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Procoagulant activity during viral infections

Saravanan Subramaniam[1,2,3], Inge Scharrer[3]

[1]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, USA, [2]Department of Medicine, Division of Hematology/Oncology, McAllister Heart Institute, University of North Carolina at Chapel Hill, USA, [3]Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany

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1. ABSTRACT

The abundance of evidence suggest that inflammation of immune and non-immune cells may lead to an imbalance of the pro- and anti-coagulant state during viral infections. During systemic infections, the endothelium plays a critical role in regulating hemostasis, and severe imbalances of endothelial function and activation can contribute to organ failure. Viral infections may elevate plasma levels of procoagulant markers such as TAT and D-dimer TF-positive MPs as well as von Willebrand factor (vWF). Although multiple clinical studies are showing the association of viral infection and increased prothrombotic risk, the pathological mechanisms have not been fully identified for most viral infections. Viral infection mediated TLRs activation is both cell type- and species-specific and explains the difficulties in correlating murine model data with the human data. In this review, we briefly discuss the TF-dependent coagulation activation, Toll-like receptors (TLRs) signaling during viral infections, and their contributions to the procoagulant response.

2. INTRODUCTION

Disseminated intravascular coagulation (DIC), thrombosis and hemorrhages are associated with vascular complications of viral infections (1). The clinical state of altered coagulation in various viral infections evident in hemorrhage and thrombosis (2). Viral hemorrhagic fever (VHF) is a syndrome characterized by the hallmark signs of (high) fever, bleeding in several organs, multi-organ failure (MOF) and eventually shock. Most of the VHF pathogens lead to endothelial activation followed by dysfunction. Endothelial stress in patients who develop VHF is characterized by mild hypotension, conjunctival vasodilation, and flushing of the skin in the early phase of the disease (3-5). In VHF bleeding often

occurs from various mucous membranes together with easy bruising and persistent bleeding after venipuncture. Most often massive bleeding happens in the gastrointestinal tract and intracerebrally (1). Studies at the clinical and molecular level have proposed several hypotheses linking viral infection and thrombotic risk. Activation of endothelial cells (ECs), monocytes (MOs), and neutrophils by viruses can induce the expression of tissue factor (TF), which is an initiator for the extrinsic coagulation cascade (6). A comprehensive review of viral infections associated with coagulation disorders has not been done. Enough evidence support that inflammation of immune and non-immune cells may lead to an imbalance of the pro- and anti-coagulant state during viral infections. Several pathological conditions by bacterial and or viral infections, such as hemolytic uremic syndrome (HUS), idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) may alter systemic immune response that leads to an imbalance in primary and secondary hemostasis (6, 7). Viruses such as Ebola, H1N1 influenza, Cytomegalovirus, Varicella-zoster, Hepatitis C Virus, Human immunodeficiency virus (HIV), Coxsackievirus B3, Marburg and Herpes simplex virus-1, Dengue, and Junin viruses, are reported to be associated with hemorrhage and thrombotic complications (8-19). This review outlines the interplay between viral infections and Toll-like receptors (TLRs) signaling, and their contributions to procoagulant activity.

2.1. Tissue factor (TF)-dependent activation of coagulation system

It has been well-documented that inflammation due to viral and bacterial infections can lead to the systemic activation of coagulation (7, 20). TF, a membrane-bound 45-kDa protein, is expressed on many cell types at different levels throughout the body (21). Histological studies revealed that TF appears to be present in all blood tissue barriers and the rapid procoagulant response is through the cells which are directly in contact with the ECs and myeloid cells (21-25). The coagulation cascade is initiated by activated VIIa exposed to TF at the site of injury (21, 26). This catalytic complex (TF: FVIIa) further activates both factor IX (FIX) and factor X (FX). FIXa and FXa enhance further activation of FX and prothrombin. MOs and macrophages (MØs) primarily express inducible TF. Most of the bacterial and viral infections stimulate the TF expression on MOs and ECs primarily by nuclear factor kappa B (NF-kappaB) activation. Furthermore, this cellular interaction potentially enhances the production of Interleukin (IL)-8, IL-1β, (CXCL)-10, and tumor necrosis factor (TNF)-α (27). Thrombin generation during inflammation shifts the system towards the procoagulant state (1, 28). Also, protease-activated receptors (PARs) activation on the ECs induces the TF expression, von Willebrand factor, and other pro-inflammatory cytokines release during systemic inflammation (29-31).

