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Pathogenesis of disseminated intravascular coagulation in patients with acute promyelocytic leukemia, and its treatment using recombinant human soluble thrombomodulin

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Abstract Acute promyelocytic leukemia (APL) is an uncommon subtype of acute myelogenous leukemia characterized by the proliferation of blasts with distinct morphology, a specific balanced reciprocal translocation *t*(15;17), and life-threatening hemorrhage caused mainly by enhanced fibrinolytic-type disseminated intravascular coagulation (DIC). The introduction of all-*trans* retinoic acid (ATRA) into anthracycline-based induction chemotherapy regimens has dramatically improved overall survival of individuals with APL, although hemorrhage-related death during the early phase of therapy remains a serious problem. Moreover, population-based studies have shown that the incidence of early death during induction chemotherapy is nearly 30 %, and the most common cause of death is associated with hemorrhage. Thus, development of a novel treatment strategy to alleviate abnormal coagulation in APL patients is urgently required. Recombinant human soluble thrombomodulin (rTM) comprises the active extracellular domain of TM, and has been used for treatment of DIC since 2008 in Japan. Use of rTM in combination with remission induction chemotherapy, including ATRA, produces potent resolution of DIC without exacerbation of bleeding tendency in individuals with APL. This review article discusses the pathogenesis and features of DIC caused by APL, as well as the possible anticoagulant and anti-leukemic action of rTM in APL patients.

Keywords Acute promyelocytic leukemia · Disseminated intravascular coagulation · Coagulopathy · Human soluble thrombomodulin · Hemorrhage

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Introduction

Acute promyelocytic leukemia (APL) constitutes approximately 10 % of all cases of adult acute myelogenous leukemia (AML) and is characterized by a specific balanced reciprocal translocation *t*(15;17), generating promyelocytic leukemia–retinoic acid receptor α (*PML–RARα*) fusion transcripts that impair signaling mediated by RARα [1, 2]. The most important clinical feature of APL is life-threatening hemorrhage, which is caused mainly by enhanced fibrinolytic-type disseminated intravascular coagulation (DIC). Although the true incidence of DIC in APL patients is unknown, a recent epidemiological survey conducted in Taiwan found that 90 (77.6 %) of 116 APL patients developed overt DIC [3].

Prior to the ATRA era, early mortality related to hemorrhagic complications was extremely high [4–8] (Table 1). For example, early death during the first course of chemotherapy was observed in 47 % of APL patients ($n = 57$) treated with combination chemotherapy with daunorubicin (DNR) and cytarabine (AraC). Approximately, 41 % of early deaths were related to hemorrhagic events, with intracranial hemorrhage being the most common cause of death (73 %) [6]. Incorporation of all-*trans* retinoic acid (ATRA) and, more recently, arsenic trioxide (ATO), into induction chemotherapy has revolutionized the treatment of individuals with APL, with 90–95 % of newly diagnosed APL patients achieving complete remission and over 85 % of patients surviving for longer than 5 years [9–23]. Despite the incorporation of ATRA, hemorrhage remains the major cause of early death (4.5 %); other

Table 1 History of APL therapy

References	Period	Induction therapy	Anticoagulant	Pt (*n*)	CR (%)	Early death (%)	Hemorrhagic death (%)
Before ATRA era							
Bernard et al. [4]	1967–1971	DNR	No	35	46	54	26
			Heparin	9	33	67	44
Cunningham et al. [5]	1974–1984	DNR/AMSA + AraC + 6TG	No	3	67	33	33
			Heparin	54	76	20	13
Cordonnier et al. [6]	1972–1982	AraC + DNR or AraC + DNR + VCR + CCNU	Heparin	57	53	47	26
Hoyle et al. [7]	1976–1986	AraC + DNR + 6MP or 5FU + VCR + PSL	Heparin	35	86	11	9
			No	80	49	43	38
			Total	115	60	33	29
GIMEMA. Rodeghiero et al. [8]	1984–1987	DNR or DXR/DNR + AraC ± 6MP/VP16	Heparin	94	62	13	9.6
			Supportive Tx	107	62	14	10
			Anti-fibrinolytic	67	64	10	8
			Total	268	62	13	10
After ATRA							
Fenaux et al. [9]	1989–1991	ATRA		26	96	4	4
		AMSA/Zorbicine + AraC		29	76	N.D	N.D
JALSG AML92 + AML89 Kanamaru et al. [10]	1992–1993	ATRA ± DNR/BHAC		109	89	8	N.D
	1989–1991	DNR + BHAC/AraC + 6MP + PSL		64	71	20	N.D
European APL91 Fenaux et al. [11]	1991–1992	ATRA + DNR + AraC		54	91	9	5.6
		DNR + AraC		47	81	8.5	6.4
			Total	101	86	8.9	5.9
Tallman et al. [12]	1992–1995	ATRA		172	72	11	6
		DNR + AraC		174	69	14	7
			Total	346	71	12	6.4
GIMEMA. Di Bona et al. [13]	1989–1997	ATRA + IDR		499	92	3.8	3
		IDR		123	76	7.3	4.1
			Total	622	89	4.5	3.2
Estey et al. [14]	1991–1995	ATRA + IDR	No	43	77	19	12
	1979–1991	Anthracycline/AMSA + AraC	No	57	68	30	18
			Total	100	72	25	15

