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REVIEW

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Platelet–leukocyte interactions in the pathogenesis of viral infections

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Abstract

Evolving evidence demonstrates that platelets have major roles in viral syndromes through previously unrecognized viral sensing and effector functions. Activated platelets and increased platelet-leukocyte aggregates are observed in clinical and experimental viral infections. The mechanisms and outcomes of platelet–leukocyte interactions depend on the interacting leukocyte as well as on the pathogen and pathological conditions. In this review, we discuss the mechanisms involved in platelet interactions with leukocytes and its functions during viral infections. We focus on the contributions of human platelet–leukocyte interactions to pathophysiological and protective responses during viral infections of major global health relevance, including acquired immunodeficiency syndrome (AIDS), dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), influenza pneumonia, and COVID-19.

KEYWORDS

platelets, platelet-leukocyte aggregates, COVID-19, Dengue, HIV, Influenza

History

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Introduction

Besides hemostatic and prothrombotic activities, platelet activation by procoagulant or inflammatory agonists plays major roles in immunoregulation through platelet–leukocyte interactions [1,2]. Activated platelets interact with leukocytes including monocytes, neutrophils, dendritic cells, and lymphocytes, triggering intercellular signaling, and amplification of the synthesis of hemostatic and inflammatory mediators. Platelet–leukocyte interactions occur in the circulating blood, at clots and thrombi, in the inflamed microcirculation endothelium as well as in the extravascular milieu of the lung and other tissues [1,2]. These interactions involve regulated adhesion molecules that signal to leukocyte reprogramming at the intersection of coagulation and immunity. [2–4] Platelet *P*-selectin binding to leukocyte *P*-selectin glycoprotein ligand (PSGL)-1 [4,5] and fibrinogen mutually binding to the platelet and leukocyte integrins α_{IIb}/β_3 and α_M/β_2 [6–8] are major molecular interactions in this process.

The interaction between platelets and neutrophils is well established in the literature. Activated platelets induce the release of neutrophil extracellular traps (NET) [3] as in platelet stimulation through TLR7 in RNA virus infections [9,10]. NET extrusion after prothrombotic or inflammatory stimulation in vivo depends on *P*-selectin-PSGL-1 binding [11]. Furthermore, neutrophils secrete matrix metalloproteinase 9, myeloperoxidase, and display-activated Mac-1 (integrin α_M/β_2) upon interaction with platelets [10,12].

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Platelets also interact with and modulate immune responses in monocytes. Thrombin-activated platelets induce PSGL1-mediated NF-κB translocation activating proinflammatory genes in monocytes, including IL-1β, IL-8, TNF-α, CCL2/MCP-1, and COX-2 [13–15]. Beyond *P*-selectin-mediated adhesion, MCP-1 secretion by monocytes depends on CCL5/RANTES from adhered platelets, and COX-2 expression depends on IL-1β signaling [13,15]. These interactions have been reported in a number of inflammatory and infectious conditions, including viral infections of major importance in public health such as dengue, HIV, and COVID-19 [2,14,16–18].

Fewer studies have reported interactions between platelets and lymphocytes. Platelet–lymphocyte interactions participate in the main T cell polarization phenotypes such as Th1 [19] and Treg [20]. Importantly, platelets have the necessary machinery for antigen presentation, including immunoproteasome, β2-microglobulin, and all human leukocyte antigens (or major histocompatibility complex in mice) class I (HLA-I or MHC-I) subunits [21,22]. Platelets can present antigens to T cells through MHC-I, contributing to $CD8^+$ T cell activation in malaria [23] and suppression in sepsis [24].

Beyond expressing innate immune receptors that allow recognition and responses to viruses [2,9,10,25], platelets also possess the cellular machinery for viral attachment, entry, and replication (Table 1) [16,26,27]. After interacting with viruses or being activated in the infection environment, platelets participate in the orchestration of innate and adaptive immunity through a variety of mechanisms from reprogramming the leukocytes to transferring viruses to target cells [16,28] (Figure 1 and Table 2). The main mechanisms of platelet activation in interactions with viruses are summarized in Table 1, and the mechanisms of platelet signaling to leukocytes and their effector responses in viral infections are summarized in Table 2. Platelets' interaction with viruses and their participation in the pathogenesis of a diverse

Table 1. Platelet interaction and responses to RNA viruses.