2.2. Endothelial cells (ECs) directed hemostasis

EC injury is a common feature of viral infection and can alter hemostasis directly or indirectly (32). Most of the viruses directly infect the ECs (33, 34). For instance, Herpes simplex, Adenovirus, Parainfluenza virus, Echovirus, Poliovirus, Measles, HIV, Mumps, CMV, and Human T-cell Leukemia Virus Type 1 are known to affect the ECs and increase the cytokines production and release (35). Dengue, Marburg, Ebola and Lassa viruses infect the ECs and enhance the TF expression on the EC surface as well as vWF, and cause cardiovascular complications (36, 37). NF-κB activation in ECs plays a significant role in inflammation and vascular barrier dysfunction (38). In ECs, NF-κB induces TF, endothelin-1 (ET-1), COX-2, eNOS, prostaglandins (PGI2/PGE2), PD-L1, chemokines (CXCL12, IL-6, and IL-8), and inhibits TM (39-46). These context-dependent responses control capillary tone (COX2, NO, ET-1, PGI2), permeability (TF/TM), immune cells recruitment and activation (chemokines, PD-L1), and platelet activation or inhibition (PGE2/PGI2/TM) that impact the vascular hemostasis. Furthermore, ECs control fibrinolysis by balancing the expression of t-PA, PAI-1, ATIII, TM, and PAF that are dynamically regulated (32, 43, 46-48). VEGF also induces the TF expression on the endothelial surface that triggers the clotting and fibrinolysis that impact both the platelet activation and permeability. Besides the EC regulated hemostatic responses, viral infections of endothelium also have the potential to cause dilation/contraction of capillary, thrombocytopenia, vascular permeability, and hemorrhagic edema (32).

2.3. Virus life cycle

A viral life cycle can be divided into three stages: (1) virus infection, which includes attachment, penetration, and coating, (2) virus replication and assembly, and (3) virus release. The initial stage of viral infections is the attachment of viral surface proteins and their receptors on the host cellular surface. This assembly penetrates the host membrane through receptor-mediated endocytosis, followed by unpacking of viral genomes by the host or viral cytoplasmic enzymes. Later these viral genomes undergo replication followed by the release of new viral particles by rupturing the host cell wall (49).

2.4. TLRs expression patterns in different cell types

TLRs expression patterns in various cell types are an important regulatory mechanism of innate immunity. Flow cytometry analysis describes that the components of TLR expression vary in cell

Table 1. Tlrs expression in immune and non-immune cells

Human cells	TLRs expression	References
Non-immune cells		
ECs	All TLRs	(173)
Fibroblasts	All TLRs	(174)
Kupffer cells	TLR1-4 and TLR9	(175, 176)
Biliary cells	All the TLRs	(176, 177)
HSCs	TLR1-2, TLR4 and TLR9	(176, 178)
Hepatocytes	All the TLRs	(176, 179, 180)
Foam Cells	TLR2, TLR3, TLR4, TLR7 and TLR9	(60, 63-68)
VSMCs	TLR1, TLR3, TLR4, and TLR6	(61)
Immune cells		
Monocytes	TLR1-2 and TLR4-8	(181)
mDCs	TLR1-5 and TLR8	(181)
pDCs	TLR1, TLR7, TLR9 and TLR10	(182-184)
Neutrophils	TLR1, TLR4-7 and TLR9-10	(185-187)
Eosinophils	TLR1 and TLR7	(188, 189)
Mast cells	TLR1-2, TLR4, and TLR6	(190, 191)
Myeloid cells	TLR-2, TLR6 and TLR8	(192, 193)
NK cells	TLR1-3 and TLR5-9	(194-196)
T cells	TLR1-5 and TLR7-8	(71, 75, 197-199)
B cells	TLR1 and TLR6-10	(60, 70, 200-202)
T_{reg} cells	TLR1-2, TLR4-6 and TLR8	(76, 203-205)