Table 1 continued

References	Period	Induction therapy	Anticoagulant	Pt (*n*)	CR (%)	Early death (%)	Hemorrhagic death (%)
European APL93 Fenaux et al. [15]	1993–1996	ATRA → DNR + AraC		109	95	7	N.D
		ATRA + DNR + AraC		99	94	6	N.D
		High WBC (>5,000/μL)		163	90	5.5	N.D
		Elderly (>66 year)		42	90	19	N.D
			Total	413	92	7	2.4
PETHEMA de la Serna et al. [16]	1996–1999	ATRA + IDR (LPA96)	No	172	91	9.3	5.1
	1999–2005	ATRA + IDR (LPA99)	Tranexamic acid	560	91	8.9	5
			Total	732	91	9.0	5
JALSG APL92 Asou et al. [17]	1992–1997	ATRA		126	94	N.D	N.D
		ATRA + DNR/BHAC		110	89	N.D	N.D
		ATRA + later DNR/BHAC		97	88	N.D	N.D
		ATRA + DNR/BHAC + later DNR/BHAC		36	86	N.D	N.D
			Total	369	90	8	3.3
JALSG APL97 Yanada et al. [18]	1997–2002	ATRA		85	N.D	N.D	0
		ATRA + later IDR/AraC		66	N.D	N.D	4.5
		ATRA + IDR/AraC ± later IDR/AraC		73	N.D	N.D	2.7
		ATRA + IDR/AraC		52	N.D	N.D	7.7
			Total	283	94	N.D	3.2
GIMEMA Lo-Coco et al. [19]	1993–2000	ATRA + IDA (AIDA0493)	Tranexamic acid	636	94	5.5	2
	2000–2006	ATRA + IDA (AIDA2000)	No	445	94	5.6	1.8
			Total	1081	94	5.6	1.9
PETHEMA/HOVON Sanz et al. [20]	2005–2009	ATRA + IDA (LPA2005)	No	402	93	7.5	3.7
	1999–2002	ATRA + IDA (LPA99)	Tranexamic acid	561	91	8.9	5
			Total	963	92	8.3	4.5
ATO							
Mathews et al. [21]	1998–2003	ATO ± HU		72	86	14	11
Shen et al. [22]	2001–2003	ATRA		20	95	5	5
		ATO		20	90	10	10
		ATRA + ATO		21	95	4.8	4.8
			Total	61	93	6.6	6.6
Hu et al. [23]	2001–2005	ATRA + ATO ± Chemotherapy		85	94	5.9	3.5
Population-based report							
Brazil Jacom et al. [24]	2003–2006	ATRA + DNR or IDA		134	68	32	26
Sweden Lehmann et al. [25]	1997–2006	ATRA ± DNR or IDA		105	N.D	29	11

Table 1 continued

References	Period	Induction therapy	Anticoagulant	Pt (*n*)	CR (%)	Early death (%)	Hemorrhagic death (%)
USA Park et al. [26]	1992–1995	N.D		224	N.D	22	N.D
	1996–2001	N.D		495	N.D	15	N.D
	2002–2007	N.D		681	N.D	18	N.D
			Total	1400	N.D	17	N.D

