

Minireview

Tissue factor mediates inflammation

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Abstract

The role of tissue factor (TF) in inflammation is mediated by blood coagulation. TF initiates the extrinsic blood coagulation that proceeds as an extracellular signaling cascade by a series of active serine proteases: FVIIa, FXa, and thrombin (FIIa) for fibrin clot production in the presence of phospholipids and Ca^{2+} . TF upregulation resulting from its enhanced exposure to clotting factor FVII/FVIIa often manifests not only hypercoagulable but also inflammatory state. Coagulant mediators (FVIIa, FXa, and FIIa) are pro-inflammatory, which are largely transmitted by protease-activated receptors (PAR) to elicit inflammation including the expression of tissue necrosis factor, interleukins, adhesion molecules (MCP-1, ICAM-1, VCAM-1, selectins, etc.), and growth factors (VEGF, PDGF, bFGF, etc.). In addition, fibrin, and its fragments are also able to promote inflammation. In the event of TF hypercoagulability accompanied by the elevations in clotting signals including fibrin overproduction, the inflammatory consequence could be enormous. Antagonism to coagulation-dependent inflammation includes (1) TF downregulation, (2) anti-coagulation, and (3) PAR blockade. TF downregulation and anti-coagulation prevent and limit the proceeding of coagulation cascade in the generation of pro-inflammatory coagulant signals, while PAR antagonists block the transmission of such signals. These approaches are of significance in interrupting the coagulation–inflammation cycle in contribution to not only anti-inflammation but also anti-thrombosis for cardioprotection.

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Historically, tissue factor (TF) is an initiator of the extrinsic pathway, an integral player in the revised theory on blood coagulation [1]. Exposure of clotting factor zymogen VII (FVII) to TF results in a proteolytic cleavage for the formation of activated serine protease FVIIa. TF/FVIIa binary complex drives blood coagulation that is propagated by an array of proteolytic activation of clotting factor zymogens (FX and prothrombin). As a consequence, the sequential generation of coagulant mediators (FVIIa, FXa, and thrombin (FIIa)) fulfills signaling cascade for fibrin clot production.

Upregulated TF expression upon vascular injury or inflammation often results in hypercoagulability, which is defined as an increasing tendency of thrombosis [2].

Hypercoagulable state is widely associated with thrombotic conditions (for review see [3]) including diabetes [4], cancers [5], disseminated/diffused intravascular coagulation (DIC) [6], and deep vein thrombosis [7]. Oral contraceptives [8], surgical procedures (e.g., cardiopulmonary bypass (CPB) [9]), aging [10], and many others [3] are also considered as the risk factors for hypercoagulability.

This review discusses that TF initiates extracellular signaling (the extrinsic blood coagulation) that in turn triggers intracellular signaling for inflammation (Fig. 1). Early evidence that an antibody against TF attenuates septic shock [11] has laid the foundation for a hypothesis: the ability of TF to mediate inflammation. As the results of hypercoagulability, the inflammatory consequence could be enormous. Clotting signals including the coagulant mediators (FVIIa, FXa, and FIIa) and fibrin production are elevated, all of which are

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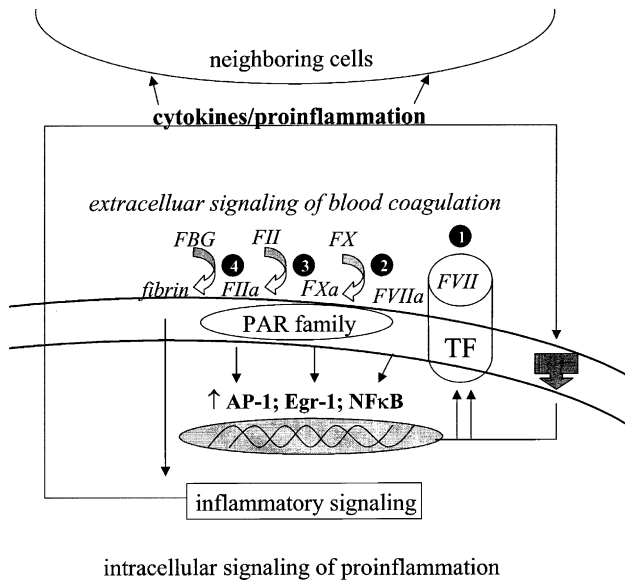