HSC, hepatic stellate cell; mDC, myeloid dendritic cell; NK, natural killer; pDC, plasmacytoid dendritic cell; T_{reg} – Regulatory T cells; TLR – Toll-like receptors

types (50-52). TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the cell surface, and TLR3, TLR7, TLR8, and TLR9 are localized intracellularly where they recognize viral and bacterial genetic materials for activation (53-55). MOs appear to lack of TLR3, TLR6, TLR7 and TLR10 expression (52, 56, 57). However, endosomes of myeloid and MO-derived dendritic cells (DCs) express TLR3. Neutrophils express all TLRs except TLR3 (52, 56, 57). Myeloid DCs is the only known cell type expresses the entire components of TLRs (54). TL3 is expressed on the cell surface of epithelial cells and fibroblasts (58). ECs express all TLRs (59, 60). Human vascular smooth muscle cells (VSMCs) constitutively express TLR1, TLR3, TLR4, and TLR6 (61). Furthermore, murine aortic SMCs constitutively express TLR2 (62). Foam Cells express TLR2, TLR3, TLR4, TLR7, and TLR9 (60, 63-68). Human and murine mast cells express all TLRs except TLR8 and TLR10 (69). Human B cells express TLR1, TLR6, TLR7, TLR9, and TLR10 (60, 70). Interestingly, TLR2 is functionally expressed by a small subset of circulating B cells (71-74). Human peripheral blood T lymphocytes express TLR1, TLR2, TLR3, TLR4, TLR5, TLR7, and TLR9 (71, 75). Regulatory T-cells express TLR8, and the TLR8-MyD88 signaling pathway controls suppressive function of T_{reg} cells (76). These observations suggest that the distinctive TLRs expression patterns in various immune and non-immune cells are playing an important role in immunity. Detailed TLRs expression in immune and non-immune cells are described in Table 1.

2.5. TLRs activation during viral infections

Toll-like receptors (TLRs) are vital for the recognition of pathogens and respond to pathogen-associated molecular patterns (PAMPs) (77, 78). Expression of TLR3, TLR7, TLR8, and TLR9 is localized predominantly to intracellular compartments where they recognize and activate during viral infections and contribute to antiviral responses by triggering the production of type I interferons (IFNs), inflammatory cytokines and chemokines (79-81). Apart from these four TLRs, TLR2 and TLR4 also shown to recognize the viral components such as envelope glycoproteins (80, 82-84).

Due to the complexity of their genomes, viruses are characterized and classified according to the underlying replication mechanisms (81). The