APL acute promyelocytic leukemia, *ATRA* all-*trans* retinoic acid; *ATO* arsenic trioxide, *Pt* patient, *n* number, *CR* complete remission, *N.D* not described, *DNR* daunorubicin, *AMSA* amsacrine, *Ara-C* cytarabine, *6TG* 6-thioguanine, *VCR* vincristine, *CCNU* lomustine, *6MP* 6-mercaptopurine, *5FU* 5-fluorouracil, *PSL* prednisolone, *DXR* adriamycin, *VP16* etoposide, *BHAC* behenoyl Ara-C, *IDR* idarubicin, *HU* hydroxyurea

causes of early death include infection (1.9 %) and differentiation syndrome (1.2 %) [20] (Table 1). Moreover, population-based studies have shown that the early death rate during induction chemotherapy remains extremely high (30 %), and the most common cause of death is associated with hemorrhage [24–26] (Table 1). Thus, development of a novel treatment strategy to alleviate coagulopathy in APL patients is urgently required.

Recombinant human soluble thrombomodulin (rTM) comprises the active, extracellular domain of thrombomodulin (TM) and inactivates coagulation by binding to thrombin [27, 28]. In addition, the thrombin–rTM complex activates protein C to produce activated protein C (APC), which inactivates factors VIIIa and Va in the presence of protein S, further inhibiting thrombin formation [29]. The use of rTM for the treatment of DIC was approved in Japan in 2008, and is effective for the management of DIC complicated by a variety of underlying diseases [30–36]. rTM possesses anti-inflammatory and cytoprotective effects [37–39], and the use of rTM significantly improved survival of mechanically ventilated patients with severe sepsis when compared with control patients who did not receive rTM [30]. Multifunctional rTM has recently come into the global spotlight as a novel agent for the management of DIC [40, 41].

Clinical manifestation of DIC in APL patients

DIC complicated by APL is characterized by exaggerated fibrinolysis and life-threatening hemorrhage. Hemorrhagic death frequently occurred within the first week after initiation of induction chemotherapy, and was nearly exclusively caused by intracranial and pulmonary hemorrhages (incidence of 65 and 32 %, respectively). These data come from the Programa de Estudio y Tratamiento de las Hemopatias Malignas (PETHEMA) group that carefully evaluated the cause of induction failure in 732 newly diagnosed APL patients who were treated with a combination of ATRA and idarubicin [16]. High blast count ($>30 \times 10^9$/L) was identified as a predictive factor for hemorrhagic death by PETHEMA as well as by the Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) group that evaluated early hemorrhagic death in 622 consecutive APL patients treated with ATRA either alone ($n = 499$) or in combination with idarubicin ($n = 123$) [13].

Notably, approximately 5 % of APL patients developed thrombotic events, including deep venous thromboses, cerebral strokes, pulmonary emboli, and myocardial infarction, during induction chemotherapy with ATRA and idarubicin [42, 43]. Initiation of therapy with ATRA rapidly corrects hyperfibrinolysis; however, normalization of thrombotic markers, such as prothrombin fragment 1 + 2

