Phenotypes of Disseminated Intravascular Coagulation

Takeshi Wada[1]   Satoshi Gando[1,2]

[1] Department of Anesthesiology and Critical Care Medicine, Division of Acute and Critical Care Medicine, Hokkaido University Faculty of Medicine, Sapporo, Japan
[2] Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan

Address for correspondence Takeshi Wada, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Division of Acute and Critical Care Medicine, Hokkaido University Faculty of Medicine, N15, W7, Kita-ku, Sapporo, Japan (e-mail: twada1@med.hokudai.ac.jp).

Abstract

Two phenotypes of disseminated intravascular coagulation (DIC) are systematically reviewed. DIC is classified into thrombotic and fibrinolytic phenotypes characterized by thrombosis and hemorrhage, respectively. Major pathology of DIC with thrombotic phenotype is the activation of coagulation, insufficient anticoagulation with endothelial injury, and plasminogen activator inhibitor-1-mediated inhibition of fibrinolysis, leading to microvascular fibrin thrombosis and organ dysfunction. DIC with fibrinolytic phenotype is defined as massive thrombin generation commonly observed in any type of DIC, combined with systemic pathologic hyperfibrinogenolysis caused by underlying disorder that results in severe bleeding due to excessive plasmin formation. Three major pathomechanisms of systemic hyperfibrinogenolysis have been considered: (1) acceleration of tissue-type plasminogen activator (t-PA) release from hypoxic endothelial cells and t-PA-rich storage pools, (2) enhancement of the conversion of plasminogen to plasmin due to specific proteins and receptors that are expressed on cancer cells and endothelial cells, and (3) alternative pathways of fibrinolysis. DIC with fibrinolytic phenotype can be diagnosed by DIC diagnosis followed by the recognition of systemic pathologic hyperfibrin(ogen)olysis. Low fibrinogen levels, high fibrinogen and fibrin degradation products (FDPs), and the FDP/D-dimer ratio are important for the diagnosis of systemic pathologic hyperfibrin(ogen)olysis. Currently, evidence-based treatment strategies for DIC with fibrinolytic phenotypes are lacking. Tranexamic acid appears to be one of the few methods to be effective in the treatment of systemic pathologic hyperfibrin(ogen)olysis. International cooperation for the elucidation of pathomechanisms, establishment of diagnostic criteria, and treatment strategies for DIC with fibrinolytic phenotype are urgent issues in the field of thrombosis and hemostasis.

Keywords
► disseminated intravascular coagulation (DIC)
► fibrinolysis
► phenotype
► plasmin
► thrombin

Introduction

Disseminated intravascular coagulation (DIC) is a consumptive thrombohemorrhagic disorder characterized by two opposing manifestations, namely thrombosis and hemorrhage.[1] Thrombosis is caused by the activation of intravascular coagulation, not restricted to the site of insult that it originates from, and causes damage to microvascular endothelial cells, which can lead to organ dysfunction associated with poor outcomes.[2] The pathogenesis of hemorrhage is

diverse and complex. One mechanism involves the consumption and exhaustion of platelets and coagulation factors sensitive to thrombin, such as factors I (fibrinogen), II (prothrombin), V, VIII, and XIII, leading to consumptive coagulopathy that accelerates oozing-type bleeding.[1] Another mechanism of hemorrhage is increased plasmin-mediated fibrinolysis and the degradation of fibrinogen in cases of excessive plasmin formation. Plasmin consumes factors V and VIII, and α2-antiplasmin, also called α2-plasmin inhibitor, a predominant inhibitor of plasmin that enhances consumptive coagulopathy and fibrin(ogen)olysis.[1]

To date, two DIC phenotypes have been identified based on the degree of thrombosis and hemorrhage.[3] Massive thrombin generation always underlies the pathogenetic mechanisms of the two phenotypes of DIC; however, the amount of plasmin generation determines whether the DIC phenotype is thrombotic, characterized by thrombosis and organ dysfunction due to reduced plasmin levels by plasmin activator inhibitor-1 (PAI-1), or fibrinolytic, characterized by bleeding due to excessive plasmin formation. This review provides a brief overview of DIC with a thrombotic phenotype, followed by an in-depth review of DIC with a fibrinolytic phenotype.

Thrombotic Phenotype

Thrombotic phenotype is a basic principle of DIC, which has long been recognized as a consumptive thrombohemorrhagic disorder. Its main pathophysiology is sustained activation of coagulation, impaired control of anticoagulation, and PAI-1-mediated inhibition of fibrinolysis.[3]

The Scientific Subcommittee (Scientific and Standardization Committee) on DIC of the International Society on Thrombosis and Haemostasis reported that generalized inflammatory responses with inflammatory cytokine release initiate extensive injury to the microvascular endothelium.[2] These processes activate coagulation pathways that escape local regulatory anticoagulation controls, resulting in excessive thrombin generation with systemic fibrin microthrombus formation. Microvascular fibrin thrombosis leads to tissue ischemia and organ dysfunction, and the subsequent consumption of platelets and coagulation factors associated with hemorrhage in tissues. Therefore, microvascular thrombosis and consumptive hemorrhage coexist in the DIC with thrombotic phenotype.

Endothelial injury induces insufficient control of anticoagulation systems, such as tissue factor pathway inhibitor, antithrombin, and protein C/thrombomodulin pathways, propagates coagulation activation, and enhances microvascular fibrin thrombosis.[3] Experimental and clinical studies have shown that inflammatory mediator-induced immediate release of tissue-type plasminogen activator (t-PA) is followed by persistent increases in the levels of PAI-1, the most important inhibitor of t-PA, which results in the sustained inhibition of fibrinolysis with enhanced thrombus formation, leading to organ dysfunction.[4–7] Many studies have demonstrated that persistently high PAI-1 levels are correlated with organ dysfunction and poor prognosis in

patients with DIC, and that PAI-1 levels are a good prognostic factor in underlying disorders of DIC.[6–9] Elevated PAI-1 causes insufficient fibrinolytic responses to coagulation activation, followed by relatively mild elevations of fibrinogen/fibrin degradation products (FDPs) and D-dimer levels, resulting in the formation of microvascular fibrin thrombosis and subsequent organ dysfunctions. Activation of coagulation, insufficient anticoagulation control, and inhibition of fibrinolysis are the major pathologies of DIC with a thrombotic phenotype. Excessive thrombin generation induces consumption coagulopathy with oozing-type hemorrhage in the mucosa and at venipuncture sites, as well as in injured or surgical fields. Indeed, this DIC is called the thrombotic phenotype but is associated with some degree of consumptive hemorrhage. Typical underlying diseases of DIC with thrombotic phenotypes are sepsis, late-phase trauma, late-phase cardiac arrest, resuscitation called postcardiac arrest syndrome, and solid malignant tumors.

The involvement of innate immune responses in the initiation and propagation of coagulation in DIC is well established.[3,10,11] In addition to coagulation, immune mechanisms impair anticoagulation control through endothelial injury and the inhibition of fibrinolysis.[10] The association of DIC with thrombotic phenotypes and innate immunity has been extensively reviewed.[10,11]

Fibrinolytic Phenotype

Brief Overview of Fibrinolysis

Activation of Plasminogen

Thrombin generation at the injury site is followed by fibrin formation in the endothelium. During these processes, both thrombin and hypoxia of endothelial cells under the fibrin thrombus immediately stimulate t-PA release from the Weibel–Palade bodies and small storage vesicles in endothelial cells.[12–14] Brain neurons, microglial cells, astrocytes, and cerebral endothelial cells have been recognized as alternative storage pools of t-PA.[14,15] t-PA and plasminogen in circulation assemble on the surface of fibrin through the lysine-binding site (LBS) in their kringle domains and form a ternary complex of t-PA–plasminogen–fibrin, which enhances the activation of plasminogen by t-PA using fibrin as a cofactor to produce plasmin.[14] Fibrin degradation by plasmin exposes the C-terminal lysine residue of fibrin, which has high affinity for the LBS of plasminogen, leading to the acceleration of plasminogen binding to fibrin and enhancement of the proteolytic activity of t-PA. Therefore, fibrin provides a platform for positive feedback mechanisms of fibrinolysis.