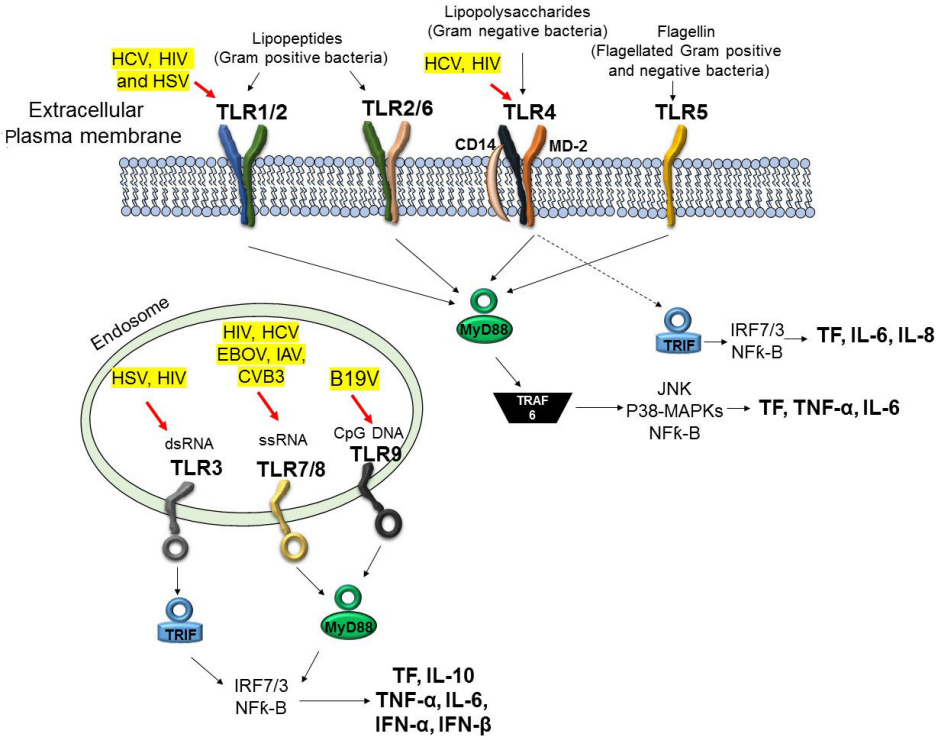

Figure 1. TLR-mediated signaling pathway during viral infections, TLR1 and TLR6 recognize their ligands as heterodimers with TLR2. For TLR4, CD14, and MD2 are required for LPS recognition and signaling. TLR3, TLR7/8, and TLR9 are intracellular TLRs and are involved in recognition of nucleic acids. TLR5, TLR3, TLR7, and TLR9 are currently thought to deliver their signal by forming homodimers after interacting with their ligands. Most TLRs signal through the MyD88 pathway to activate NF-κB and AP1, except for TLR3. TLR3 and TLR4 can signal through the MyD88-independent pathway (TRIF pathway) to activate INF-β. TF: tissue factor, TNF-α: tumor necrosis factor alpha: IL: interleukin, TRIF: TIR-domain-containing adapter-inducing interferon-β, MyD88: Myeloid differentiation primary response gene 88, NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells, IFN: Interferons, JNK: Jun N-terminal kinases, P38-MAPKs: p38 mitogen-activated protein kinases, HSV: Herpes simplex virus, HCV: Hepatitis C virus, EBOV: Ebola virus, IAV: Influenza A virus, CVB3: Coxsackievirus, MD2: myeloid differentiation factor 2, B19V: Parvovirus B19, dsRNA: Double-stranded RNA, ssRNA: single-stranded RNA, CpG: cytosine-guanine dinucleotide.

nucleic acid in viral genomes can be either DNA or RNA, single- or double-strands, positive or negative in polarity, and molecules with a continuous or segmented configuration (81). Viruses detected by TLRs lead to the production of IFNs as well as proinflammatory cytokines through the activation of signal transcription factors such as IRF3, IRF7, and NF-kappaB (85-89). Type 1 interferons, INF-α, and INF-β are potent adaptive immune modulators during viral infections.

3. PROCOAGULANT ACTIVITY DURING VIRAL INFECTIONS

3.1. Ebola virus (dsRNA)

Ebola virus (EBOV) is a negative-sense RNA virus of the Filoviridae family and is responsible for a severe disease characterized by the unexpected onset of fever, malaise, diarrhea, and vomiting, severe liver damage and various coagulation deficits accompanied by other non-specific signs (90) (Table 2). Also, 30–50 % of cases with hemorrhagic symptoms were observed among Ebola virus infected patients, and the mortality of over 90 % is due to the multiorgan dysfunction (91). EBOV infection in macaques upregulates the TF expression and alter the coagulation responses which contribute to DIC (92). The high mortality rate of EBOV infections shows that the immune system fails to control viral replication (93). *In vitro* studies have shown that Ebola virus impairs dendritic cell responses, including cytokine production, maturation, and ability to induce T-cell proliferation (94, 95). TF inhibitor improved the survival rate (33 %) of infected macaques (10, 96). Blood samples from patients infected with the Sudan species of EBOV showed elevated levels of D- dimer from day 4-8 days after onset (97). Interestingly, two independent groups demonstrated that TF activation was associated with EC permeability and FVII depletion, suggesting that alteration of the capillary leakage was an EC-mediation regulated coagulation response (39, 98). Similarly, inhibition of the TF-FVIIa complex reduced the cytokine storm and mortality in a rhesus monkey model of Ebola hemorrhagic fever (96). Furthermore, TF-positive MPs are released from EBOV-infected monocytes/macrophages *in vitro* and increased numbers of TF-positive MPs in plasma of EBOV-infected macaques (10, 96). McElroy and colleagues reported that vWF, a protein that promotes