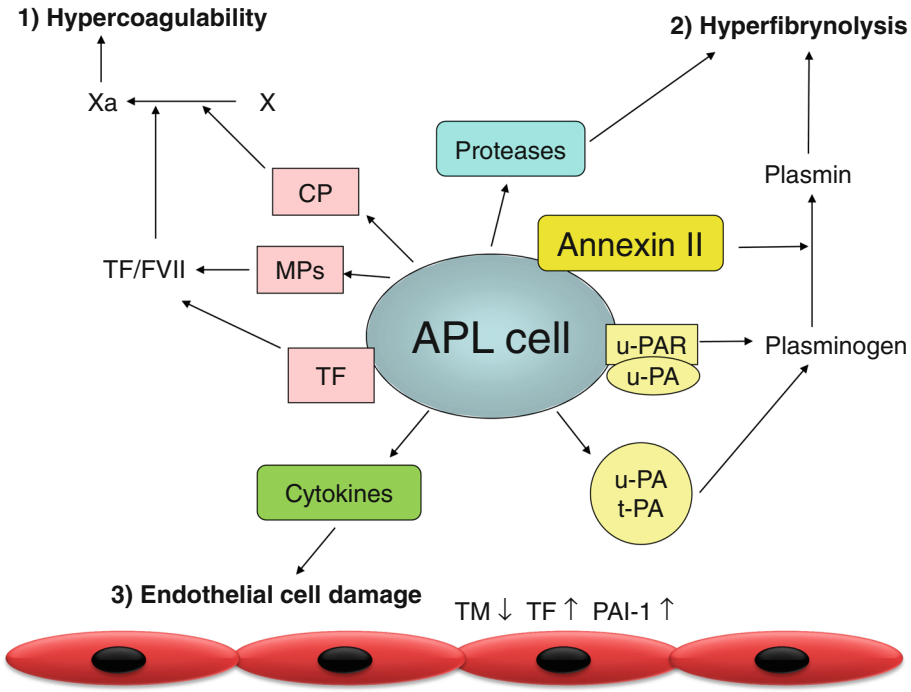

Fig. 1 **1** Hypercoagulability. APL cells express TF, CP and MPs, which activate the coagulation cascade. **2** Hyperfibrinolysis. APL cells produce t-PA, u-PA and u-PAR, which activate plasminogen. APL cells aberrantly express annexin II on their cell surface, which mediates conversion of plasminogen to plasmin. Elastases produced by APL cells may cleave fibrinogen and degrade fibrinolytic inhibitors, resulting in hyperfibrinolysis. **3** Endothelial cell damage. APL cells produce various types of inflammatory cytokine, including IL-1β, IL-6 and TNF-α, all of which cause endothelial cell damage and downregulate expression of TM in parallel with upregulation of TF and PAI-1 on the cell surface of endothelial cells, resulting in hypercoagulability. *TF*, tissue factor; *CP*, cancer procoagulant; *MPs*, microparticles; *t-PA*, tissue-type plasminogen activator; *u-PA*, urokinase-type plasminogen activator; *u-PAR*, u-PA receptor; *IL-1β*, interleukin-1β; *IL-6*, interleukin-6; *TNF-α*, tumor necrosis factor-α; *TM*, thrombomodulin; *PAI-1*, plasminogen activator inhibitor-1

(F1 + 2) and thrombin antithrombin complex (TAT), does not occur until 2 weeks after treatment with ATRA [44]. It may be that ATRA impairs the balance between coagulation and fibrinolysis and thereby causes a hypercoagulable state. It should also be noted that severe thrombotic complications occurred in six of 26 patients who died before initiation of chemotherapy [43]. This PETHEMA study identified a low level of fibrinogen and microgranular morphology (M3 variant) as an independent prognostic factor for thrombosis [43]. Importantly, prophylactic use of tranexamic acid did not impact hemorrhagic mortality, but it did tend to increase the incidence of thrombotic complications [43].

Pathogenesis of DIC caused by APL

Hypercoagulability

Plasma markers of clotting activation, such as TAT, F1 + 2, and fibrinopeptide A (FPA), are markedly elevated in APL patients [44–46], indicating the presence of hypercoagulability. There are three different types of procoagulants aberrantly produced by APL cells: tissue factor (TF), cancer procoagulant (CP), and microparticles (MPs) (Fig. 1). TF, a transmembrane glycoprotein, forms a complex with factor VII (FVII) to activate coagulation factor X (FX), which generates thrombin. As APL cell line NB4 underwent apoptosis after exposure to cytotoxic agents, thrombin generation was augmented in association with enhanced TF activity. The exteriorization of phosphatidylserine on the surface of APL cells during apoptosis allows interaction with the extracellular domain of TF, leading to its activation [47]. These observations are clinically relevant; DIC is exacerbated in APL patients when tumor lysis occurs after initiation of induction chemotherapy with cytotoxic agents, such as anthracycline and AraC. CP, a cysteine proteinase procoagulant produced from fetal and malignant cells, directly activates FX and generates thrombin in the absence of FVII. Among the different cytological subtypes of AML, the activity of CP was greatest in APL cells [48, 49]. MPs might also be involved in hypercoagulability in APL patients. MPs are released from APL cells, as evidenced by their expression of CD33 cell surface antigen and TF. The number of $CD33^{+}$ MPs strongly correlated with leukocyte counts and

plasma levels of D-dimer in APL patients [50]. APL cell-derived MPs decreased coagulation time and increased thrombin generation in a TF-dependent manner [50]. Exposure of leukemia cells to anthracycline increased the release of TF^+ MPs in vitro [51]. This may account for the exacerbation of DIC during remission induction chemotherapy.