Fig. 1. TF upregulation drives a coagulation–inflammation cycle. TF initiates the extrinsic blood coagulation (italics) that is mediated by sequential serine protease (e.g., FVII, FX, and FII) activations; FVIIa, FXa, and FIIa are coagulant mediators fulfilling the clotting signaling in the extracellular compartment. Reaction 1 presents TF-dependent FVII activation. Reaction 2 activates FX to FXa, which is catalyzed by TF/FVIIa binary complex. In Reaction 3, FII undergoes proteolytic activation catalyzed by prothrombinase containing active FXa. FIIa then cleaves FBG, and fibrin clot is formed following polymerization and stabilization/crosslinking (Reaction 4). The coagulant signals including the mediators (FVIIa, FXa, and FIIa) and fibrin are proinflammatory. In general, PAR superfamily transmits FVIIa, FXa, and FIIa signaling, which activates intracellular signaling pathways including transcription factors. Therefore, TF plays a diverging role in triggering diverse inflammation. Moreover, the elicited inflammation such as cytokines, adhesion molecules, and growth factors through their corresponding receptors in turn feedback upregulates TF expression, presenting TF converging role. Such TF diverging and converging roles sustain the coagulation–inflammation cycle. The local inflammation could further trigger neighboring cell activations, manifesting as global inflammation. Anti-coagulants inhibiting Reaction 2, 3, or 4 limit the corresponding downstream generation of proinflammatory mediators: FXa, FIIa, and fibrin. PAR antagonists block the signal transmission of the coagulant mediators. As a result, the cycle is interrupted.

proinflammatory becoming the focus of this review. Moreover, the elicited inflammation promotes coagulation through feedback upregulation on TF expression that sustains the extrinsic coagulation and coagulation-dependent inflammation to refuel the coagulation–inflammation cycle. TF downregulation, anti-coagulation, or the blockade of clotting signals is of significance in suppressing coagulation-dependent inflammation.

TF upregulation responsible for the extrinsic hypercoagulability

Fig. 1 (italics) depicts TF-initiated blood coagulation taking place as extracellular signaling in the presence of

Ca^{2+} and phospholipids. TF is known as a cellular receptor for FVII and its active form FVIIa [12]. TF (CD142), a member of Type II cytokine receptor superfamily, is a single-chain polypeptide integral membrane glycoprotein. It consists of 263 amino acid (aa) residues with an intracellular C-terminus (21 aa), a transmembrane domain (23 aa), and a 219-aa extracellular N-terminus containing FVII/FVIIa binding domains. Upon initial binding to TF, FVII zymogen undergoes proteolytic activation (Reaction 1). For clotting propagation, the resulting FVIIa/TF binary complex (the extrinsic Xase) catalyzes the activation of FX zymogen to FXa (Reaction 2). FII is consequently converted to FIIa (Reaction 3) by the active prothrombinase complex consisting of FXa and FVa. At the termination stage (Reaction 4), soluble fibrinogen (FBG) undergoes proteolytic cleavage at the N-terminal of α and β chain catalyzed by FIIa to release fibrinopeptide A and B, respectively. The exposed polymerizing sites are responsible for fibrin gel formation that is further stabilized and crosslinked by FXIIIa. Thereby, insoluble fibrin clots are formed [1,3].

TF upregulation is defined as its enhanced availability for exposure to FVII/FVIIa. TF expression is often elevated upon vascular injury or inflammation (systemic and local), initiating the extrinsic hypercoagulability. Mimicking endotoxemia by incubation of whole blood with bacterial endotoxin (LPS), the upregulation of monocyte TF activity is responsible for the enhanced extrinsic coagulation without any effect on FVII, FX or FIIa [13]. In many cell types, TF expression is susceptible to upregulation by LPS, TNF- α , IL-1, IL-2, IL-6, interferon- γ (IFN- γ), C-reactive protein (CRP), oxidized low-density lipoprotein (OxLDL), lipoprotein (a) (Lp(a)), homocysteine, FIIa, plasmin, angiotensin II (AT II), complement C5a, hypoxia, *C. pneumoniae*, and many others for review see ref. [14]. In some cases without elevated TF synthesis, the enhanced TF bioavailability in cellular apoptotic condition [15], cellular stimulation by Ca^{2+} ionophores [16], or plasma TF [17] also initiates hypercoagulability.

Coagulation–inflammation cycle

TF upregulation plays diverging as well as converging roles in constructing a coagulation–inflammation cycle. TF-initiated extracellular coagulation provokes intracellular signaling, presenting TF diverging role in undergoing coagulation-dependent inflammation (Fig. 1). The coagulant mediators (FVIIa, FXa, and FIIa) and fibrin are proinflammatory, all of which independently activate cells.

On the other hand, TF is a target susceptible to various inflammatory responses [14], presenting its converging role in undergoing inflammation-dependent coagulation. Accordingly, such TF upregulation results

in elevations in proinflammatory coagulant mediators (FVIIa, FXa, and FIIa) and fibrin production. Thus, TF converging and diverging roles sustain the cycle (Fig. 1), resulting in enormous inflammation. This review focuses on TF diverging role in inflammation and antagonisms to coagulation-dependent inflammation.