Table 2. Viral infections and TLR dependent procoagulant responses

Virus	Family	Genome structure	TLRs	Procoagulant responses	REFERENCES
Herpes simplex virus (HSV)	*Herpesviridae*	dsDNA	TLR2,3 and TLR9	↑ TF expression ↓ TM expression	(20, 206-208)
Human immunodeficiency virus (HIV)	*Retroviridae*	ssRNA (+)	TLR2-4, TLR7	- ↑ IL-6 - ↑ hsCRP and - ↑ D-Dimer - ↑ TF^{+}-MPs - ↓ Protein C and protein S - ↑ Platelet activation - ↑ vWF - ↓ ADAMTS13	(123, 131, 132, 134, 142, 145, 209-211)
Hepatitis C virus (HCV)	*Flaviviridae*	ssRNA (+)	TLR2, TLR3, TLR4 and TLR7/8	↑ TF expression ↓ TM expression ↑ CXCL12 ↑ TF^{+}-MPs ↑ vWF	(153, 154, 156, 158, 212-214)
Ebola virus (EBOV)	*Filoviridae*	ssRNA (-)	TLR3	↑ TF expression ↑ Vascular permeability ↑ D-Dimer ↑ TF^{+}-MPs ↑ vWF	(39, 92, 97, 99, 215)
Coxsackievirus (CVB3)	*Picornaviridae*	ssRNA (-)	TLR3, TLR7 and TLR8	↑ Platelet activation Ventricular thrombus formation Thromboembolism	(172, 216-218)
Influenza A virus(IAV)	Orthomyxoviridae	ssRNA (-)	TLR3, TLR7 and TLR8	Alveolar wall hyperemia Pulmonary and small vessel thrombosis Fibrin crosslinks DIC Hemorrhage ↑ TAT ↑ vWF ↓ ADAMTS13	(1, 81, 116, 118, 122, 219, 220)
Parvovirus B19 (B19V)	*Parvoviridae*	CpG DNA	TLR9	- Thrombotic Microangiopathy	(165, 221, 222)

IL-6: Interleukin 6; TLR: Toll-like receptor; TF^{+}-MPs: Tissue factor-positive Microparticles; vWF: Von Willebrand factor; TM: Thrombomodulin; DIC: disseminated intravascular coagulation; TAT: Thrombin-Antithrombin Complex; ADAMTS 13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

platelet adhesion to the injured endothelium, is elevated in SUDV-infected individuals compared to healthy individuals (99). These findings suggest that anticoagulation therapy during EBOV infection could restore the hemostasis and reduce the over activation of the coagulation cascade.

3.2. Influenza A virus (ssRNA)

Influenza A virus (IAV) is a negative-sense RNA virus of the Family Orthomyxoviridae (100) (Table 2). The 1918 flu epidemic was a major demographic event in the United States and worldwide. Over 20 million deaths worldwide, approximately half a million in the United States during 1917 to 1918 due to the severe H1N1 virus infection (101, 102). A correlation between IAV epidemics and high mortality was observed along with cardiovascular complications such as acute cardiac injury, acute myocardial infarction, deep vein thrombosis, and pulmonary embolism (103-107). Increasing clinical case reports confirmed that IAV infection showed excessive coagulation (108). Microvascular endothelial barrier dysfunction due to IAV may contribute in a subset of patients with influenza to the development of severe lung injury (109). Patients with a severe IAV infection (H7N9), often showed characteristic changes in coagulation, including alveolar wall hyperemia, pulmonary capillary and small vessel thrombosis, fibrin crosslinks, DIC, and hemorrhage (108, 110, 111). Intranasally infected chickens with H5N1 showed micro-thrombosis in the lung within 24 h postinfection (112). Muramoto *et al*. revealed that H5N1 infected chickens showed both micro-thrombosis and thrombocytopenia (113). Furthermore, it has been suggested that the replication of HPAI viruses in ECs could negatively regulate thermoregulation, innate immune response and facilitate the systemic spread of the virus to the brain, skin, and visceral organs (112, 114). IAV leads to a prothrombotic state by downregulating the anticoagulant and fibrinolysis components (106, 115-117). For instance, elevated coagulation marker, thrombin-antithrombin complex (TAT), was observed in both pandemic and HPAI-H5N1 virus-infected ferrets (1, 118). In turn, abnormal coagulation promotes hemorrhage and thrombosis, which is

often associated with the vast inflammation observed during a severe IAV infection (106, 119, 120). IAV infection Induces platelet-endothelial adhesion due to the elevated levels of vWF (121). Elevated levels of plasma vWF and reduced level of ADAMTS13 were reported in several case report studies with thrombotic microangiopathy during the acute phase of H1N1 influenza (116, 122). Thus, ECs play a distinct role in IAV infections. Nevertheless, a precise mechanism behind the prothrombotic response *in vivo* is elusive. Some of the clinical and preclinical data confirm that the IAV infections worsen the innate immunity and endothelial system and thereby activates procoagulant and proinflammatory cascades.