APL cells produce a variety of inflammatory cytokines, including interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) [52]. These cytokines cause endothelial cell damage and downregulate the expression of TM in parallel with upregulation of TF and plasminogen activator inhibitor-1 (PAI-1) on the cell surface of endothelial cells, resulting in hypercoagulability [53, 54] (Fig. 1).

Hyperfibrinolysis

Laboratory findings of DIC in patients with APL are characterized by marked hypofibrinogenemia and an increase in ratio of fibrin/fibrinogen degradation products (FDP)/D-dimer. Moreover, a decrease in the levels of plasminogen, α-2-antiplasmin and plasminogen activator inhibitor 1 (PAI-1) and an increase in the levels of urokinase-type plasminogen activator (u-PA) and plasmin/α-2-antiplasmin complex were noted in APL patients [55–58]. These observations may explain the exaggerated fibrinolysis in APL patients. Further studies have demonstrated that APL cells expressed several key mediators of plasmin generation, such as tissue-type plasminogen activator (t-PA), u-PA and its receptor, u-PAR. The u-PA/u-PAR complex enhances activation of cell-bound plasminogen [59, 60] (Fig. 1).

One of the most important factors responsible for exaggerated fibrinolysis in APL is the cell surface phospholipid-binding protein, annexin II (Fig. 1). Annexin II is expressed on endothelial cells and macrophages and acts as a cell surface receptor for plasmin and t-PA [61]. t-PA-mediated conversion of plasminogen to plasmin on annexin II results in a 60-fold increase in plasmin generation when compared with that in the fluid phase [62]. Intriguingly, APL cells express higher levels of annexin II and more efficiently generate plasmin than *t*(15;17) fusion gene-negative AML cells [63]. Importantly, exposure of APL cells to ATRA downregulates the expression of annexin II and inhibits plasmin activity in vitro [63].

Another molecule that may be related to hemorrhagic diatheses in APL is thrombin-activatable fibrinolysis inhibitor (TAFI). Thrombin protects fibrin clots from plasmin-mediated fibrinolysis via activation of this carboxypeptidase; thrombin bound to TM efficiently activates TAFI, which hampers fibrinolysis by removing C-terminal lysine residues on fibrin that are otherwise important for binding of plasminogen and t-PA, thereby efficiently generating plasmin [64, 65]. It has been suggested that TAFI may block exaggerated fibrinolysis in this manner. In fact, inhibition of TAFI activity by a carboxypeptidase inhibitor stimulated fibrinolysis in an animal model [66]. Notably, activity of TAFI was inhibited by 60 % in APL patients [67].

Granulocytic proteases, including elastases, are abundantly produced by APL cells. These proteases are thought to cleave fibrinogen and degrade fibrinolytic inhibitors, leading to augmented fibrinolysis [68, 69] (Fig. 1). However, the contribution of granulocytic proteases released by APL cells to hemorrhagic events is not clear; even after improvement of coagulopathy in APL patients in response to ATRA, plasma levels of elastases remained high [69]. In addition, recent studies comparing elastase-mediated fibrinolytic activity between sepsis-induced DIC and APL-related coagulopathy showed that levels of elastase-degraded fibrin (ogen) were significantly higher in sepsis patients [70].

Management of DIC caused by APL

Intensive supportive care consisting of fresh frozen plasma, fibrinogen, and/or cryoprecipitate and platelet transfusions to maintain the levels of fibrinogen and platelets above 100–150 mg/dL and 30–50 $\times$ 10^9/L, respectively, is strongly encouraged by European LeukemiaNet [71]. Of note, 18 (6.5 %) of 279 APL patients treated with an ATRA-containing regimen developed severe hemorrhage, and these patients received frequent transfusions to maintain the levels of fibrinogen and platelet count above 150 mg/dL and 30 $\times$ 10^9/L, respectively [18]. Only 40 and 71 % of patients achieved target levels of fibrinogen and platelet, respectively, at the onset of bleeding [18]. This observation suggests that intensive transfusion during remission induction chemotherapy is not sufficient to overcome coagulopathy. Therefore, novel treatments are clearly required to promptly correct abnormal coagulation in APL patients.