Another plasminogen activator, urokinase (urinary)-type plasminogen activator (u-PA), is found in urine and is synthesized in monocytes/macrophages and epithelial cells. u-PA is characterized by the action of plasminogen through the u-PA receptor, without fibrin as a cofactor. Its primary function in inflammation and wound healing is related to cell migration and degradation of the extracellular matrix.[16] Typically, u-PA does not exist in the plasma; however, once fibrin-bound plasmin is generated, plasmin converts

single-chain u-PA (scuPA) (also called proUK) in the circulation into u-PA, which cleaves plasminogen to plasmin. The role of the u-PA receptor is the co-localization of scuPA and plasminogen on the cell surface expressing the u-PA receptor, enhancing plasmin generation.[16]

Plasmin cleaves non-cross-linked fibrin and factor XIIIa-cross-linked fibrin, with the subsequent formation of each degradation product. Cross-linked FDPs consist of various complexes of DD/E and DY/YD, of which DD/E is considered the fundamental unit and is called a D-dimer. In the DD/E complex, the two D moieties are covalently bound, and the E fragment exists freely and is noncovalently complexed with DD.[16] Clinically, elevated D-dimer levels indicate ongoing fibrin formation and degradation by plasmin, which is distinct from fibrinogenolysis.[17] Plasmin escapes from its physiological inhibitor of α2-antiplasmin and degrades fibrinogen in the circulation into fragments X, Y, D, and E. FDP measured using plasma usually includes fibrinogen and FDPs.

Controls of Fibrinolysis

Fibrinolytic pathways are controlled in three steps: inhibition of plasminogen activation, neutralization of plasmin action, and modification of the fibrin structure. PAI-1, a serine protease inhibitor, efficiently forms a 1:1 complex with t-PA and inhibits the action of t-PA on plasminogen in the circulation. Another serine protease inhibitor, α2-antiplasmin, rapidly complexes with plasmin at the LBS through its C-terminal lysine residue and inhibits the action of plasmin on fibrin. Furthermore, α2-antiplasmin is cross-linked to fibrin through factor XIIIa, which protects fibrin from plasmin binding and stabilizes fibrin thrombi. The third mechanism controlling fibrinolysis occurs in a thrombin-dependent manner. The thrombin–thrombomodulin complex converts thrombin-activatable fibrinolysis inhibitor (TAFI) to activated TAFI (TAFIa), which cleaves the C-terminal lysine residue of partially degraded fibrin, resulting in the inhibition of t-PA and plasminogen binding to this residue, thus attenuating fibrinolysis.[18]

α2-macroglobulin acts as a backup for the plasmin inhibitor of α2-antiplasmin. When α2-antiplasmin is consumed, α2-macroglobulin also complexes with t-PA.[16] The C1-(esterase) inhibitor (C1-INH) inhibits plasmin formation by controlling factor XIIa and kallikrein–kinin system (KKS), and acts as a major inhibitor of complement pathways.

Alternative Pathways of Fibrinolysis

Factor XIIa-driven KKS is deeply involved in inflammation and fibrinolysis.[19] Extracellular RNA from injured cells, neutrophil extracellular traps adhering neutrophil DNA, polyphosphates of the microorganisms and released from platelets activate factor XII-dependent coagulation pathway, subsequently initiate KKS.[20–22] Factor XIIa directly activates plasminogen to generate plasmin and inhibits PAI-1. Kallikrein, which is converted from prekallikrein by factor XIIa, also activates plasminogen to plasmin and cleaves high-molecular-weight kininogen to generate bradykinin. Bradykinin and its metabolite, des-Arg9-bradykinin (DABK), bind to kinin B2 and kinin B1 receptors, respectively, both of which produce inflammatory cytokines. Furthermore, bradykinin stimulates the release of t-PA from endothelial cells via the kinin B2 receptor.[19]

Another alternative pathway is leukocyte-mediated fibrinolysis.[7,23] Leukocyte elastase has been known to cleave fibrinogen and fibrin and inactivates PAI-1, with subsequent promotion of fibrinolysis.[24,25] Leukocyte elastase degrades crosslinked fibrin, which is distinct from the plasmin-mediated digestion of crosslinked fibrin.[25] However, leukocyte elastase also impairs clot lysis degrading plasminogen and plasmin.[26,27] The net results on the fibrinolysis by leukocyte elastase have not yet been confirmed.

The activators and inhibitors of fibrinolysis and factor XIIa-induced KKS-mediated fibrinolysis are shown in ►Figs. 1 and 2, respectively.

Definition

DIC with a fibrinolytic phenotype is defined as the co-existence of uncontrollable thrombin generation and systemic pathologic hyperfibrinogenolysis due to fibrin-independent fibrinolytic system activation during the same insult.[1,3,19,28] Generally, pure fibrinogenolysis is considerably rare and may only be observed when pharmaceutical t-PA is administered to healthy volunteers; however, in the pathological milieu, irrespective of infectious and noninfectious insults, some amount of fibrin is always formed. Therefore, massive thrombin generation and systemic pathologic hyperfibrin(ogen)olysis usually coexist in the DIC with fibrinolytic phenotype. Similar to the thrombotic phenotype, systemic thrombin generation and insufficient anticoagulation controls associated with endothelial injury always underlie on the increased fibrin(ogen)olysis in this type of DIC. In contrast, the degree of fibrinolysis inhibition by PAI-1 depends on the underlying disorders of DIC and systemic pathological fibrin(ogen)olysis.[28,29] ►Fig. 3 shows the overlaps and distinctions between the two DIC phenotypes.