3.3. Human immunodeficiency virus (ssRNA)

Human Immunodeficiency Virus (HIV) is a positive-sense single-stranded enveloped RNA virus of the family Retroviridae (Table 2). Activation of coagulation pathways among HIV-positive patients may contribute to risk for non-AIDS related conditions. Cardiovascular diseases are the leading cause of death among HIV-infected individuals, and rates of CVD appear to be increased in HIV versus non-HIV-infected groups (123). Independent studies have revealed that HIV replication is a significant determinant of endothelial dysfunction (124, 125). Immune activation and inflammation during HIV infection may explain some of the excess cardiovascular risks (126-129). Due to the endothelial dysfunction and a proinflammatory state, HIV-infected individuals may also be in a hypercoagulable condition (130). The Strategies for Management of Anti-Retroviral Therapy (SMART) study found that mortality was strongly related to IL-6 and hsCRP and D-Dimer (131). However, IL-6 and hsCRP, but not D-dimer, were associated with the development of AIDS events (123, 132). Plasma D-dimer strongly predicts the risk of all-cause mortality and specific conditions like CVD and thromboembolic events among HIV patients (133). Baker and colleagues measured the TF-dependent procoagulant activity on circulating microparticles (MP-TF) in the plasma of 163 HIV-positive participants treated with and without viral suppression (134). The results demonstrated a 39% reduction in MP-TF activity in viral suppression treated participants (p<0.0.0.1.) compared to non-treatment. Furthermore, MP-TF activity is correlated modestly with vWF (r=0.3.6.; p<0.0.0.1.) and IL-6 (r=0.2.0.; p=0.0.4.), and D-dimer (r=0.2.4.; p=0.0.1.), levels among the participants treated with viral suppression (134). Funderburg and colleagues have conducted a series of seminal studies characterizing the TF expression in monocytes from HIV-infected patients and reported that the TF expression was increased on monocytes among the HIV-infected and was correlated with the HIV viral load (135, 136). However, the degree to which HIV-mediated injury and dysfunction of endothelial surfaces up-regulate the TF-mediated coagulation is not defined clearly. Thus, the procoagulant response is possibly due to multiple mechanisms such as HIV-mediated systemic inflammation and reduction in anticoagulants (e.g., antithrombin, protein C and protein S), platelet activation (137, 138) and the procoagulants (e.g., fibrinogen, prothrombin, and factor VII) dependents on hepatocyte function (139-141). Activation of TLR3 inhibits HIV replication in MØs (142). Hurley *et al.* reported that during HIV infection, the thrombin-PAR1 signaling axis contributes to adaptive immune responses over increased T-cell motility and production of proinflammatory cytokines (49, 143). A case-control study reported that High levels of vWF and low levels of ADAMTS13 were associated with stroke in young HIV-infected patients (144). Similarly, van den Dries *et al.* reported that a marked increase in vWF levels as well as a correlation of vWF to first and recurrent venous thromboembolic events in HIV patients (145). Mackman and other groups found that PAR-1 and PAR-2 modulate the immune response to viral infection (49, 146-148). Further studies are required to understand the differences in altered hemostatic imbalance during HIV infection compared to other disease states to design specific therapeutic strategies to treat HIV-associated prothrombotic complications.