(1) Clotting signals are proinflammatory

Several lines of evidence reveal *in vivo* coagulation-dependent inflammation. Anti-TF Ab prevents septic shock [11] and depresses macrophage expression of adhesion molecule CD18 [18], suggesting the proinflammatory role of TF. Elevated plasma level of FVII shows significant correlations to CRP and IL-6. Administration with recombinant FVIIa enhances IL-6 and -8 productions in healthy human subjects [19]. FXa/PL infusion increases IL-6 and CRP in baboons [20]. FIIa with fibrin(ogen) dependency induces macrophage adhesion and the production of IL-6 and MCP-1 [21]. IL-6 is proposed to be a soluble benchmark coupled with its responding signal CRP for the clinical diagnoses of inflammation.

At the cellular level, the coagulant mediators (FVIIa, FXa, and FIIa) show diverse cell activation. Table 1 summarizes those inflammation transmitted by protease-activated receptors (PAR). The ability of PAR activating peptides to mimic inflammation confirms the proposal that the coagulant mediators are proinflammatory. Interestingly, PAR depending on its activators could mediate distinct inflammatory actions.

PAR, expressed ubiquitously in many cell types, belongs to the superfamily of heterotrimeric G-protein coupled receptors [22]. There are four major isoforms of which the expression is not affected by exogenous LPS, TNF- α , IL-1 β , or IFN- γ [23,24]. In general, PAR-1, 3 or 4 is responsible for FIIa signaling. PAR-1, 2 or 3 mediates FXa signaling, while PAR-2 transmits FVIIa signal (Table 1).

PAR activation involves a proteolytic cleavage of the extracellular domain, resulting in the formation of a new N terminus that in turn acts as a tethered ligand [22] to interact with heterotrimeric G proteins. Some patterns of the complex protease cleavage have been reported [25]. The involved sequence of PAR-1 (TLDPRSFLLRNP) and PAR-2 (SSKGRSLIGKY) are cleaved between R and S. FIIa cleaves PAR-3 (TLPIKTFRGAP) and PAR-4 (LPAPRGYPGQV) at K/T and R/G, respectively.

(i) PAR-1 is a primary FIIa receptor. FIIa activates PAR-1 to mediate its major proinflammation including the induction of IL-6 [21,26,27], IL-8 [28], TGF- β [29], MCP-1 [21,26,28], PDGF [29], bFGF [29], ICAM-1 [30], P-selectin [31], or VEGF [32,33]. PAR-1-dependent FIIa action also enhances intracellular Ca²⁺ ([Ca²⁺]_i) mobilization, Erk1/2 phosphorylation [34], iNOS [35], COX-2 [36], and PI hydrolysis [37]. The G $_{\alpha q}$ and G $_{\beta\gamma}$

components of PAR-1 mediate the activation on transcription factor NF κ B [30]. In addition, PAR-1-dependent FXa signaling elicits IL-6 [28,38], IL-8 [28], or MCP-1 [39] expression.

Consistently, PAR-1 activating peptides elicit a broad spectrum of inflammation. TRAP enhances IL-6 [27], PGE2 [39], PGDF or P-selectin expression [40]. SFLLRN induces the production of IL-6 [41], IL-8 [42], iNOS [35], NO [43], PGE2 [41], MCP-1 [42], or P-selectin [44]. SFLLKNPND-KYEPF elicits the expression of ICAM [30] and VEGF [32]. A recent study has reported that activated protein C (APC) activates PAR-1 to induce MCP-1 expression in EC [45].

(ii) PAR-2 mediates FXa signaling to induce the expression of IL-6 [38]/-8 [28], PDGF or MCP-1 [28] as well as Erk1/2 activation [46]. In TF-expressing cells, FVIIa elicits VEGF [47] and activates PAR-2 to enhance SMC migration [48], MAPK phosphorylation, and [Ca²⁺]_i mobilization [49]. Enhanced IL-8 expression in response to FVIIa is mediated by PAR-2, facilitating cell migration [50].

PAR-2-mediated tryptase or trypsin action elicits the production of TNF- α [51], IL-1 β [51], IL-6 [51–53], or IL-8 [53,54] and increases [Ca²⁺]_i [54]. Its signaling also activates Erk [53], AP-1 [53], c-Jun [53], p38 MAPK [53], or NF κ B [54]. Apart from enhanced PI hydrolysis [37], a PAR-2 activating peptide (SLIGKV) not only elicits [41] IL-6, IL-8, and PGE2, but also activates p38 MAPK [55] and MEK/Erk [56] to upregulate TNF- α secretion [57]. SLIGRL induces PGE2 production [39] and Erk activation [46]; enhanced NO production [43] or P-selectin expression [58] accounts for relaxation or leukocyte rolling, respectively. Agonist proteinase-3 (PR3) enhances IL-8, MCP-1, and ICAM-1 expression [59]. Moreover, an *in vivo* comparison of null mutant (PAR-2 $-/-$) with wide-type (PAR-2 $+/+$) mice confirms that PAR-2 is responsible for the induction of IL-6, ICAM-1, and E-selectin expression [60]. Diverse PAR-2 actions also involve pigmentation [61], vasodilation [62], and pain [63]/itch [64] transmission.