Diagnosis

DIC with a fibrinolytic phenotype can be diagnosed in two steps: the first step is the diagnosis of DIC using published DIC diagnostic criteria, and the second step is the proof of systemic pathologic hyperfibrin(ogen)olysis. Shortening the euglobulin clot lysis time without thrombocytopenia may be useful for characterizing an isolated increase in fibrin(ogen) olysis.[1] However, in the clinical setting, extremely high FDP levels that exceed D-dimer levels and low fibrinogen levels suggest hyperfibrinogenolysis in addition to fibrinolysis. Asakura proposed cutoff values for these parameters as FDP ≥80 µg/mL and fibrinogen <100 mg/dL.[29] Because of the acute-phase reactant, fibrinogen levels less than the lower limit of normal may be a reasonable cutoff value instead of 100 mg/dL. Hyperfibrinogenolysis exceeding fibrinolysis was confirmed by an increased FDP/D-dimer ratio >2.0, which is supported by previous reports studying representative diseases of DIC with a fibrinolytic phenotype, including postcardiac arrest syndrome,[30] trauma,[31] and postpartum hemorrhage.[32]
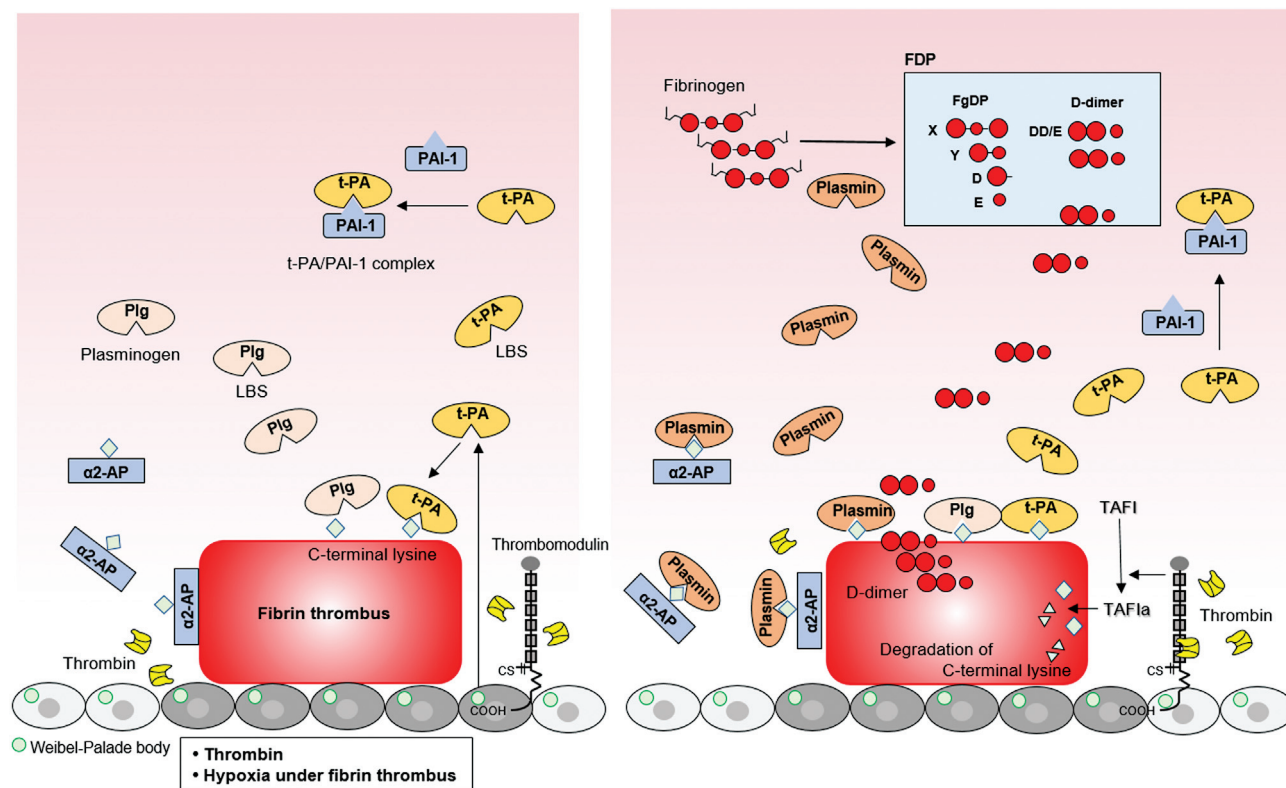
Fig. 1 Brief summary of fibrinolytic system. Primary stimulators of secondary fibrinolysis are thrombin and hypoxia of endothelial cells under fibrin thrombus. Plasminogen and t-PA released from endothelial cells due to these stimulations meet on the fibrin thrombus, and subsequently degrade fibrin. Three major inhibitors of fibrinolysis are PAI-1, α2-antiplasmin, and TAFI. Fibrin degradation by plasmin forms D-dimer, while excessive plasmin escaped from α2-antiplasmin degrades fibrinogen in the circulation. α2AP, α2-antiplasmin; FDP, fibrinogen/fibrin degradation products; FgDP, fibrinogen degradation products: LBS, lysine binding site; PAI-1, plasminogen activator inhibitor-1; Plg, plasminogen, TAFI, thrombin activatable fibrinolysis inhibitor; t-PA, tissue-type plasminogen activators.

In DIC patients associated with acute promyelocytic leukemia, a typical underlying DIC disorder with a fibrinolytic phenotype, the differences between FDP and D-dimer levels were only observed when the α2-antiplasmin levels decreased to <60%, which suggests that α2-antiplasmin <60% may be used as a supportive measure for the diagnosis of systemic pathologic hyperfibrin(ogen)olysis.[33] Extremely low α2-antiplasmin levels associated with high FDP and low fibrinogen levels have also been observed in patients with DIC with a fibrinolytic phenotype at an early stage of trauma and in patients with solid malignant tumors.[34,35] ►Table 1 shows examples of the diagnostic criteria for DIC with a fibrinolytic phenotype.

Pathomechanisms and Underlying Disorders

The control of fibrin(gen)olysis requires a balance between the promotion by lysis activators and impairment by lysis inhibitors. Systemic pathologic hyperfibrin(ogen)olysis develops under basic disorders that accelerate the promotion of lysis, which leads to the consumption of lysis inhibitors and degradation of coagulation factors, further enhancing bleeding.[1] t-PA and u-PA are the two major lysis activators that promote hyperfibrin(gen)olysis in patients with DIC with a fibrinolytic phenotype. The prominent acceleration of t-PA release from endothelial cells or tissues composed of a large amount of t-PA has been considered a mechanism of

systemic pathologic hyperfibrin(ogen)olysis.[14,36] Other mechanisms include increased production of t-PA and promotion of t-PA- and u-PA-mediated conversion of plasminogen to plasmin via specific protein or receptor.[37] Excessive plasmin generation as a result of these mechanisms consumes α2-antiplasmin in the circulation, further enhancing fibrin(gen)olysis. The main pathomechanisms and underlying disorders of systemic pathologic hyperfibrin(ogen)olysis are shown in ►Table 2 and ►Fig. 4.

Acceleration of t-PA Release from Endothelial Cells

Hypoxia stimulates t-PA release from endothelial cells within minutes by promoting Weibel–Palade body exocytosis.[12–14,38] Both Weibel–Palade bodies and small storage granules are expected to release t-PA through hypoxia-induced increases in intracellular ionized calcium, similar to the mechanism of thrombin.[14] Hypoxia due to shock-induced hypoperfusion also elicits an approximately 300% increase in t-PA levels associated with the lowering and elevation of plasminogen and FDP, respectively.[39] Oxygen deprivation decreased t-PA gene transcription and then t-PA mRNA levels remained unchanged for 24 hours, whereas the expression of PAI-1 mRNA was increased through induction of hypoxia-inducible factor-1α, consequently increasing PAI-1 activity and antigen levels in plasma for 4 to 16 hours.[40–43] These studies indicate that t-PA-mediated systemic pathologic hyperfibrin(ogen)
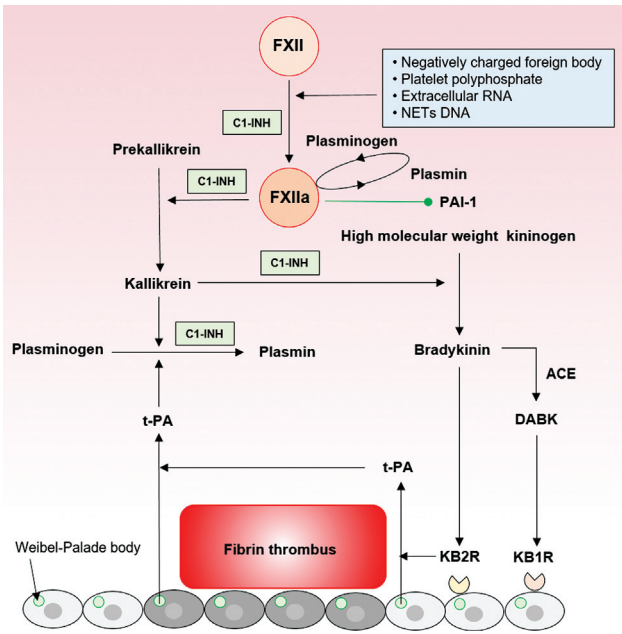
Fig. 2 Factor XIIa and KKS in fibrinolysis. Factor XIIa and KKS are involved in the fibrinolytic system through plasmin formation by factor XIIa and kallikrein, and bradykinin-induced t-PA release from endothelial cells via kinin B2 receptor. Major inhibitor in these fibrinolytic systems is C1-INH. ACE, angiotensin converting enzyme; C1-INH, C1-(esterase) inhibitor; DABK, des-Arg9-bradykinin; KB1R, kinin B1 receptor; KB2R, kinin B2 receptor; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue-type plasminogen activator.