3.4. Hepatitis C virus (ssRNA)

Hepatitis C Virus (HCV) is a positive-sense single-stranded RNA virus of the family Flaviviridae (Table 2). HCV infection is associated with increased thrombotic risk by direct endothelial damage, activation of TF, altered fibrinolysis and increased platelet aggregation and activation (149). Endothelial damage takes place in HCV-infected patients mainly by two mechanisms. HCV viral RNA binds to toll-like receptor (TLR)-3 in ECs leading to inflammation (150) and increased expression of TNF-α. Furthermore, damaged ECs recruit immune cells via the chemokine CXCL 12 expression on the EC surface (151). Secondly, the endothelial damage associated with cryoglobulinemia is due to a type 3 hypersensitivity reactions with formation of immune complexes of antibodies directed against the viral RNA which further activates ECs (152). Both the mechanisms synergistically increase TNF-α expression which leads to up-regulation of TF and downregulation of thrombomodulin (TM) expression (153). Furthermore, Hodowanec and colleagues confirmed that increased in TF-positive MPs in patients with chronic HCV infection potentially enhances procoagulant activity (154). Directly- acting- antivirals (DAAs) treatment in HCV positive patients with cirrhosis resulted in improvement of the pro- and anticoagulant factors (155). Similarly, chronic HCV infection is associated with endothelial dysfunction and increased endothelial surface as well as plasma vWF levels and liver fibrosis (156, 157).

3.5. Coxsackievirus (ssRNA)

Coxsackievirus is a negative-sense RNA virus of the Picornaviridae family (Table 2). CVB3 infection initiates by coupling of the virus to host-cell receptors. CVB3 is dependent upon binding to both CAR (coxsackievirus, and adenovirus receptor), and DAF (decay accelerating factor or CD55) as the primary receptor, and co-receptor, respectively (158). Kishimoto and colleagues reported that CB6 myocarditis carries a significant risk of thromboembolism (16). A clinical study of fatal cases of Coxsackievirus A4, B3, and B4 infections in children reported myocarditis with CA4 infection and CB3 and the other case that had hepatic necrosis with coagulopathy (159). CVB3 Myocardial inflammation is associated with a significant increase in platelet activation and ventricular thrombus formation independent of the hemodynamic conditions (160).

3.6. Herpes simplex virus (dsDNA)

Herpes simplex virus (HSV) is a double-stranded, linear DNA genome of the herpesvirus family Herpesviridae (Table 2). HSV can evade the normal cellular control programs by stimulating the expression of thrombogenic activity on cells (161). Infection of vascular endothelial cells (HUVECs) with HSV enhances the TF activity and reduces TM expression (19, 20). HSVs can capture the host-cell (IKK)/NF-kappaB pathway, which regulates critical cell functions from apoptosis to inflammatory responses (162). Sutherland and colleagues reported that TF and glycoprotein C on HSV type 1 (HSV-1) are cofactors for PAR-1 that enhance the infection by triggering thrombin production (163). However, thrombin combined with FXa/FVIIa increased HSV-1 infection suggesting that PAR-1 and PAR-2 are independently involved in virus propagation (163, 164). HSV-1 and HSV type 2 (HSV-2) and CMV possess phospholipid and have endogenous mechanisms to activate FX. By this mechanism, these viruses induce thrombin-independent of cells, which may represent the earliest influence on host vasculature (161).

3.7. Parvovirus B 19 Infection (CpG DNA)

Parvovirus B19 (B19V) is a single-stranded DNA (CpG DNA) virus of the family Parvoviridae (Table 2). Human B19V is considered an etiologic agent of aplastic anemia in immunosuppressed patients. Murer and colleagues reported the occurrence of Thrombotic Microangiopathy associated with Parvovirus B19 infection after renal transplantation. This study reported four cases of thrombotic renal graft microangiopathy presumably secondary to B19 infection (165). However, not much literature exists on procoagulant activity during Parvovirus B 19 infection.

4. PROCOAGULANT ACTIVITY THROUGH TLRS ACTIVATION BY VIRAL MIMETIC LIGANDS

During viral (and bacterial) infections, there is an extensive interplay between different signaling cascades which modulate systemic inflammation, coagulation, and vascular barrier function. During systemic infections, the endothelium plays a critical role in regulating these systems, and imbalances as a result of endothelial activation followed by dysfunction can contribute to organ failure (166). There are many known ligands identified that activate various TLRs, which can be studied to elucidate the biochemical signaling mechanisms. Oligonucleotides that act as TLR9 agonists can lead to cellular activation and cytokine production against viruses (167). Kebir and filep examined the influence of bacterial DNA (CpG DNA) by activating endosome TLR9 and TF activity. CpG DNA (1 to 32 μg/ml) significantly induced the TF expression in both protein and mRNA levels and TF activity by NF-kappaB activation (168, 169). The TLR3 agonist, poly I:C (structurally similar to double-stranded RNA), induces proinflammatory cytokines and the TF expression in cultured endothelial cells, but not monocytes(170, 171), and activates the coagulation system in mice (172).