(iii) PAR-3 is a low-affinity substrate but a high-affinity effector of FIIa [65]. Its activation by FIIa or FXa results in the expression of IL-6, IL-8, or MCP-1 [28]. PAR-3 activating peptide TFRGAP [66] induces Erk1/2 activation and [Ca²⁺]_i, while SFNGGP [39] slightly elicits PGE2 release.

(iv) FIIa is able to activate PAR-4 regardless of its low affinity. In contrasting to PAR-1, PAR-4 mediates FIIa signaling in leukocyte rolling and adhesion [67]. A PAR-4 activating peptide (GYPGQV) [41,68] elicits TNF- α , IL-6, IL-8, or PGE2. GYP-GKF enhances PGE2 production [39], [Ca²⁺]_i, and

Table 1
PAR transmitting the signals of coagulant mediators

Receptor	Activator	Inflammatory event/consequence
PAR-1	FIIa	↑ IL-6, -8; MCP-1; ICAM-1; PDGF (AB/BB); bFGF; TGFβ; VEGF; P-selectin; HBEGF; Erk; NFκB; iNOS; Cox-2; PI hydrolysis; [Ca ²⁺] _i ; platelet aggregation; macrophage adhesion
	FXa	↑ IL-6, -8; MCP-1; PDGF; VEGF; TF; NFκB; MAPK
	TRAP	↑ IL-6; PDGF; P-selectin; platelet aggregation; Cox-2
	SFLLRN	↑ IL-6 & -8; MCP-1; P-selectin; platelet aggregation; iNOS; NO; PGE2; GTPase; [Ca ²⁺] _i ; NFκB
	TFLLR	↑ NO; relaxation
	TFLLRNPNDK	↑ [Ca ²⁺] _i
	SFLLRNPNDKYEPF	↑ ICAM; VEGF
	APC	↑ MCP-1; MAPK phosphorylation
PAR-2	FVIIa	↑ IL-8; PDGF; SMC migration; [Ca ²⁺] _i ; MAPK
	FXa	↑ IL-6, -8; MCP-1; PDGF; TF; Erk; [Ca ²⁺] _i
	trypsin	↑ TNF-α; IL-1β, -6, -8; Erk; AP-1; c-Jun; [Ca ²⁺] _i ;
	trypsin	↑ TNF-α; [Ca ²⁺] _i ; Erk; p38 MAPK; NFκB; IKK; TF
	SLIGKV	↑ TNF-α; IL-6, -8; MEK; Erk1/2; p38 MAPK; NO; TF; PGE2; [Ca ²⁺] _i ; PI hydrolysis; SMC migration
	SLIGRL	↑ IL-6 and -8; PGE2 release; P-selectin; leukocyte rolling; NO;
	PR3 (+/+) vs. (-/-)	↑ IL-8; MCP-1; ICAM-1 ^a ↑ IL-6; ICAM-1; E-selectin
PAR-3	FIIa	↑ IL-6, -8; MCP-1; [Ca ²⁺] _i
	FXa	↑ IL-6, -8; MCP-1; VEGF
	SFNGGP	↑ PGE2 release
	TFRGAP	↑ Erk; [Ca ²⁺] _i
PAR-4	FIIa	↑ leukocyte rolling and adhesion
	GYPGQV	↑ TNF-α; IL-6 and -8; PGE2
	GYPGKF	↑ IL-6, -8; PGE2 release; [Ca ²⁺] _i ; platelet aggregation
	AYPGKF	↑ p38 MAPK; PLC; SrC

↑ Denotes upregulation.

^a Compared to null mutant (PAR-2 -/-) mice.

platelet aggregation [69]. AYPGKF [70] activates p38 MAPK, PLC and SrC.

- (v) Toll-4 is proposed to mediate FBG proinflammation [71] including IL-6 and MCP-1 production [21], while fibrin and its fragments elicit IL-1β [72], IL-6 [73], IL-8 [74], and ICAM [74] expression through undefined mechanism(s).