Virus/ PAMP	Receptor	Platelet response	Ref.
HIV-1	DC-SIGN	Binding, internalization and inactivation by α-granules proteins	[25,40]
HIV-1	DC-SIGN, CLEC-2	Binding, internalization and transinfection to T-cell	[25]
HIV-1 Tat	integrin β3, CCR3	Platelet activation, *P*-selectin and CD-40 L translocation and release	[31]
DENV	DC-SIGN, Heparan sulfate	Virus attachment, internalization and replication	[26]
DENV	DS-SIGN	Platelet activation, mitochondrial dysfunction and apoptosis	[41]
DENV	CLEC2	Release of alpha- and dense-granules, shedding of extracellular vesicles	[37]
DENV NS1	TLR4	Platelet activation, secretion of stored cytokines, synthesis of IL-1β; platelet apoptosis and thrombocytopenia in mice	[27,42]
IAV	TLR7	Platelet activation, C3 release, platelet-neutrophil aggregate formation	[10]
IAV-IgG	FcγRIIA	P-selectin surface expression, integrin αIIb/β3 activation, extracellular vesicles release and 12-HETE synthesis	[43]

variety of infections have been reviewed elsewhere [16,44,45]. This review will focus on the discussion of platelet–leukocyte interactions in four viral infections with global impact on human health: HIV, dengue, influenza, and COVID-19.

Platelet–leukocyte Interactions in HIV Infection

Human Immunodeficiency Virus (HIV) is a member of the Lentivirus genus of the Retroviridae family and is classified into two types, HIV-1, and −2, HIV-1 being the main agent of acquired immunodeficiency syndrome (AIDS). Usually, HIV-1 enters the target T-cells through sequential interactions of the HIV-1 envelope glycoprotein 120 (GP120) with the cellular receptor CD4 and the co-receptors CCR5 or CXCR4[46]. HIV-infection leads to systemic T cell destruction and a decrease in cell-mediated immunity, opening the way for a wide range of opportunistic infections and cancers. Besides, HIV-1 can promote inflammation through infection and activation of other immune cells [47. Several combinations of antiretroviral therapy (ART) regimens emerged in the late 1990s, suppressing viral replication and changing HIV from a progressive and fatal illness into a chronic manageable disease [47]. However, even though suppression of viral replication and absence of opportunistic infections are achieved through ART, people living with HIV still experience earlier mortality and increased incidence of noninfectious comorbidities including cardiovascular diseases, neurocognitive disorders, and non-AIDS cancers [48,49].

Beyond direct attachment to T-cells, HIV-1 can spread from antigen-presenting cells to target T-cells through intercellular transmission, so-called HIV-1 transinfection [50], in which dendritic cells internalize HIV-1 through DC-SIGN or other CLRs without membrane fusion, and store endosomal infective viral particles to be transferred to T-cells during antigen presentation [50,51]. Similarly, platelets interact with HIV-1 GP-120 leading to binding, engulfment, and internalization through DC-SIGN and CLEC2 [25,40]. Ultrastructural studies of platelets from an AIDS patient (high viremia and thrombocytopenia) or platelets infected *in vitro* have shown platelets engulfment and internalization of HIV-1 in endosome-like structures [40,52]. Chaipan et al have reported platelet capture of HIV-1 through DC-SIGN and CLEC2, preserving its infectivity and transferring it to T-cells *in vitro* (Figure 1B) [25]. Recently, platelet HIV-1 transinfection to T-cells and macrophages was evidenced in HIV-infected subjects with poor immunological recovery after ART [28]. Platelet HIV-1 transinfection depends on platelet-T-cell aggregates formation through *P*-selectin [29] and platelet–macrophage interaction through integrin α_{IIb}/β_3 [28]. Even though platelets can present antigens to T-cells [23,24], the participation of HLA-I antigen presentation in platelet HIV-1 transinfection remains unknown.