European LeukemiaNet does not recommend the use of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic agents for the management of coagulopathy in APL patients, as the ability of these agents to reduce hemorrhagic risk was found to be questionable [71]. Only one retrospective study conducted in the UK found that heparin was clinically beneficial (Table 1); however, the dose of heparin and the treatment period varied between each patient, according to their physicians' decisions. Also, the induction therapy regimen was not uniform in this retrospective study [7].

rTM was approved for the treatment of DIC in Japan in 2008. A phase III trial comparing the efficacy and safety of rTM and low-dose heparin showed that rTM significantly

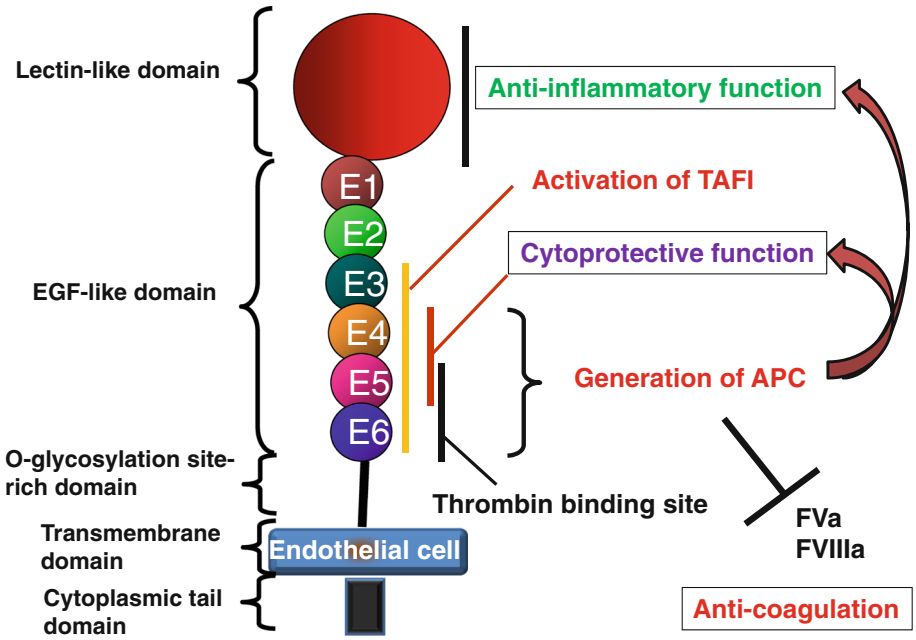

Fig. 2 The structure and function of TM. The EGF-like domain of TM exerts anticoagulant effects by inactivating thrombin and indirectly inhibiting coagulation factor Va and VIIIa via APC. On the other hand, the E3456 repeats of the EGF-like domain are responsible for activation of TAFI, leading to anti-fibrinolysis. The lectin-like domain of TM possesses anti-inflammatory function. The E45 repeats of the EGF-like domain exert cytoprotective effects in an APC-independent manner. APC also exerts anti-inflammatory and cytoprotective effects. rTM comprises the functionary active extracellular domains of TM. *TM*, thrombomodulin; *EGF*, epidermal growth factor; *TAFI*, thrombin-activatable fibrinolysis inhibitor; *APC*, activated protein C; *FVa*, activated factor V; *FVIIIa*, activated factor VIII; *rTM*, recombinant human soluble thrombomodulin

improved DIC that was associated with hematological malignancies or infections [72]. This clinical trial excluded almost all patients with APL, because concomitant use of ATRA was prohibited. Since 2008, the use of rTM has proved effective and safe in individuals with DIC and APL [73–75]. Use of rTM in combination with chemotherapy including ATRA rescued APL patients ($n = 9$) from DIC earlier than control patients ($n = 8$) who did not receive rTM [73]. No bleeding-related mortality was noted during induction chemotherapy in APL patients who received rTM [73]. Notably, severe hemorrhage requiring red blood cell transfusion at the time of diagnosis of APL was reduced after initiation of rTM [74]. Use of rTM in combination with ATO for relapse of APL promptly improved DIC without any adverse effect in one case report [75]. These observations suggest that rTM is a promising agent for the management of coagulopathy in APL patients, although the sample size in these studies is extremely small.

