF path and TF path in intravascular injury (Fig. 1b), which produces vessel-designated thrombotic or organ phenotypic thrombotic disorders (e.g., middle cerebral artery thrombosis, hemorrhagic stroke, DVT, arterial thrombosis, and others). All of grossly localized thrombosis phenotypes are the macrothrombotic disorder. Currently, the notion of ' thrombosis' typically implies 'TF-initiated ''macrothrombus' to clinicians and coagulation scientists because the concept of different blood clots from different pathogenesis has not been appreciated yet.

Microthrombogenesis occurs in endotheliopathy due to lone activation of ULVWF path. Anatomically, the endothelial barrier stays intact. Disseminated endotheliopathy is a serious functional alteration of the endothelium without anatomical breach into EVT. It triggers no bleeding, but promotes undesirable endothelial

molecular response, which includes endothelial exocytosis of ULVWF and platelet activation. Long elongated ULVWF strings become anchored to ECs and recruit circulating platelets to assemble platelet-ULVWF complexes, which are microthrombi strings [2–4]. This process is called microthrombogenesis and results in EA-VMTD. Figure 2 is the details of microthrombogenesis in disseminated EA-VMTD based on 'two-activation theory of the endothelium', which I have elaborated in this author's previous publications [1–4,11,12,36].

Fibrinogenesis occurs as a result of increased expression of TF in intravascular space, leading to pathologic hemostasis via TF path (i.e., APL). In real life, there is no circumstance that will cause bleeding from EVT damage in intravascular vascular injury without the endothelial damage. For TF to come in to contact with circulating FVII, the gate of the intravascular luminal lining of the endothelium should be opened first. Thus, in-vivo trauma-induced 'fibrin clots' never occurs alone without 'microthrombi' strings. In another word, thrombi caused by intravascular injury are either microthrombi or macrothrombus. However, in APL, since TF released from leukemic promyelocytes is already in contact with FVII in circulation, fibrinogenesis is very much active to form 'fibrin clots', which disorder we now call consumptive coagulopathy or true DIC. This author would like to tell that this particular rare disease (i.e., APL) alone has offered me an unbelievable insight solving the last piece of the important puzzle by putting together in the understanding of normal hemostasis and thrombogenesis.

Platelet aggregation in the thrombogenesis of HIT-TS is the result of nonhemostatic process. It has been explained already earlier in article.

Thrombotic disorders

The above mechanisms of thrombogenesis explain the pathogenesis of every thrombotic disorder. The thrombotic disorders can be classified by the character of the blood clots as done in this article illustrated in Table 1, or by the difference of thrombogenesis as done in my previous article [1] and briefly in Table 2 of current article. Either way, from two different perspectives, is satisfactory for clinical application since 'two-path unifying theory' fits well in both ways (Tables 1 and 2).

Classification and examples

The general classification can be presented as follows:

(1) Macrothrombotic disorders
  (a) Vascular phenotypes (e.g., coronary artery thrombosis)
  (b) Organ phenotypes (e.g., heart attack)
  (c) Ischemic phenotypes (e.g., myocardial infarction)
  (d) Expressive phenotypes (e.g., STEMI)

(2) Vascular microthrombotic disease (VMTD)
  (a) Disseminated VMTD
    (i) Hereditary (GA-VMTD) (i.e., Hereditary TTP)
    (ii) Acquired
      - Antibody-associated (AA-VMTD) (i.e., Autoimmune TTP)
      - Endotheliopathy-associated (EA-VMTD) (i.e., TTP-like syndrome)
        - False DIC, including acute 'DIC' and chronic 'DIC'
        - Sepsis-associated 'DIC'
        - EA-DIT
        - MODS (i.e., HUS)
  (b) Localized VMTD
    (i) Neonatal (e.g., Kasabach–Merritt syndrome?)
    (ii) Acquired (e.g., Heyde's syndrome)
  (c) Focal VMTD (focal or multifocal)
    (i) Hereditary (e.g., HERNS syndrome)
    (ii) Acquired (e.g., Susac syndrome)

(3) True DIC (i.e., consumptive coagulopathy in APL)
(4) HIT-TS

Special comments on acute 'DIC' and chronic 'DIC'

Acute (overt) 'DIC' is thrombo-hemorrhagic syndrome occurring in endotheliopathy-associated DIT (EA-DIT/VMTD) [2,3], but chronic (covert) 'DIC' is EA-DIT/VMTD [2,3] without hemorrhagic syndrome. Chronic 'DIC' is the same to EA-DIT/VMTD, which almost always occurs in critical illnesses such as sepsis, trauma, immunologic disease, complication of pregnancy, surgery and transplant, and others, but acute 'DIC' sometimes occurs in chronic 'DIC' if it is associated with chronic liver cirrhosis or FHF [57–59].

In the beginning, the pathogenesis of both acute 'DIC' and chronic 'DIC' is exactly the same, which is caused by complement activation, forming C5b-9 and leading to endotheliopathy [2–4]. Endotheliopathy promotes activation of inflammatory pathway and microthrombotic pathway. The former causes inflammation and the latter activates microthrombogenesis, leading to DIT. DIT causes consumptive thrombocytopenia and orchestrates several phenotype syndromes, including mcroangiopathic hemolytic anemia (MAHA), TTP-like syndrome and hypoxic multiorgan dysfunction syndromes (MODS). Until this point, the patient develops only EA-DIT/VMTD without hemorrhagic disorder and, therefore, EA-DIT/VMTD is called chronic 'DIC'. However, the patient with underlying chronic liver cirrhosis is very vulnerable to microthrombosis-induced liver damage, leading to acute hepatic necrosis, which clinical phenotype could be fulminant hepatic failure and acute liver failure [60–62]. These phenotypes are likely to be associated with thrombocytopenia and MAHA.

Acute hepatic necrosis causes hepatic coagulopathy due to decreased production of fibrinogen, FII, FV, FVII, FIX, and FX – but not due to their consumption. Hepatic coagulopathy in EA-DIT/VMTD causes thrombo-hemorrhagic syndrome, which is deadly disease called acute 'DIC'. Thus, contemporary term DIC is a misnomer, should be renamed as EA-DIT/VMTD, which often presents with TTP-like syndrome. Both TTP and TTP-like syndrome as well as 'DIC' belong to VMTD.

Conclusion

All thrombotic disorders occur as a result of 'normal hemostasis' after intravascular injury except in two conditions (i.e., TTP and APL), in which thrombotic disorders occurs as a result of 'pathologic hemostasis'. In intravascular normal hemostasis, the nature of thrombogenesis is determined by the levels of vascular damage and activated path of hemostasis. Different 'blood clots' can be formed through different paths of thrombogenesis. These different paths create different characters of blood clots and clinical diseases. Now, there is no reason to cling to the idea that complicated molecular pathogenesis is involved in thrombogenesis. The mechanisms of thrombogenesis can be understood through five essential hemostatic components and thrombogenesis based on 'two-path unifying theory' and 'two activation theory of the endothelium'. Since microthrombogenesis develops in complement-activated endotheliopathy in critically ill patients, easily understandable molecular events, including exocytosis of ULVWF, platelet activation, and defective proteolysis of ULVWF due to ADAMTS13 insufficiency, are involved in microthrombotic pathway. It is a high time to return to the basics of hemostasis not only in redesigning therapeutic regimens of various thrombotic disorders, but also in identifying preventive measures for life-threatening thrombotic disorders.

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Conflicts of interest

The author Jae C. Chang, MD, has neither actual nor potential personal or financial conflicts of interest in regard to this article.

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