HIV-1 replication is regulated by a complex network of cytokines and chemokines [32]. Chemokines are critically involved in the control of HIV-1 replication due to the role of specific chemokine receptors, most notably CCR5 and CXCR4, as cell-surface co-receptors for HIV-1 entry. Consequently, the chemokines that bind such receptors work as endogenous inhibitors of HIV-1 [32,34]. Holme et al. [53] demonstrated increased platelet activation with exhausted CCL5/RANTES secretion in AIDS patients, which were correlated with the onset of immune suppression and increased inflammation, and was recovered after ART. We recently reported persistent platelet activation and exhaustive granule secretion in people living with HIV even after years of virological control through ART [54]. CCL5/RANTES is known to modulate HIV-1 replication in mononuclear phagocytes by binding CCR5 coreceptors [34]. PF4/CXCL4 is another important chemokine released by platelets that possess relevant antiviral activity against HIV-1 [32,33]. Auerbach et al. [32] showed that recombinant human PF4/CXCL4 or native PF4/CXCL4 dose-dependently inhibited the infection of T-cells and macrophages by different HIV-1 strains *in vitro*. This inhibition happened independently on the coreceptor used by the HIV-1 variant, occurring through direct interaction of PF4/CXCL4 with GP120 [32]. Tsegaye et al. [33] demonstrated through co-culture experiments that platelets can inhibit HIV-1 spread in T-cells in a concentration- and activation status-dependent manner. They showed that exhausted platelets did not maintain the inhibitory capacity, while activated platelets supernatants could inhibit HIV-1 infection, and identified PF4/CXCL4 as the main viral-restrictive factor in platelet-T-cell co-cultures [33].

Platelet-monocyte aggregates are also increased in HIV-infected subjects, being associated with HIV-associated thrombocytopenia and cognitive impairment [18,55,56]. Platelet-derived CD40L contributes to neuroinflammation by promoting blood-brain barrier permeability and platelet-monocyte aggregate formation [18,30]. Analysis of postmortem brain tissue sections from HIV-associated encephalopathy show increased platelet-monocytes aggregates in vessel lumen or attached to the brain microvasculature, suggesting an association with HIV-induced neuroinflammation [18]. Mechanistically, the HIV-1 transactivator of transcription (Tat), a viral protein released in the extracellular milieu, mediates platelet activation through β3 integrin and CCR3 increasing the translocation and secretion of CD40L and *P*-selectin [31]. Experimental Tat injection in mice shows leukocyte adhesion, rolling, and transmigration through the blood–brain barrier depending on platelet-derived CD40L (Figure 1C) [30]. These data indicate a major role of platelet CD40L and platelet–leukocyte interaction with HIV-associated neuroinflammation.

Platelet–leukocyte Interactions in Dengue Pathogenesis

Dengue is an arboviral disease caused by Dengue virus (DENV) and transmitted by *Aedes* mosquitoes. Dengue infection may present different manifestations from asymptomatic infection to severe dengue syndromes [57]. Severe dengue is characterized by