Table 1 Proposed diagnostic criteria for DIC with a fibrinolytic phenotype

1. Diagnosis of DIC
This can be achieved by using a published DIC scoring system.
2. Diagnosis of systemic pathologic hyperfibrin(ogen)olysis.
Can be achieved when (1), (2), and (3) are satisfied.
Alternatively, can be made when two of (1), (2), (3), and (4) are satisfied.
(1) Fibrinogen $<$ lower limit of normal
(2) FDP $\geq$ 80 µg/Ml
(3) FDP/D-dimer ratio $>$ 2.0
Supportive measurements when possible
(4) α2-antiplasmin $<$ 60%
Diagnosis
The fulfillment of both criteria 1 and 2 met the diagnosis of DIC with a fibrinolytic phenotype.

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrinogen/fibrin degradation product.

olysis continues for several hours after exposure to hypoxia and then progresses to the inhibition of t-PA by complexing with PAI-1. DIC with a fibrinolytic phenotype progresses to a thrombotic phenotype because of increased levels of PAI-1 within short hours after the insult.

Examples of this type of systemic pathologic hyperfibrin(ogen)olysis are early phases of cardiac arrest and resuscita-tion, trauma and traumatic shock, and postpartum critical bleeding.[8,28,34,44–46] Massive and immediate t-PA release, followed by PAI-1 increase several hours later, has been confirmed in DIC with a fibrinolytic phenotype due to these insults. Details of systemic pathologic hyperfibrin(ogen)olysis caused by cardiac arrest and trauma are reviewed else-where.[8,28,34] Among the underlying disorders of critical post-partum bleeding, amniotic fluid embolism is associated with high t-PA levels and typical hyperfibrin(ogen)olysis.[47] The significance of amniotic fluid embolism-induced hyperfibrin(ogen)olysis in the postpartum bleeding is still debated.[44] Asphyxia- and drawing-induced hypoxia also causes typical
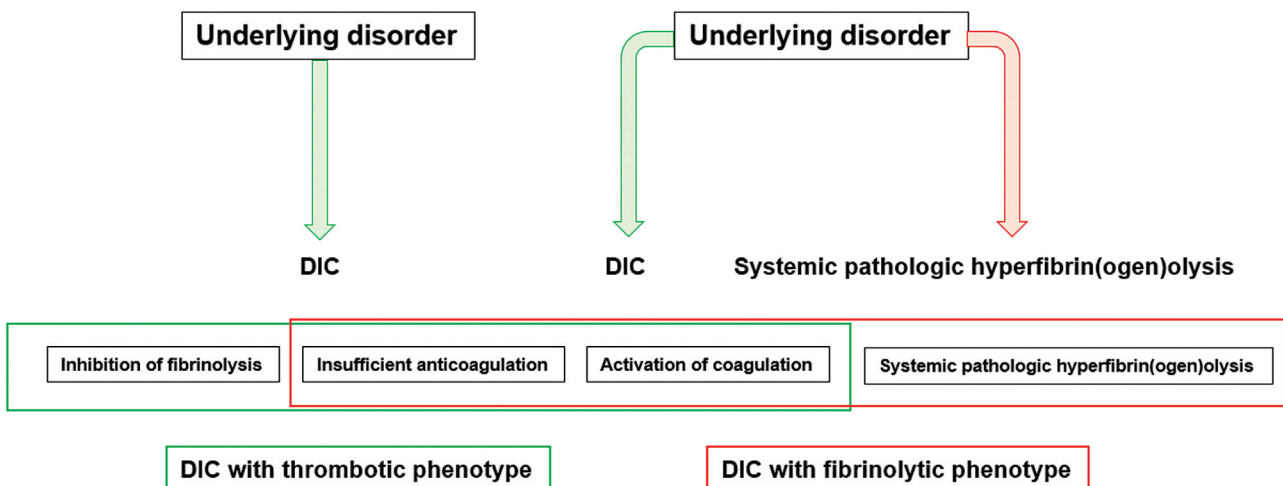

Fig. 3 Two phenotypes of DIC. Basic principle of DIC is a thrombotic phenotype characterized by activation of coagulation, insufficient anticoagulation with endothelial injury, and inhibition of fibrinolysis by PAI-1. Thrombotic phenotype gives rise to organ dysfunction due to microvascular fibrin thrombosis. DIC with fibrinolytic phenotype is defined as simultaneous development of both DIC and systemic pathologic hyperfibrin(ogen)olysis under one insult, which shows typical oozing-type bleeding. Thrombin generation due to activation of coagulation and insufficient anticoagulation always underlies both phenotypes of DIC. DIC, disseminated intravascular coagulation.

Table 2 Pathomechanism-related underlying diseases of DIC with a fibrinolytic phenotype

t-PA release from endothelial cells	t-PA release from storage pools	Conversion of plasminogen to plasmin

• Trauma and traumatic shock
• Cardiac arrest and resuscitation
• Postpartum critical bleeding
• Asphyxia and drawing
• Heat stroke
	• Isolated traumatic brain injury
	• Malignant solid tumor
	  Prostate cancer
	  Breast cancer
	  Lung cancer
		Cell surface expression of u-PA receptor
		• Prostate cancer
		Cell surface expression of Annexin A2 and S100A10
		• Acute promyelocytic leukemia
		Endothelial expression of Annexin A2 and S100A10
		• Trauma and traumatic shock
		• Cardiac arrest and resuscitation
		• Postpartum critical bleeding
		• Asphyxia and drawing
		• Heat stroke

DIC with a fibrinolytic phenotype associated with massive bleeding by high amount of t-PA release.[48] The early stage of heat stroke elicits hyperfibrin(ogen)olysis due to heat-induced direct endothelial injury associated with high t-PA and FDP and low fibrinogen and α2-antiplasmin without elevation of PAI-1, especially in bleeders and those with bleeding with DIC.[49–51]

Acceleration of t-PA Release from Storage Pools

The storage pool of t-PA is released into the circulation, which leads to systemic pathologic hyperfibrin(ogen)olysis independent of hypoxia and hypoperfusion. Expression of t-PA is observed in neurons, microglial cells, astrocytes, oligodendrocytes, and endothelial and epithelial cells in the
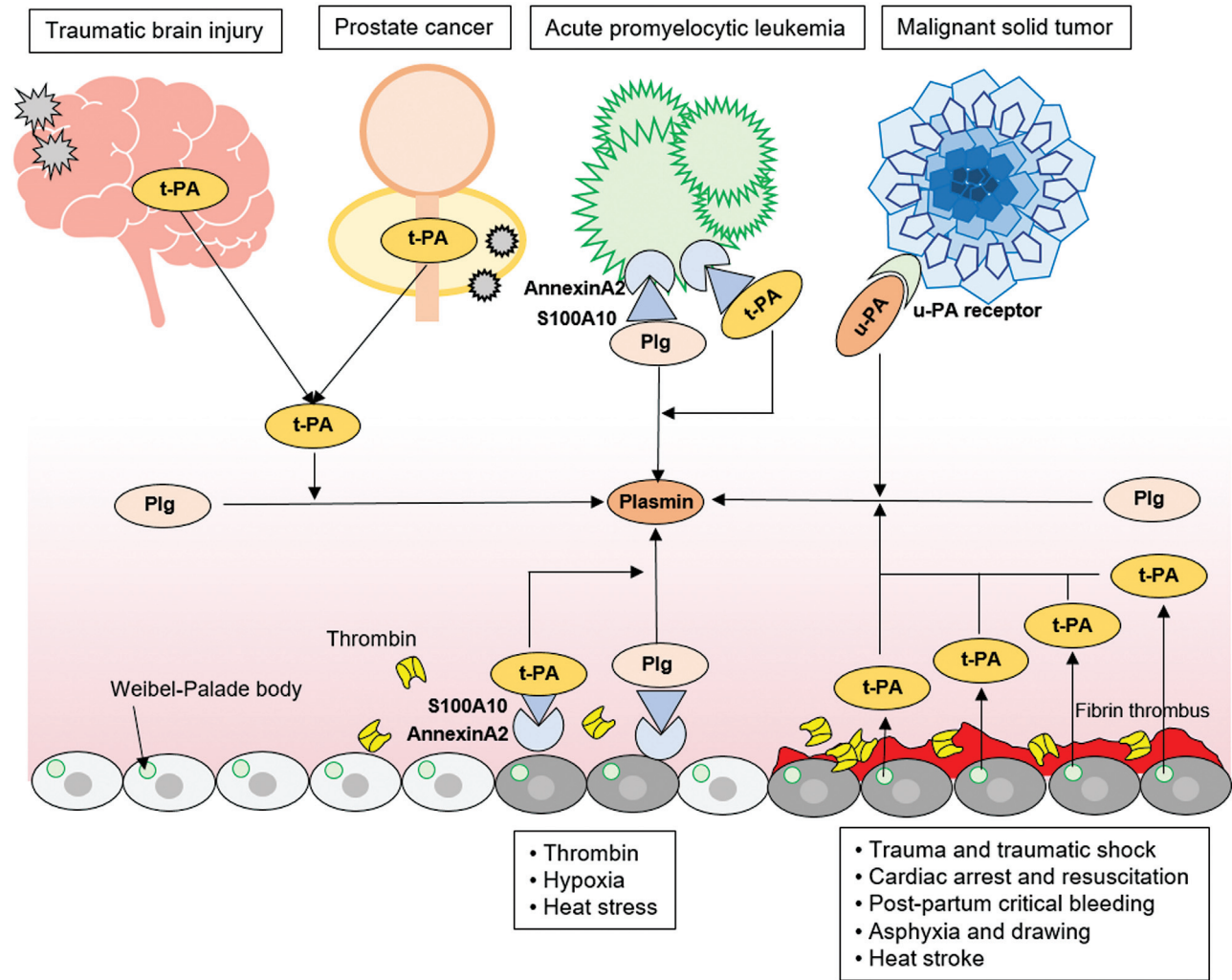