5. CONCLUSION REMARKS AND FUTURE DIRECTIONS

Activation of the coagulation system in viral infection is a defensive mechanism to DIC and subsequent hemorrhage during Ebola and Dengue hemorrhagic fevers. Viral infections lead to endothelial dysfunction and increase the plasma and EC surface vWF levels. Various TLR activation studies on different cell types demonstrated that the procoagulant activity is highly linked with innate immunity. It is crucial to explicate the viral infection mediated prothrombotic risk resulting from extreme TLRs activation. *In vitro* and *in vivo* studies suggested that viral infections lead to TLRs activation and TF expression on cell surfaces such as ECs, MOs, fibroblasts, and DCs. Experiments with viral mimetic ligands *in vitro* revealed that the viral infection-dependent procoagulant activity is potentially ECs dependent. Upon polyI:C stimulation, human DCs, and MOs failed to activate NF-kappaB and to produce the proinflammatory cytokines TNF-α and IL-6 but were able to do so in ECs. However, the same cell types (ECs, DCs, and MOs) from murine source activate NF-kappaB and produce TNF-α and IL-6. The complexity of the species- and cell type-specific response and difference in the intracellular signaling mechanisms during viral infection mediated TLR3 activation explains the difficulties in correlating murine model data with human data. Several important questions need to be investigated to understand the role of viral mediated activation of TLRs and prothrombotic risk.

Why are there differences between human cell types stimulated with the same TLR ligand?

What is the primary cell source for TF to induce procoagulant response during viral infection?

Considering the species complexity, what is the optimal animal model to study the viral infection mediated procoagulant response?

Do any proinflammatory receptors complement the TLRs dependent procoagulant activity?

Which viruses directly produce dsRNA or ssRNA in various cell types (ECs, DCs, MOs) and activate TLRs signaling?

Is the TF-dependent hypercoagulation due to direct viral mediated TLRs activation or elevation of procoagulant cytokine status by viral infections?

6. ACKNOWLEDGMENTS

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Abbreviations: ATIII: Antithrombin III, B19V: Parvovirus B19, CMV: Cytomegalovirus , COX-2: Cyclooxygenase 2, CVB3: Coxsackievirus 3, CVD: Cardiovascular diseases, CXCL10: C-X-C motif chemokine 10, CXCL12: C-X-C motif chemokine 12, DCs: Dendritic cells, DIC: Disseminated intravascular coagulation, ECs: Endothelial cells, eNOS: Endothelial nitric oxide synthase, ET-1: Endothelin-1, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus, HUS: Hemolytic uremic syndrome, IAV: Influenza A virus, IFNs: Interferons, IKK: IkB kinase, IL-1ß: Interleukin 1ß, IL-8: Interleukin 8, ITP: Idiopathic thrombocytopenic purpura, MOF:

Multi-organ failure, MOs: Monocytes, MØs: Macrophages, MP-TF: Microparticles: Tissue factor, NF-kB: Nuclear factor kappa B, NO: Nitric oxide, PAI: Plasminogen activator inhibitor, PAMPs: Pathogen-associated molecular patterns, PAR1, 2: Protease-activated receptor 1, 2, PGI2/PGE2: Prostaglandin I2/E2, SMART: Strategies for Management of Anti-Retroviral Therapy, TAT: Thrombin-antithrombin complex, TF: Tissue factor, TLRs: Too-like receptors, TM: Thrombomodulin , TNF-a: Tumor necrosis factor alpha, t-PA: Tissue plasminogen activator, Treg: T regulatory cells, TTP: Thrombotic thrombocytopenic purpura, VHF: Viral hemorrhagic fever, VSMCs: Vascular smooth muscle cells

Key Words: Procoagulant activity, Toll-Like Receptors, Tissue Factor, Viral Infections, Review

Send correspondence to: Inge Scharrer, Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany, Tel: 06131 176004, Fax: 0 6131 1734 49. E-mail: Inge.Scharrer@unimedizin-mainz.de