(2) TF upregulation refueling the cycle

The diverging role derives the converging role, vice versa; TF upregulation refuels and energizes the cycle. Despite how the cycle gains its initial momentum, coagulation and inflammation occurring extra- and intra-cellularly always promote each other. Increasing evidence not only reveals TF converging role, but also lends supports to the notion of a feedback upregulation on TF expression. It is noted that FVIIa [75], FXa [75,76], and FIIa [77] promote TF expression, implying the existence of a feedback loop for completing the coagulation–inflammation cycle. The ability of PAR-2 agonists (trypsin, PR3, and SLIGKV) to induce TF mRNA [78] is in agreement with such feedback upregulation by the proinflammatory coagulant mediators. The direct evidence for TF converging role comes from the demonstration that TNF-α [79], ILs [80], IFNγ [81], CRP [82], MCP-1 [82,83], ICAM-1 [84], P-selectin [85], CD40/CD40L [86], VEGF [87], PDGF [88],

or many others [14] substantially induce TF expression. Consistent with such view of the operational cycle, anti-coagulants (e.g., TF pathway inhibitor (TFPI) [89], FVIIa inhibitor (FVIIai) [90], DX9065a [76], ZK 807834 [38], LMWH [91,92], heparin [93], hirudin [94], hirulog [95], and AT III [96]) diminish TF expression.

The long-range impact of the coagulation–inflammation cycle could be enormous. The cycle takes place in a given cell and expands globally involving smooth muscle cell (SMC) proliferation [29,66], endothelial cell (EC) activation [97], platelet activation [98], leukocyte activation [99], lymphocyte differentiation [100], and diverse cellular activations, many of which are involved in thrombotic events.

Antagonisms to coagulation-dependent inflammation

TF hypercoagulability accompanied by the elevations in the coagulant signals (FVIIa, FXa, FIIa, and fibrin) results in enormous inflammation. TF downregulation, anti-coagulation, and PAR blockade antagonize coagulation-dependent inflammation (Table 2) and interrupt the cycle.

(1) TF downregulation relevant to anti-inflammation

In view of TF refueling the cycle, TF downregulation is of anti-inflammatory potential by preventing the initiation

Table 2
In vivo and in vitro antagonisms to the coagulation–inflammation cycle

	Target action	Anti-inflammatory consequence
<i>TF downregulation</i>		
TF antisense	↓ TF expression	↓ leukocyte adhesion
TF antibody	↓ TF function/activity	↓ septic shock; leukocyte infiltration; HMC II; CD18
Herbimycin, genistein, etc.	↓ PTK; TF synthesis	↓ TNF; IL-1; MCP-1; ICAM; VEGF
PD98059, SB 203580, etc.	↓ MAPK; TF synthesis	↓ TNF; CRP; IL-6, -8; MCP-1; ICAM-1; E/L selectin; VEGF
Calphostin C, H7, cherleythrine, etc.	↓ PKC; TF synthesis	↓ IL-6, -8; MCP-1; ICAM-1; P-selectin; VEGF; bFGF
Statins	↓ Egr-1; TF synthesis	↓ TNF; IL-6, -8; CRP; MCP-1; VCAM-1; CD40/40L; MMP-9; NO
Aspirin	↓ NFκB, Egr-1, c-Jun; TF synthesis	↓ TNF; IL-6, -8; CRP; MCP-1; ICAM/VCAM; P/E-selectin; VEGF; iNOS
Curcumin	↓ AP-1, NFκB, Egr-1; TF synthesis	↓ TNF; IL-1β, -6, -8; MCP-1; ICAM/VCAM; E-selectin; VEGF
Adenosine	CAMP elevation; ↓ TF synthesis	↓ IL-6, -8; MCP-1; ICAM/VCAM; E-selectin
PDE inhibitors	CAMP elevation; ↓ TF synthesis	↓ VCAM; E-selectin
Pentoxifylline	CAMP elevation; ↓ TF synthesis	↓ VCAM; VEGF
3-Deazaadenosine	CAMP elevation	↓ TNF; ICAM/VCAM
NKH 477	CAMP elevation	↓ TNF; IL-6; VCAM
8-Br-cAMP, cilostazol	CAMP elevation	↓ MCP-1
<i>Anti-coagulation</i>		
FVIIa inhibition	↓ FVIIa signaling; FXa, FIIa, fibrin	↓ TNF; IL-6, -8; Erk
FXa inhibition	↓ FXa signaling; FIIa, fibrin	↓ TNF; IL-6; MCP-1; P-selectin; leukocyte adhesion
FIIa inhibition	↓ FIIa signaling; fibrin	↓ IL-6, -8; MCP-1; ICAM/VCAM; P-selectin; VEGF; Erk; [Ca ²⁺] _i ; NFκB
TFPI	↓ FVIIa signaling; FXa, FIIa, fibrin	↓ TNF; IL-6, -8; MCP-1; VCAM-1; PDGF; MMP-1, 2
APC	↓ FXa, FIIa, fibrin	↓ TNF; IL-1, -6, -8
AT III	↓ FIIa, fibrin	↓ TNF; IL-1, -2, -4, -6, -8; IFN; MCP-1; ICAM/ VCAM; E-selectin; VEGF; NFκB
<i>PAR blockade</i>		
PAR-1 antagonist	↓ PAR-1 reception	
RWJ 58259; 56110		↓ CD61; platelet aggregation; restenosis; thrombus formation
SCH 79797; 203099		↓ P-selectin; platelet aggregation; [Ca ²⁺] _i
Refluden		↓ macrophage adhesion
SR 48968; 140333		↓ contractile
BMS 197525; 200261		↓ platelet aggregation; GTPase; [Ca ²⁺] _i
E5510		↓ VEGF; PDGF; Erk; [Ca ²⁺] _i
PAR-2 antagonist	↓ PAR-2 reception	
Blocking antibody		↓ IL-6, -8
SR 48968; 140333		↓ contractile
FSLLRV		↓ [Ca ²⁺] _i signaling; relaxation; proteolysis
LSIGRL		↓ [Ca ²⁺] _i signaling; relaxation; proteolysis
PAR-3 antagonist	↓ PAR-3 reception	N/A
PAR-4 antagonist	↓ PAR-4 reception	
YD-3		↓ platelet aggregation; [Ca ²⁺] _i
PAR downregulation	↓ PAR expression/function	N/A