Fig. 4 Pathomechanisms of systemic pathologic hyperfibrin(ogen)olysis and underlying disorders. Three major pathomechanisms are acceleration of t-PA release from hypoxic endothelial cells and t-PA rich storage pools and enhancement of conversion of plasminogen to plasmin due to specific protein and receptor. Plg, plasminogen; t-PA, tissue-type plasminogen activator; u-PA, urokinase (urinary)-type plasminogen activator.

brain.[14,15] Specific areas, such as the hypothalamus, corpus callosum, hippocampus, amygdala, cerebellum, and spinal cord, are rich in t-PA.[36] Experimentally isolated traumatic brain injury demonstrated immediate t-PA release in the cerebrospinal fluid, not based on de novo synthesis, which peaked at 3 hours.[52] A clinical study confirmed that hyperfibrinolysis in isolated traumatic brain injury was not associated with shock and hypoperfusion, which supports the hypothesis that t-PA is released from brain storage pools through disruption of the blood–brain barrier (BBB).[53–55] Isolated traumatic brain injury usually causes DIC with a thrombotic phenotype associated with remote organ microvascular fibrin thrombosis.[56,57] However, some of these patients develop DIC with a fibrinolytic phenotype at an early stage of trauma, showing high t-PA levels associated with elevated FDP, D-dimer, and FDP/D-dimer ratios and low α2-antiplasmin levels.[54,58,59] Systemic pathologic hyperfibrin(ogen)olysis progresses to fibrinolysis inhibition by increased PAI-1 shortly after injury, which is consistent with DIC with a thrombotic phenotype.[54,58] Development of systemic pathologic hyperfibrin(ogen)olysis may depend on the severity of brain injuries, types of injury (with and without BBB disruption), and areas of injured brain abound with t-PA.[36,53,58]

Malignant solid tumors such as breast, lung, and prostate cancers produce t-PA, and exhibit high plasma t-PA levels.[35,60,61] The release of t-PA from prostate cancer cells may be a mechanism of systemic pathologic hyperfibrin(ogen)olysis.[62,63] However, in addition to t-PA, solid cancers can produce u-PA and express u-PA receptors on their membranes, suggesting other mechanisms of systemic pathologic hyperfibrin(ogen)olysis in solid cancers.[35,61]

Acceleration of Conversion of Plasminogen to Plasmin

The u-PA and u-PA receptor system controls matrix degradation and remodeling through the conversion of plasminogen to plasmin, followed by fibrinolysis in the local tumor microenvironment, which also plays a role in tumor invasion and metastasis.[64] Increased levels of u-PA both in plasma and cancer tissues and overexpression of the u-PA receptor in cancer cells have been observed in patients with solid cancers, especially prostate cancer.[35,60,61,65] u-PA receptor-bound u-PA promotes the co-localization of circulating scuPA and plasminogen on the cancer cell surface, enhancing plasmin production through increased efficiency of plasminogen activation and reciprocal activation of scuPA.[16,66] This has been considered one of the mechanisms of systemic pathologic hyperfibrin(ogen)olysis observed in prostate cancer.

Acute promyelocytic leukemia is a typical example of DIC with a fibrinolytic phenotype associated with systemic pathologic hyperfibrin(ogen)olysis due to the accelerated conversion of plasminogen to plasmin.[67] Annexin A2 forms a heterotetramer with S100A10 (also designated as p11), known as the plasminogen receptor on various cells, which binds t-PA and plasminogen through its C-terminal lysine residue.[68,69] The close localization of t-PA and plasminogen on this heterotetramer accelerates the t-PA-mediated rapid

conversion of plasminogen to plasmin, reinforcing fibrinolysis. The heterotetramer provides a platform for the assembly of t-PA and plasminogen on the cell surface; therefore, overexpression of annexin A2 and S100A10 in acute promyelocytic leukemia cells may be the main mechanism of systemic pathologic hyperfibrin(ogen)olysis and bleeding in this type of leukemia.[37,68,69]

As discussed previously, fibrin thrombosis provides a scaffold for the acceleration of fibrinolysis through the exposure of its C-terminal lysine residue to t-PA and plasminogen. The heterotetramer of annexin A2 and S100A10, with a C-terminal lysine residue on the endothelial cells, plays the same role and acts as a backup system for fibrin-enhanced fibrinolysis. Thrombin, hypoxia, and heat stress immediately upregulate endothelial cytoplasm annexin A2 on the endothelial cell surface with the simultaneous expression of S100A10, which elicits heterotetramer-mediated fibrinolysis.[70–72] Taken together, the annexin A2 and S100A10 systems may be strengthening mechanisms for systemic pathologic hyperfibrin(ogen)olysis due to cardiac arrest, trauma, postpartum bleeding, drawing, and heat stroke.

Aortic aneurysms are recognized as localized intravascular coagulation with increased fibrin(ogen)olysis; however, some patients develop DIC with a fibrinolytic phenotype associated with bleeding and enlargement of the aneurysm.[1,73,74] Although increased expression of mRNA levels of t-PA, u-PA, and annexin A2 in aneurysmal tissues suggests the involvement of these systems in increased fibrin(ogen)olysis,[75,76] further studies are needed to elucidate the exact pathomechanisms of increased fibrin(ogen)olysis in patients with aortic aneurysms.

Alternative Pathways of Fibrinolysis

Participation of leukocyte elastase-induced fibrin(ogen)olysis has been speculated in the pathomechanisms of systemic pathologic hyperfibrin(ogen)olysis in trauma and acute promyelocytic leukemia.[77,78] As discussed above, the net contribution of leukocyte elastase to fibrin(ogen)olysis has not yet been confirmed. Critically low levels of C1-INH have been reported in cases of amniotic fluid embolism, including in patients who develop DIC.[79] Administration of C1-INH concentrate to patients with DIC with fibrinolytic phenotype improved vital signs, consciousness, and uterine bleeding.[80] These studies suggest the participation of factors XIIa and KKS in bradykinin generation in the pathomechanisms of systemic pathologic hyperfibrin(ogen)olysis in postpartum critical bleeding caused by amniotic fluid embolism. ►Table 2 summarizes the underlying disorders of DIC with fibrinolytic phenotype.