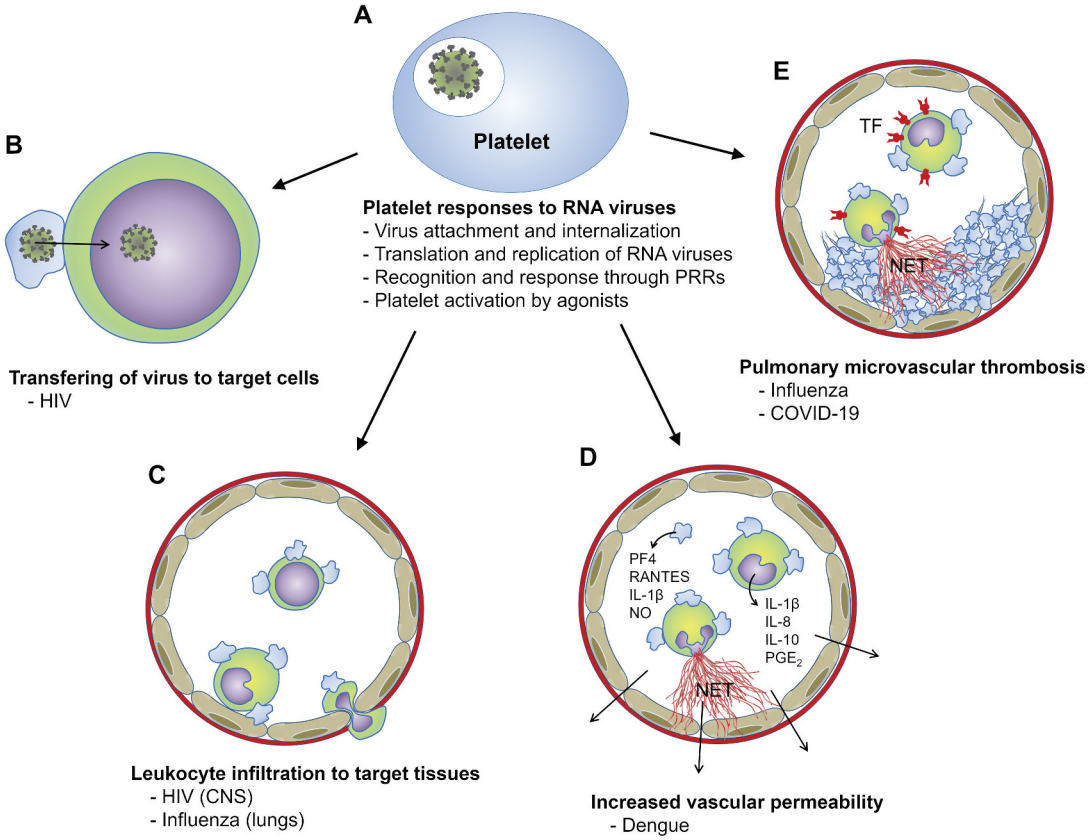

Figure 1. **Platelet–leukocyte interactions in viral diseases**. (**A**) Platelets become activated after interaction with RNA viruses through diverse mechanisms from virus attachment to surface receptors, viral particle internalization, viral genome translation and replication, generation of pathogen-associated molecular patterns (PAMPs) that are recognized by pattern recognition receptors (PRRs) and generation of inflammatory mediators and agonists. (**B**) Infected platelets may store infective viral particles or positive-sense viral RNA and transfer them to target cells, as shown for HIV-1. (**C**) Platelet-leukocyte and platelet-endothelial cell interactions facilitate leukocyte transmigration to target tissues, as the lungs in influenza pneumonia and the central nervous system (CNS) in HIV-associated encephalopathy. (**D**) activated platelets secrete inflammatory mediators and reprogram leukocyte responses, amplifying inflammation and contributing to vasculopathy in dengue. (**E**) Platelets induce TF expression in monocytes and TF-positive NET release in neutrophils, contributing to a procoagulant phenotype in COVID-19. Pulmonary microvascular thrombosis with platelet-neutrophil occlusive thrombi is observed in COVID-19 and influenza pneumonia, even though more frequent in COVID-19. PF4, platelet factor 4; RANTES, regulated on activation normal T-cell expressed and secreted; IL, interleukin; NO, nitric oxide; PGE_2, prostaglandin E_2; NET, neutrophil extracellular traps; TF, tissue factor. See the text for details and references.

increased vascular leakage, severe hemorrhage and organ failure [57]. Although the pathophysiological mechanisms of severe dengue are not fully elucidated, it involves a cytokine storm that leads to endothelial and cardiovascular dysfunction [58,59]. Thrombocytopenia is found in both mild and severe dengue, with lower platelet counts encountered in severe cases [58,60].