↓ Denotes suppression.

N/A, not available.

of hypercoagulability. The downregulation is achieved by blocking TF expression including its function.

- (i) *Blockade of TF expression and function.* Anti-TF Ab has long been reported to attenuate septic shock [11]. TF neutralizing antibody suppresses reactive oxygen species, major histocompatibility complex class II (MHC-II), CD18 expression [18], and leukocyte infiltration [101]. Antisense TFmRNA suppresses TF expression [102], preventing leukocyte adhesion. Such approaches could provide specific inhibition to coagulation-dependent inflammation.
- (ii) *Inhibition of TF synthesis.* TF expression is generally mediated by the activation of protein tyrosine kinase

(PTK), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), and transcription factors (AP-1, NFκB, or Egr-1) while negatively correlating to intracellular cAMP content [14]. Accumulating evidence shows that TF synthesis is abolished by the inhibition of PTK, MAPK, PKC, or transcription factors. So, does the elevation in intracellular cAMP level downregulate TF synthesis. Table 2 summarizes that such inhibitors for suppressing TF synthesis also exhibit diverse anti-inflammatory effects.

- PTK inhibition by herbimycin, genistein, or tyrothostin downregulates MCP-1 [103,104], ICAM [105], or VEGF [106] expression. Diphenylethylodinium inhibits IL-1 production [107].

- MAPK inhibition by PD 98059 or SB 203580 offsets the expression and release of IL-6 [53,108], IL-8 [53], MCP-1 [109], ICAM [110,111], VEGF [32], and E-selectin [112]. A p38 MAPK inhibitor (BIRB 796 BS) significantly diminishes LPS-induced TNF- α , IL-6, CRP, and L-selectin expression [113].
- PKC inhibition by calphostin C, chelerythrine, H7, or staurosporine effectively blocks the expression of IL-6, ICAM-1 [105,114,115], MCP-1 [43], VEGF [33,105], IL-8 [43], P-selectin [116,117].
- Inhibitors for transcription factors (e.g., statin, curcumin, and aspirin) suppress IL-6/-8 release [108,118–123], IL-1 β [119], TNF- α secretion [68,120,124, 125,91], and the expression of VEGF [126,127], ICAM/VCAM [118,128–132], E [124,133]/P [134]-selectin, and MCP-1 [119,130,135,136], CRP [121,91], MMP [137,138], and CD40/CD40L [139].
- Elevation of intracellular cAMP by 8-bromo-cAMP [140], cAMP phosphodiesterase inhibitor (cilostazol) [141], adenylate cyclase activator (NKH 477) [142], adenosine [143], 3-deazaadenosine [144,145], PDE inhibitors (rolipram and ORG 9935) [146], and pentoxifylline [127] reduce TNF [142,144], IL-6/-8 [143], MCP-1 [140,141,143], VCAM [127,142–146], E-selectin [143,146], and VEGF [127] expression. In contrast, adrenomedullin induces cell surface expression of the adhesion molecules E-selectin, VCAM-1, and ICAM-1 [147].

It, however, remains inconclusive whether the anti-inflammatory effects entirely result from TF downregulation. Proinflammatory process per se relies on the activation of intracellular signaling. The expression of TNF- α [107,125], ILs [53,108,122], CRP [113,91], MCP-1 [109,136], ICAM/VCAM [105,109,114,123,129,132], selectins [112,133], or VEGF [32,105] is mediated by the upregulation of PTK, MAPK, PKC, Src, PKC, or transcription factors. Moreover, NF κ B activation is considered as a hallmark of inflammation [148]. Nonetheless, such inhibitors of intracellular signaling could be recognized as double-bladed swords not only preventing TF-dependent events but also providing the direct anti-inflammation.