Prognosis and Treatment

DIC with fibrinolytic phenotype due to cardiac arrest,[30] trauma,[31,81] isolated traumatic brain injury,[55] drawing,[48] and amniotic fluid embolism-induced postpartum bleeding[47] predicted poor outcome and low probability of survival of the patients. Severe coagulopathy complicated by systemic pathologic hyperfibrin(ogen)olysis is associated with fatal outcomes of postpartum bleeding.[44] Although the phenotype was not

mentioned, heat stroke associated with DIC significantly correlated with hospital mortality.[82] Primary hyperfibrinolysis due to malignant solid tumors is rare; however, it is a critical, life-threatening condition.[35] Before the induction of all-*trans*-retinoic acid (ATRA), DIC with a fibrinolytic phenotype in acute promyelocytic leukemia was acknowledged as a fatal complication due to severe bleeding.[67,83]

Two strategies are required for the treatment of DIC with a fibrinolytic phenotype: one for DIC and the other for systemic pathologic hyperfibrin(ogen)olysis. For DIC treatment, refer to the guidelines published by the International Society on Thrombosis and Haemostasis.[84] Recognizing the duration is important for the treatment of systemic pathologic hyperfibrin(ogen)olysis. Systemic pathologic hyperfibrin(ogen)olysis due to t-PA release from endothelial cells and its storage pool continues for several hours after the insult, followed by the inhibition of fibrinolysis by PAI-1. In contrast, systemic pathologic hyperfibrin(ogen)olysis caused by the acceleration of plasminogen activation lasts until recovery from underlying disorders.

Although the target populations were different, the results of CRASH-2, CRASH-3, and WOMAN provided useful information for the treatment of systemic pathologic hyperfibrin(ogen)olysis.[85–87] Common points of these megatrials are the early administration of tranexamic acid, if possible within 3 hours of insults, which improves patient outcomes. Delay may exacerbate inhibition of fibrinolysis by PAI-1 or u-PA-related bleeding.[52,88] The use of tranexamic acid in trauma has been debated regarding the presence or absence of shock-induced fibrinolysis.[89,90] Shock-induced hypoperfusion and hypoxia are potent stimulators of thrombin and plasmin generation,[14,43] which has been confirmed in trauma patients irrespective of tranexamic use, especially in those with DIC with fibrinolytic phenotype.[91,92] Prospective validation of target patients for tranexamic use for short-duration DIC with fibrinolytic phenotypes such as trauma is mandatory. Plasma transfusion has received attention as another method of controlling hyperfibrin(ogen)olysis. In recent clinical trauma research, transfusion of cryoprecipitate, which includes antifibrinolytic factors such as PAI-1 and factor XIII, restored key fibrinolytic regulators and limited plasmin generation to form stronger clots.[93] Valid therapeutics for systemic pathologic hyperfibrin(ogen)olysis induced by malignant solid tumors are scarce. Antifibrinolytic therapies based on the physician's experience may be common worldwide. Regulation of expressions of annexin A2 and S100A10 by ATRA has dramatically changed treatment strategies for acute promyelocytic leukemia and disease-induced DIC with fibrinolytic phenotype.[83,94,95] Thrombosis is an intriguing complication of ATRA therapy, and the use of tranexamic acid during ATRA therapy triggers fatal thromboembolism.[83,96] Therefore, a valid therapeutic strategy for both DIC and systemic pathologic hyperfibrin(ogen)olysis in acute promyelocytic leukemia remains lacking.[67] Anticoagulant therapies against DIC may be potentially effective; however, there can be a risk of exacerbating hemorrhage in DIC with the fibrinolytic phenotype, which is characterized by bleeding symptoms. A randomized control trial published in 1998 failed to show the efficacy of high-dose antithrombin treatment for severely injured patients, while a recent basic study using a porcine trauma model demonstrated that antithrombin administration in addition to coagulation factors resulted in a significant reduction of blood loss compared with supplementation of coagulation factors alone.[97] A recent clinical study has also indicated that the correction of antithrombin activity may contribute to improving the outcomes of trauma cases.[98] Importantly, this study suggested that it is necessary to consider the type of hemorrhage (simple type bleeding or oozing type bleeding), the type of coagulation changes (DIC or not), and when antithrombin should be administered (acute phase or subacute phase) to effectively identify target populations that benefit from anticoagulant therapies.[98]

Definite DIC diagnosis and confirmation of the existence of systemic pathologic hyperfibrin(ogen)olysis appear to be the initial steps in the treatment of DIC with a fibrinolytic phenotype. Therefore, the development of diagnostic criteria for systemic pathologic hyperfibrin(ogen)olysis is an urgent issue. Next, the selection of antifibrinolytic drugs and the duration of their use should be considered. Elucidation of these points will improve the prognosis of patients with DIC with fibrinolytic phenotype.

Conclusion

Two phenotypes of DIC have been systematically reviewed for the first time. DIC is a consumptive thrombohemorrhagic disorder with two opposing manifestations: thrombosis and hemorrhage. Hemorrhage originates from DIC-induced secondary fibrinolysis and primary hyperfibrin(ogen)olysis, independent of fibrin clot formation. DIC with a fibrinolytic phenotype is defined as the co-existence of DIC and systemic pathologic primary hyperfibrin(ogen)olysis. Elucidation of clear pathomechanisms and establishment of diagnostic criteria and treatment strategies for systemic pathologic hyperfibrin(ogen)olysis seem to be critical for the improvement of patient prognosis in DIC with a fibrinolytic phenotype. The international cooperation of experts on DIC and fibrinolysis is warranted to solve these issues.

References

1 Marder VJ, Feinstein DI, Colman RW, Levi M. Consumptive thrombohemorrhagic disorders. In: Colman RW, Marder VJ, Clowes AW, George JN, Goldharber SZ, eds. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 5th ed. Philadelphia, PA: Lippincott Wiliams & Wikins; 2006:1571–1600

2 Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi MScientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86(05):1327–1330

3 Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev Dis Primers 2016;2:16037

4 Suffredini AF, Harpel PC, Parrillo JE. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. N Engl J Med 1989; 320(18):1165–1172

5 Levi M, ten Cate H, van der Poll T, van Deventer SJ. Pathogenesis of disseminated intravascular coagulation in sepsis. JAMA 1993;270 (08):975–979

6 Hack CE. Fibrinolysis in disseminated intravascular coagulation. Semin Thromb Hemost 2001;27(06):633–638

7 Gando S. Role of fibrinolysis in sepsis. Semin Thromb Hemost 2013;39(04):392–399

8 Gando S, Wada T. Disseminated intravascular coagulation in cardiac arrest and resuscitation. J Thromb Haemost 2019;17 (08):1205–1216

9 Gando S, Nakanishi Y, Tedo I. Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. Crit Care Med 1995;23(11):1835–1842

10 Alhamdi Y, Toh CH. Recent advances in pathophysiology of disseminated intravascular coagulation: the role of circulating histones and neutrophil extracellular traps. F1000 Res 2017; 6:2143

11 Popescu NI, Lupu C, Lupu F. Disseminated intravascular coagulation and its immune mechanisms. Blood 2022;139(13): 1973–1986

12 Huber D, Cramer EM, Kaufmann JE, et al. Tissue-type plasminogen activator (t-PA) is stored in Weibel-Palade bodies in human endothelial cells both in vitro and in vivo. Blood 2002;99(10): 3637–3645

13 Lowenstein CJ, Morrell CN, Yamakuchi M. Regulation of Weibel-Palade body exocytosis. Trends Cardiovasc Med 2005;15(08): 302–308