Platelets from DENV-infected patients are highly activated and higher levels of platelet activation are associated with dengue severity [61]. Activated platelets have been shown to participate in inflammatory amplification in dengue by interacting with leukocytes and reprogramming the inflammatory mediator profile, which is considered important players in dengue pathogenesis [14,61,62]. Studies from our group and others have demonstrated that activated platelets from patients with dengue or platelets infected with DENV *in vitro* secrete inflammatory chemokines, as PF4/CXCL4 and CCL5/RANTES, newly synthesized cytokines, as IL-1β, and small molecules, as nitric oxide [14,61–63]. Such mediators are potentially involved in dengue-associated vasculopathy. We have previously shown that platelet NLRP3 inflammasome activation, IL-1β synthesis, and shedding in extracellular vesicles is associated with vascular leakage during dengue infection [62] (Figure 1D).

It has been demonstrated that platelets can internalize DENV through DC-SIGN and heparan sulfate proteoglycans [26]. Moreover, DENV-infected platelets sustain viral genome translation and replication [26,27,64]. However, DENV-infected platelets are not capable of secreting new viral particles [27,64], implicating that platelets produce an abortive replication cycle. Despite the abortive infection, DENV engagement to DC-SIGN induces both platelet activation and apoptosis in vitro [41], which are also increased in platelets from patients [41,65]. Recently, we have reported that activation of DENV-infected platelets depends on viral genome translation with secretion of the viral nonstructural protein 1 (NS1), a TLR4 ligand [27]. These reports highlight that DENV activates platelets through receptor attachment and viral internalization leading to an abortive replication cycle that triggers platelet thromboinflammatory responses by generating viral PAMPs, such as NS1, and engaging innate immune receptors, such as TLR4. Aside from DC-SIGN, it has been reported that DENV activates platelets through mechanisms involving CLEC2 [37], but whether interaction through CLEC2 leads to virus internalization and replication remains unknown.

DENV infection induces platelet *P*-selectin, CD40L, and HLA-I surface expression [41,61,66], which are all involved in platelet–leukocyte interactions. We have previously demonstrated that DENV infection increases the HLA-I surface expression on platelets depending on proteasome activity [61]. Although increased platelet-lymphocyte aggregation has been observed in

Table 2. Platelet signaling to leukocyte in viral infections.

Disease	Interacting leukocyte	Platelet-leukocyte signaling	Response	Ref
HIV	T-cells	P-selectin	HIV-1 transinfection	[29]
	Macrophages	Integrin α_{IIb}/β_3	HIV-1 transinfection	[28]
	$GR1^+CCR2^+$ Leukocytes	CD40-L	Adhesion, rolling and migration through the BBB	[30]
	B-cells	CD40-L	Immunoglobulin class switch	[31]
	T-cells	PF4/CXCL4 release	Blocking of HIV-1 GP-120, impairment of HIV-1 spreading	[32,33]
	Monocytes and macrophages	RANTES/CCL5 release	Suppression of HIV-1 replication	[34]
Dengue	Monocytes	P-selectin	Secretion of IL-1β, IL-8 and IL-10	[14]
	Monocytes	Phosphatidylserine	Platelet phagocytosis and IL-10 secretion	[14,35]
	Monocytes	Platelet adhesion plus MIF release	Lipid droplets biogenesis and PGE_2 secretion	[36]
	Neutrophils	Extracellular vesicles engagement to CELC5 and TLR2	NET release and increased vascular permeability in mice	[37]
Influenza	Neutrophils	C3 release	NET and myeloperoxidase release	[10]
	Neutrophils	PF4/CXCL4 release	Recruitment to the lungs and viral clearance in mice	[38]
COVID-19	Monocytes	P-selectin and integrin α_{IIb}/β_3	TF expression	[17]
	Neutrophils	C5a and thrombin generation	TF expression and NET release	[39]

patients with dengue [67], new studies are still necessary to investigate whether DENV-infected platelets can present DENV antigens to lymphocytes, contributing to DENV-specific T cell activation or suppression or to platelet destruction and thrombocytopenia.