(2) Anti-coagulation relevant to anti-inflammation.

Anti-coagulants target the coagulant mediators; the inhibition of TF-dependent FVII activation (Reaction 1), FVIIa (Reaction 2), FXa (Reaction 3), and FIIa (Reaction 4) diminishes their downstream generation of proinflammatory coagulant mediators and fibrin production (Fig. 1 and Table 2). The direct inhibitors of FVIIa, FXa,

or FIIa readily diminish their signaling. Natural and pharmacological anti-coagulants show a variety of anti-inflammatory effects (Table 2), which in some cases is also mediated by coagulation-independent actions. Thus far, little is known about the relevance of the inhibition on TF-dependent FVII activation to anti-inflammation.

- FVIIa inhibition.* Recombinant nematode anti-coagulant protein c2 diminishes coagulation-dependent IL-6 and IL-8 productions [19]. Active site-inhibited FVIIa depresses LPS-inducible plasma levels of TNF- α [149], IL-6 [90,150,151], and IL-8 [150,151]. FVIIai abolishes PAR-2-mediated VIIa signaling of Erk1/2 phosphorylation [49] in TF-expressing cells. Natural anti-coagulant TFPI interferes with LPS reception [152]. With respect to its ability to directly inhibit FXa followed by a feedback inhibition on TF/FVIIa complex, TFPI suppresses coagulation-dependent IL-8 production [153] or VCAM-1 expression [77]. In VSMC, TFPI reduces the autocrine release of PDGF-BB, MCP-1, and MMP-2 in response to FVIIa and FXa [154]. Its coagulation-independent action includes the direct suppression in TNF- α , IL-6, and IL-8 production [155], reducing mortality from *Escherichia coli* septic shock in baboons. The failure in human studies [149,156,157], however, warrants further research to clarify any clinical anti-inflammatory potential.
- FXa inhibition.* LMWH, enoxaparin, or DX9065a suppresses P-selectin, TNF- α , IL-6 [91], or MCP-1 [76] expression, resulting in depressed platelet activation [158] and leukocyte adhesion to EC [159]. A direct inhibitor (ZK-807834) blocks PAR-1 and PAR-2 mediated FXa signaling in eliciting IL-6 [38]. Natural anti-coagulant APC inhibits prothrombinase or the intrinsic FXase for downregulating Reaction 3 or FXa generation; it inactivates MAPK/AP-1/NF κ B pathway [160], [Ca²⁺] signaling [161], apoptosis [162], and the production of IL-1, -6, -8 or TNF- α [163]. APC is recognized as one of the effective anti-inflammatory agents in clinical application. APC consistently reduces septic mortality and blocks DIC upon *E. coli* infection in either animal or human models [164–167].
- FIIa inhibition.* Heparin shows a variety of inflammatory potentials [168]. Heparin-bonded circuit prevents the increases in IL-6 and IL-8 in CPB patients without any effect on P-selectin [169], while heparin bolus reduces neutrophil activation without affecting platelet aggregation [170]. Heparin and delteparin downregulate PAR-1 cleavage [171], blocking PAR-1-mediated VEGF release in response to FIIa [33]. In addition, heparin per se directly binds P- [172] and L- [173] selectins, exhibiting coagulation-independent anti-inflammation.

Direct FIIa inhibitor (hirudin) binds to FIIa active site and prevents PAR-1 from cleavage [171], thereby diminishing FIIa-induced ICAM/VCAM expression [174] and PAR-1-mediated FIIa signaling in eliciting VEGF [32,33], IL-6 [175], IL-8 [42], or MCP-1 [42]. Interestingly, hirudin inhibits LPS-mediated NF κ B activation [176]. A hirudin analog (lepirudin) alleviates LPS-induced platelet activation [177], and an active site inhibitor (melagatran) diminishes P-selectin expression [171].

Natural anti-coagulant anti-thrombin III (AT III) mediates pentasaccharide and heparin actions to inhibit FXa and FIIa, respectively. Representing its coagulation-dependent anti-inflammatory relevance, AT III blocks FXa-induced IL-6, IL-8, MCP-1, ICAM/VCAM, and E-selectin expressions [178] in addition to arresting FIIa-induced (PAR-1-dependent) VEGF release [33] and MCP-1 expression [179]. Apart from inactivating NF κ B [176], AT III direct anti-inflammatory action includes the suppression in IFN- γ and ILs (e.g., 1, 2, 4, 6, 8) production, which is mediated by enhanced PGI production and diminished inducible nitric oxide synthase (iNOS) [180]. However, the discrepancy exists concerning the survival rate being improved in baboons [181] but not in severe human sepsis treated with the high dose of AT III [182]. Further research warrants verifying its anti-inflammatory potential.