Structure and function of TM

TM is a glycosylated type I transmembrane molecule of 557 amino acids with multiple domains. Each domain possesses distinct properties. The molecule consists of an NH_2-terminal lectin-like region followed by six tandem epidermal growth factor (EGF)-like structures, an o-glycosylation site-rich domain, a transmembrane domain, and a cytoplasmic tail domain [76] (Fig. 2). rTM comprises the extracellular domains of TM. TM is ubiquitously expressed on endothelial cells and binds to thrombin, forming a 1:1 complex via E45 repeats in an EGF-like domain and acting as an anticoagulant [28]. In addition, the thrombin–TM complex activates protein C to produce APC, which inactivates factors VIIIa and Va in the presence of protein S, thereby inhibiting further thrombin formation [29]. The minimum structure essential to generate APC is localized in E456 repeats of the EGF-like domain [77]. On the other hand, E3456 repeats are responsible for activation of TAFI, which acts as an anti-fibrinolytic [64, 65].

TM possesses anti-inflammatory properties; the lectin-like domain of TM binds to and inactivates high-mobility group box 1 protein (HMGB1), a proinflammatory cytokine that stimulates production of inflammatory cytokines, such as IL-6 and TNF-α, via toll-like receptor 4 and that serves as a receptor for advanced glycation end products [37]. In addition, the lectin-like domain of TM inhibits lipopolysaccharide-induced cytokine production and adhesion of neutrophils to endothelial cells in association

with suppression of extracellular signal-regulated kinase (ERK) and nuclear factor κ B (NF-κB) [38].

Intriguingly, TM exerts endothelial cytoprotective effects against inflammatory cytokines or calcineurin inhibitors via upregulation of myeloid cell leukemia sequence 1 (Mcl-1) proteins in a process that is mediated by the ERK signal transduction pathway [39]. This cytoprotective effect is also mediated by E45 repeats of the EGF-like domain, and is independent of APC [39]. Of note, TM also exerts anti-inflammatory and cytoprotective effects via APC-dependent mechanisms [78–81].

Possible action of rTM in APL cells

An in vitro study demonstrated that exposure of APL cells to rTM significantly downregulates levels of annexin II, resulting in a decrease in plasmin production [82]. rTM-induced downregulation of annexin II in APL cells was dependent on APC, but the precise mechanisms by which this occurs remain unknown. ATRA also inhibited plasmin production in association with downregulation of annexin II in APL cells [63]. Interestingly, when rTM was combined with ATRA, inhibition of plasmin production in APL cells was synergistically enhanced [82]. Remarkably, rTM alone was able to induce myeloid differentiation and growth arrest of APL cells in association with induction of CCAAT/enhanced binding protein ε, an essential nuclear transcription factor for myeloid differentiation in an APC-dependent mechanism [82]. Again, rTM synergized with ATRA to produce anti-APL effects [81]. ATRA increased TM levels in acute myeloid leukemia HL60 cells as they differentiated toward neutrophils [83]. ATRA can regulate the expression of TM via the RA response element located on the 5′-flanking region of this gene [84]. Thus, TM may, at least in part, mediate ATRA-induced myeloid differentiation of APL cells. ATRA also induced the expression of TM on the cell surface of endothelial cells [85]. ATRA may normalize abnormal coagulation via induction of TM on the endothelium and APL cells in individuals with APL.

A major clinical problem in addition to coagulopathy in APL patients after initiation of ATRA and/or ATO is differentiation syndrome (DS), formerly known as retinoic acid syndrome. DS is characterized by unexplained fever and acute respiratory distress with vascular capillary leakage [86–88]. The patho-etiology of DS remains to be fully elucidated, but the insults to the respiratory and vascular endothelium caused by cytokines released by differentiated myeloid cells are considered to be involved in the development of this potentially lethal syndrome [89]. rTM may counteract DS, as rTM successfully alleviated capillary leakage in individuals with engraftment syndrome and sinusoidal obstruction syndrome that developed after hematopoietic stem cell transplantation [35, 36].

Conclusions

Introduction of ATRA and ATO into remission induction chemotherapy for individuals with APL has dramatically improved clinical outcome of this fatal subtype of leukemia; however, the incidence of life-threatening hemorrhagic and thrombotic events in APL patients at the time of diagnosis and/or during induction chemotherapy is still higher than expected. Use of the anticoagulant, rTM, which has additional activity against exaggerated fibrinolysis, inflammation, and endothelial cell damage, is a promising treatment strategy to safely rescue APL patients from life-threatening coagulopathy. Further large cohort studies are clearly required to establish the safety and efficacy of rTM for management of coagulopathy in patients with APL.

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