Increased platelet-monocyte aggregates formation in dengue patients' blood has been demonstrated, especially in patients with thrombocytopenia and vascular leak [14,67]. Ex vivo aggregates formed by platelets from dengue patients and monocytes from healthy volunteers induce the secretion of IL-1β, IL-8, and IL-10 [14]. In addition, the combined signaling of platelet adhesion plus MIF from infected platelets drives lipid droplets biogenesis and PGE_2 synthesis in monocytes [36]. Mechanistic experiments have shown that the reprogramming of the monocytes depended on *P*-selectin-mediated adhesion and recognition of phosphatidylserine on apoptotic platelets, which induced IL-10 secretion [14]. Consistently, apoptotic platelets from patients or *in vitro* infection are phagocytosed when co-cultured with monocytes depending on phosphatidylserine recognition [35]. Altogether, these findings suggest that platelet-monocyte aggregation and phagocytosis may contribute to thrombocytopenia and immunoregulation in dengue (Figure 1D).

Regarding platelet–neutrophil interaction, platelets activated by DENV through CLEC2 release extracellular vesicles that act upon neutrophil CLEC5 and TLR2, inducing NET extrusion [37]. In a platelet-neutrophil-endothelial cell co-culture infection model, CLEC5- and TLR2-dependent NETosis increased endothelial permeability in vitro [37]. These findings were confirmed *in vivo* by an infection of the $STAT1^{-/-}$ mice model, which presented reduced NET deposition in the spleen, lower vascular permeability, and increased survival of experimental infection when presenting CLEC5 co-deficiency [37]. Further improvement in NETosis, plasma leakage, and survival was achieved in $STAT1^{-/-}CLEC5^{-/-}$ mice treated with anti-TLR2 antibodies [37]. Hence, CLEC5- and TLR2-mediated NETosis induced by CLEC2-dependent platelet extracellular vesicles play a pathogenic role in experimental DENV infection (Figure 1D).

Platelet–leukocyte Interactions in Influenza Pneumonia

Influenza is an air-born single-stranded RNA virus widely disseminated around the world. The H1N1 influenza A virus (IAV), which reached pandemic proportions in 2009, causes exacerbated inflammation of the airways, pulmonary microvascular thrombosis (Figure 1E) and may lead to respiratory failure and death [68]. Lately, many studies have demonstrated an important participation of platelets during influenza-mediated lung inflammation, with platelet activation in the lungs contributing to inflammatory infiltration (Figure 1C) [10,43,69]. Indeed, activated platelets and platelet-monocyte aggregates are observed in increased numbers in patients with the most severe form of H1N1 influenza [68]. Moreover, influenza vaccination also leads to increased platelet–monocyte interactions that have been associated with the expansion of $CD16^+$ pro-inflammatory pool of monocytes [35]. However, whether and how platelet–monocyte aggregates contribute to the expansion of inflammatory monocytes in influenza or other infections in humans remains to be demonstrated.

Experimental models of influenza A infection in mice demonstrated accumulation of platelets and platelet-leukocyte aggregates in vascular and extravascular compartments in the lung. Through the use of different strategies to inhibit platelet activation and platelet-leukocyte aggregation, a role for platelets and platelet-leukocyte aggregates in fueling the dysregulation of inflammation and promoting the pathogenesis of influenza virus infections has been established [35].

Platelets may also participate in protective immune response in influenza through PF4-mediated neutrophil recruitment to the lungs [38]. Experimentally infected PF4-deficient mice present increased weight loss and mortality, which was associated with defective innate immune response, lower levels of neutrophil infiltration in the lungs, and increased viral loads in the bronchoalveolar wash [38]. Therefore, platelet activation in the lungs participates either in pathological or protective immune responses to influenza pneumonia by orchestrating leukocyte infiltration (Figure 1C).