14 Kruithof EK, Dunoyer-Geindre S. Human tissue-type plasminogen activator. Thromb Haemost 2014;112(02):243–254

15 Medcalf RL. Fibrinolysis: from blood to the brain. J Thromb Haemost 2017;15(11):2089–2098

16 Mutch NJ. BN. Plasminogen activation and regulation of fibrinolysis. In: Marder VJ, Aird WC, Bennet JS, Schulman S, White GC, eds. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. Philadelphia, PA: Lippincott Williams & Willkins; 2013: 314–333

17 Longstaff C. Measuring fibrinolysis: from research to routine diagnostic assays. J Thromb Haemost 2018;16(04):652–662

18 Plug T, Meijers JC. Structure-function relationships in thrombin-activatable fibrinolysis inhibitor. J Thromb Haemost 2016;14(04): 633–644

19 Gando S, Wada T. Thromboplasminflammation in COVID-19 coagulopathy: three viewpoints for diagnostic and therapeutic strategies. Front Immunol 2021;12:649122

20 Kannemeier C, Shibamiya A, Nakazawa F, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. Proc Natl Acad Sci U S A 2007;104(15):6388–6393

21 Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol 2013;13(01):34–45

22 Baker CJ, Smith SA, Morrissey JH. Polyphosphate in thrombosis, hemostasis, and inflammation. Res Pract Thromb Haemost 2018; 3(01):18–25

23 Plow EF. Leukocyte elastase release during blood coagulation. A potential mechanism for activation of the alternative fibrinolytic pathway. J Clin Invest 1982;69(03):564–572

24 Wu K, Urano T, Ihara H, et al. The cleavage and inactivation of plasminogen activator inhibitor type 1 by neutrophil elastase: the evaluation of its physiologic relevance in fibrinolysis. Blood 1995; 86(03):1056–1061

25 Kohno I, Inuzuka K, Itoh Y, et al. A monoclonal antibody specific to the granulocyte-derived elastase-fragment D species of human fibrinogen and fibrin: its application to the measurement of granulocyte-derived elastase digests in plasma. Blood 2000;95 (05):1721–1728

26 Bach-Gansmo ET, Halvorsen S, Godal HC, Skjønsberg OH. Impaired clot lysis in the presence of human neutrophil elastase. Thromb Res 1995;80(02):153–159

27 Cruz DBD, Helms J, Aquino LR, et al. DNA-bound elastase of neutrophil extracellular traps degrades plasminogen, reduces plasmin formation, and decreases fibrinolysis: proof of concept in septic shock plasma. FASEB J 2019;33(12):14270–14280

28 Gando S, Otomo Y. Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock. Crit Care 2015;19(01):72

29 Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. J Intensive Care 2014;2(01):20

30 Wada T, Gando S, Ono Y, et al. Disseminated intravascular coagulation with the fibrinolytic phenotype predicts the outcome of patients with out-of-hospital cardiac arrest. Thromb J 2016;14:43

31 Sawamura A, Hayakawa M, Gando S, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res 2009;124(05):608–613

32 Sugawara J, Suenaga K, Hoshiai T, et al. Efficacy of recombinant human soluble thrombomodulin in severe postpartum hemorrhage with disseminated intravascular coagulation. Clin Appl Thromb Hemost 2013;19(05):557–561

33 Okajima K, Koga S, Okabe H, Inoue M, Takatsuki K. Characterization of the fibrinolytic state by measuring stable cross-linked fibrin degradation products in disseminated intravascular coagulation associated with acute promyelocytic leukemia. Acta Haematol 1989;81(01):15–18

34 Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. Ann Surg 2011;254(01):10–19

35 Winther-Larsen A, Sandfeld-Paulsen B, Hvas AM. Hyperfibrinolysis in patients with solid malignant neoplasms: a systematic review. Semin Thromb Hemost 2021;47(05):581–588

36 Lemarchant S, Docagne F, Emery E, Vivien D, Ali C, Rubio M. tPA in the injured central nervous system: different scenarios starring the same actor? Neuropharmacology 2012;62(02):749–756

37 Kolev K, Longstaff C. Bleeding related to disturbed fibrinolysis. Br J Haematol 2016;175(01):12–23

38 Pinsky DJ, Naka Y, Liao H, et al. Hypoxia-induced exocytosis of endothelial cell Weibel-Palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. J Clin Invest 1996;97(02):493–500

39 Moore HB, Moore EE, Lawson PJ, et al. Fibrinolysis shutdown phenotype masks changes in rodent coagulation in tissue injury versus hemorrhagic shock. Surgery 2015;158(02):386–392

40 Gertler JP, Perry L, L'Italien G, et al. Ambient oxygen tension modulates endothelial fibrinolysis. J Vasc Surg 1993;18(06): 939–945, discussion 945–946

41 Pinsky DJ, Liao H, Lawson CA, et al. Coordinated induction of plasminogen activator inhibitor-1 (PAI-1) and inhibition of plasminogen activator gene expression by hypoxia promotes pulmonary vascular fibrin deposition. J Clin Invest 1998;102(05): 919–928

42 Liao H, Hyman MC, Lawrence DA, Pinsky DJ. Molecular regulation of the PAI-1 gene by hypoxia: contributions of Egr-1, HIF-1alpha, and C/EBPalpha. FASEB J 2007;21(03):935–949

43 Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019;181:77–83

44 de Lloyd L, Jenkins PV, Bell SF, et al. Acute obstetric coagulopathy during postpartum hemorrhage is caused by hyperfibrinolysis and dysfibrinogenemia: an observational cohort study. J Thromb Haemost 2023;21(04):862–879

45 Kruithof EK, Tran-Thang C, Gudinchet A, et al. Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors. Blood 1987;69(02):460–466

46 Gando S, Kameue T, Nanzaki S, Nakanishi Y. Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. Thromb Haemost 1997;77(02):278–282

47 Matsunaga S, Masuko H, Takai Y, Kanayama N, Seki H. Fibrinogen may aid in the early differentiation between amniotic fluid embolism and postpartum haemorrhage: a retrospective chart review. Sci Rep 2021;11(01):8379

48 Schwameis M, Schober A, Schörgenhofer C, et al. Asphyxia by drowning induces massive bleeding due to hyperfibrinolytic disseminated intravascular coagulation. Crit Care Med 2015;43(11):2394–2402

49 al-Mashhadani SA, Gader AG, al Harthi SS, Kangav D, Shaheen FA, Bogus F. The coagulopathy of heat stroke: alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah. Blood Coagul Fibrinolysis 1994;5(05):731–736

50 Bouchama A, Al-Mohanna F, Assad L, et al. Tissue factor/factor VIIa pathway mediates coagulation activation in induced-heat stroke in the baboon. Crit Care Med 2012;40(04):1229–1236

51 Matsumoto H, Takeba J, Umakoshi K, et al. Successful treatment for disseminated intravascular coagulation (DIC) corresponding to phenotype changes in a heat stroke patient. J Intensive Care 2019;7:2

52 Hijazi N, Abu Fanne R, Abramovitch R, et al. Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice. Blood 2015;125(16):2558–2567

53 Hayakawa M, Maekawa K, Kushimoto S, et al. Hyperfibrinolysis in severe isolated traumatic brain injury may occur without tissue hypoperfusion: a retrospective observational multicentre study. Crit Care 2017;21(01):222

54 Wada T, Shiraishi A, Gando S, et al. Pathophysiology of coagulopathy induced by traumatic brain injury is identical to that of disseminated intravascular coagulation with hyperfibrinolysis. Front Med (Lausanne) 2021;8:767637

55 Wada T, Gando S, Maekaw K, et al. Disseminated intravascular coagulation with increased fibrinolysis during the early phase of isolated traumatic brain injury. Crit Care 2017;21(01):219

56 Kaufman HH, Hui KS, Mattson JC, et al. Clinicopathological correlations of disseminated intravascular coagulation in patients with head injury. Neurosurgery 1984;15(01):34–42