(3) PAR blockade relevant to anti-inflammation.

PAR at the interface of the extracellular coagulation and intracellular signaling mediates the coagulant signals (Fig. 1). By turning off the transmission of FVIIa, FXa, and FIIa signaling, various PAR antagonists prevent coagulation-dependent inflammatory consequences (Table 2).

- (i) *PAR-1 antagonist*. RWJ 58259 [183] selectively blocks PAR-1, resulting in the attenuation in CD61 expression, platelet aggregation, thrombus formation, and restenosis. Similarly, SCH 79797 and 203099 depress P-selectin expression and platelet aggregation [31], while Refluden suppresses macrophage adhesion [21]. BMS 197525 [184] and 200261 [44] abolish platelet aggregation. A FIIa receptor antagonist (E5510) diminishes VEGF [33] or PDGF [185] expression. It remains unknown whether PAR-1 blocking antibody has any therapeutical application.
- (ii) *PAR-2 antagonist*. Two hexapeptides (FSLTRY and LSIQRL) block the ability of trypsin to activate PAR-2 [186], thereby diminishing [Ca²⁺]_i signaling, relaxation, or proteolysis. Anti-PAR-2 Abs and trypsinase inhibitors (GW-45 and GW-61) cause significant decreases in IL-6 and IL-8 release from human peripheral blood eosinophils [53]. Other antagonists (SR 48968 and 140333) reduce contractile [41].
- (iii) *PAR-3 antagonist*. Little is known about the availability of any antagonist against PAR-3 signaling.
- (iv) *PAR-4 antagonist*. A non-peptide PAR-4 antagonist (YD-3) [1-benzyl-3-(ethoxycarbonylphenyl)-indazole] [52] selectively depresses GYPGKF-induced platelet aggregation and [Ca²⁺]_i.
- (v) Concerning PAR downregulation, IL-4 suppresses PAR-1, -2, and -3 mRNA expression [26]. Cathepsin G and neutrophil elastase facilitate the internalization of PAR-1 [187]/-2 [188] to desensitize/disarm the reception function. The ubiquitination of PAR-2 by β -arrestin attenuates PAR-2 signaling induced by trypsins, trypsinase, and coagulation mediators (FVIIa and FXa) [189]. By increasing GTPase activity of G_q, NO donors and cGMP [190] terminate PAR-1 signaling and exhibit vascular smooth muscle relaxation.

Remarks

This review addresses the proinflammatory potential of TF, apart from its diverse functions in blood coagulation, wound repairs, embryonic development, angiogenesis, tumor metastasis, cell adhesion/migration, and innate immunity. TF upregulation by enhanced exposure to FVII/FVIIa initiates blood coagulation, resulting in hypercoagulability. In addition to the increased tendency of thrombosis [2], hypercoagulability develops inflammatory state to refuel and sustain the coagulation–inflammation cycle. Both thrombosis and inflammation are risk factors for cardiovascular dysfunctions [14] not to mention the close relationship between the two.

TF hypercoagulability could contribute to atherosclerosis that is recognized as an inflammatory disease apart from its characteristics of enhanced thrombosis and lipid accumulation. Atherogenic factors: OxLDL, Lp(a), or homocysteine upregulate not only TF but also ICAM-1, VCAM-1, MCP-1, or selectin expression [14]. The coupling of TF upregulation with inflammation also reveals when cardiovascular risk index CRP is concerned. CRP is capable of upregulating TF expression accompanied by the elevated expression of inflammatory elements such as IL-6, VCAM/ICAM, and MCP-1 expression [191]. So does atherogenic factor AT II induce TF synthesis and the expression of inflammatory mediators. It is not surprising that statins offer rapid anti-atherogenic benefits from downregulating TF synthesis accompanied by the depressed inflammation of TNF- α , IL-6, IL-8, CRP, VCAM-1, CD40/40L, and MCP-1 expression. Aspirin shows the similar effects with TF downregulation and anti-inflammation including the suppression in TNF, CRP, ILs, adhesion molecules, and growth factors.

In view of the inflammatory and thrombotic natures of cardiovascular complications, interruption of the coagulation–inflammation cycle is of great interests in cardioprotection. Anti-coagulants and PAR antagonism arrest TF diverging role in inflammation to diminish the consequence of TF hypercoagulability. Anti-coagulants offer a broad spectrum of management on cardiovascular disorders. PAR blockade also draws increasing attentions to its therapeutical applications for anti-thrombosis without any effect on the coagulation cascade. Further research on anti-coagulation and PAR antagonism is warranted, continually establishing their broad relevance to cardioprotection.

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