57 Stein SC, Smith DH. Coagulopathy in traumatic brain injury. Neurocrit Care 2004;1(04):479–488

58 Cardenas JC, Matijevic N, Baer LA, Holcomb JB, Cotton BA, Wade CE. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. Shock 2014;41(06):514–521

59 Mathur R, Suarez JI. Coagulopathy in isolated traumatic brain injury: myth or reality. Neurocrit Care 2023;38(02):429–438

60 Nielsen VG, Matika RW, Ley ML, et al. Tissue-type plasminogen activator-induced fibrinolysis is enhanced in patients with breast, lung, pancreas and colon cancer. Blood Coagul Fibrinolysis 2014;25(03):248–253

61 Bell WR. The fibrinolytic system in neoplasia. Semin Thromb Hemost 1996;22(06):459–478

62 Kulić A, Cvetković Z, Libek V. Primary hyperfibrinolysis as the presenting sign of prostate cancer: a case report. Vojnosanit Pregl 2016;73(09):877–880

63 Wada Y, Uchiba M, Kawano Y, et al. Severe bleeding tendency caused by a rare complication of excessive fibrinolysis with disseminated intravascular coagulation in a 51-year-old Japanese man with prostate cancer: a case report. J Med Case Rep 2012;6:378

64 D'Alessio S, Blasi F. The urokinase receptor as an entertainer of signal transduction. Front Biosci (Landmark Ed) 2009;14(12):4575–4587

65 Kimura S, D'Andrea D, Iwata T, et al. Expression of urokinase-type plasminogen activator system in non-metastatic prostate cancer. World J Urol 2020;38(10):2501–2511

66 Ellis V. Functional analysis of the cellular receptor for urokinase in plasminogen activation. Receptor binding has no influence on the zymogenic nature of pro-urokinase. J Biol Chem 1996;271(25):14779–14784

67 Ikezoe T. Pathogenesis of disseminated intravascular coagulation in patients with acute promyelocytic leukemia, and its treatment using recombinant human soluble thrombomodulin. Int J Hematol 2014;100(01):27–37

68 Luo M, Hajjar KA. Annexin A2 system in human biology: cell surface and beyond. Semin Thromb Hemost 2013;39(04):338–346

69 Madureira PA, O'Connell PA, Surette AP, Miller VA, Waisman DM. The biochemistry and regulation of S100A10: a multifunctional plasminogen receptor involved in oncogenesis. J Biomed Biotechnol 2012;2012:353687

70 Peterson EA, Sutherland MR, Nesheim ME, Pryzdial EL. Thrombin induces endothelial cell-surface exposure of the plasminogen receptor annexin 2. J Cell Sci 2003;116(Pt 12):2399–2408

71 Huang B, Deora AB, He KL, et al. Hypoxia-inducible factor-1 drives annexin A2 system-mediated perivascular fibrin clearance in oxygen-induced retinopathy in mice. Blood 2011;118(10):2918–2929

72 Deora AB, Kreitzer G, Jacovina AT, Hajjar KA. An annexin 2 phosphorylation switch mediates p11-dependent translocation of annexin 2 to the cell surface. J Biol Chem 2004;279(42):43411–43418

73 Fisher DF Jr, Yawn DH, Crawford ES. Preoperative disseminated intravascular coagulation associated with aortic aneurysms. A prospective study of 76 cases. Arch Surg 1983;118(11):1252–1255

74 Tromholt N, Jørgensen SJ, Hesse B, Hansen MS. In vivo demonstration of focal fibrinolytic activity in abdominal aortic aneurysms. Eur J Vasc Surg 1993;7(06):675–679

75 Shireman PK, McCarthy WJ, Pearce WH, Shively VP, Cipollone M, Kwaan HC. Elevations of tissue-type plasminogen activator and differential expression of urokinase-type plasminogen activator in diseased aorta. J Vasc Surg 1997;25(01):157–164

76 Hayashi T, Morishita E, Ohtake H, Oda Y, Asakura H, Nakao S. Expression of annexin II in experimental abdominal aortic aneurysms. Int J Hematol 2009;90(03):336–342

77 Hayakawa M, Sawamura A, Gando S, et al. Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. Surgery 2011;149(02):221–230

78 Oudijk EJ, Nieuwenhuis HK, Bos R, Fijnheer R. Elastase mediated fibrinolysis in acute promyelocytic leukemia. Thromb Haemost 2000;83(06):906–908

79 Tamura N, Kimura S, Farhana M, et al. C1 esterase inhibitor activity in amniotic fluid embolism. Crit Care Med 2014;42(06):1392–1396

80 Todo Y, Tamura N, Itoh H, Ikeda T, Kanayama N. Therapeutic application of C1 esterase inhibitor concentrate for clinical amniotic fluid embolism: a case report. Clin Case Rep 2015;3(07):673–675

81 Wada T, Shiraishi A, Gando S, et al. Disseminated intravascular coagulation immediately after trauma predicts a poor prognosis in severely injured patients. Sci Rep 2021;11(01):11031

82 Hifumi T, Kondo Y, Shimazaki J, et al. Prognostic significance of disseminated intravascular coagulation in patients with heat stroke in a nationwide registry. J Crit Care 2018;44:306–311

83 Barbui T, Finazzi G, Falanga A. The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. Blood 1998;91(09):3093–3102

84 Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. J Thromb Haemost 2013;11(04):761–767

85 Roberts I, Shakur H, Afolabi A, et al; CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377(9771):1096–1101, 1101.e1–1101.e2

86 CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 2019;394(10210):1713–1723

87 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389(10084):2105–2116

88 Medcalf RL. The traumatic side of fibrinolysis. Blood 2015;125 (16):2457–2458

89 Ageron FX, Shakur-Still H, Roberts I. Effects of tranexamic acid treatment in severely and non-severely injured trauma patients. Transfusion 2022;62(Suppl 1):S151–S157

90 Moore EE, Moore HB, Gonzalez E, Sauaia A, Banerjee A, Silliman CC. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. Transfusion 2016;56(Suppl 2):S110–S114

91 Gando S, Shiraishi A, Wada T, et al; JAAM FORECAST TRAUMA Study Group. Effects of tranexamic acid on coagulofibrinolytic markers during the early stage of severe trauma: a propensity score-matched analysis. Medicine (Baltimore) 2022;101(32): e29711

92 Gando S, Shiraishi A, Wada T, et al. A multicenter prospective validation study on disseminated intravascular coagulation in trauma-induced coagulopathy. J Thromb Haemost 2020;18(09): 2232–2244

93 Morrow GB, Feller T, McQuilten Z, et al. Cryoprecipitate transfusion in trauma patients attenuates hyperfibrinolysis and restores normal clot structure and stability: results from a laboratory substudy of the FEISTY trial. Crit Care 2022;26(01):290

94 Olwill SA, McGlynn H, Gilmore WS, Alexander HD. All-trans retinoic acid-induced downregulation of annexin II expression in myeloid leukaemia cell lines is not confined to acute promyelocytic leukaemia. Br J Haematol 2005;131(02):258–264

95 Holloway RW, Thomas ML, Cohen AM, et al. Regulation of cell surface protease receptor S100A10 by retinoic acid therapy in acute promyelocytic leukemia (APL)*. Cell Death Dis 2018;9(09): 920

96 Hashimoto S, Koike T, Tatewaki W, et al. Fatal thromboembolism in acute promyelocytic leukemia during all-trans retinoic acid therapy combined with antifibrinolytic therapy for prophylaxis of hemorrhage. Leukemia 1994;8(07):1113–1115

97 Grottke O, Honickel M, Braunschweig T, Reichel A, Schöchl H, Rossaint R. Prothrombin complex concentrate-induced disseminated intravascular coagulation can be prevented by coadministering antithrombin in a porcine trauma model. Anesthesiology 2019;131(03):543–554

98 Wada T, Shiraishi A, Gando S, et al. Association of antithrombin with development of trauma-induced disseminated intravascular coagulation and outcomes. Front Immunol 2022;13:1026163