Although the mechanisms involved in platelet activation during influenza have not been fully elucidated, platelets have been shown to sense and to respond to IAV and to agonists generated during the infection. Immune complexes formed by IAV with specific (H1N1) or cross-reactive (H3N2) IgG were able to activate platelets promoting degranulation, 12-HETE synthesis, and MVs release through FcγRIIA signaling [43]. In this model, a synergism between FcγRIIA and thrombin amplifies platelet responses in influenza [43]. A recent study has shown that the relationship between platelet TRL7, complement C3, and NET extrusion in influenza (Figure 1E) [10]. Analysis of platelets from influenza patients or platelets infected with IAV in vitro demonstrated virus endocytosis by platelets and co-localization with

TRL7 in endosomes [10]. In vitro experiments showed TRL7-dependent platelet C3 release which mediated NET and myeloperoxidase release by neutrophils [10]. C3 levels and NETosis were both increased in patients with influenza, and platelets were the main source of C3 in IAV-infected mice [10]. Accordingly, platelet depletion protected infected mice from NET extrusion in circulation.

Platelet–leukocyte Interactions in COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is an emergent pathogen responsible for the coronavirus disease 2019 (COVID-19) and the current pandemic. A state of hypercoagulability is a major pathological mechanism and cause of mortality in COVID-19 [70,71], and pulmonary and extrapulmonary microvascular thrombosis have been proposed as a main mechanism of multiorgan impairment [72–74]. Histopathological analysis of COVID-19 deaths or nonhuman primate infection models have revealed lung thromboinflammatory features including neutrophil and macrophage infiltration, NET-containing pulmonary microvascular thrombosis, and endothelial inflammation with platelet-fibrin deposition [72–76] (Figure 1E). Comparative autopsy studies revealed that these thromboinflammatory vascular occlusions were almost ten times more frequent in lungs from COVID-19 fatalities than those from individuals with influenza pneumonia [74,76,77].

Severe COVID-19 is associated with platelet hyperactivity and increased platelet-monocyte, lymphocyte, and neutrophil aggregates' formation [17,78,79]. Increased platelet activation and platelet-monocyte aggregates formation were present in severe COVID-19 patients, but not in patients with mild self-limiting COVID-19 syndrome and predict patients' poor outcomes, including the requirement of mechanical ventilation and in-hospital mortality [17]. Increased platelet activation and platelet–monocyte interaction in severe COVID-19 support pathologic tissue factor (TF) expression in monocytes [17], the main trigger of coagulation and intravascular thrombosis [80]. Increased TF expression was observed on monocytes that were tethered with platelets in severe COVID-19 patients compared to monocytes alone in the same sample. Moreover, platelets from severe COVID-19 patients could induce TF expression ex vivo in monocytes from healthy volunteers [17]. In addition, platelet activation and monocyte TF expression were positively correlated with plasma levels of D-dimers, supporting a role in COVID-19-associated hypercoagulability. Mechanistically, activated platelets from severe COVID-19 patients licensed monocyte TF expression through *P*-selectin-mediated adhesion and *P*-selectin and integrin α_{IIb}/β_3 signaling [17] (Figure 1E).

COVID-19 deaths show extensive areas of tissue microvascular thrombosis containing platelet-neutrophil complexes and NETosis [72,73] and intravascular and airway NETosis is associated with increased hypercoagulability and mortality in severe COVID-19 patients [39,72,73]. Interaction with platelets from severe COVID-19 patients is sufficient to induce NET extrusion ex vivo [39,72]. Importantly, NETs generated in severe COVID-19 express TF [39], and platelets from severe COVID-19 patients trigger TF-positive NETs in control neutrophils [39]. Platelet activation and TF expression on platelet-monocyte and platelet-neutrophil aggregates were associated with COVID-19 severity and mortality [17,79]. Therefore, interaction with platelets is key for monocyte and neutrophil thromboinflammatory activities in COVID-19, including the induction of NETosis and TF [17,39,72], contributing to the state of hypercoagulability (Figure 1E).

The mechanisms underlying platelet activation in severe COVID-19 are not yet completely understood. Our group and others have shown that circulating inflammatory and/or procoagulant mediators generated in severe COVID-19 activates platelets [17,79,81]. Platelets from healthy volunteers exposed to plasma from severe COVID-19 patients become activated ex vivo [17,81]. Whole blood from healthy volunteers reconstituted with COVID-19 plasma displays platelet activation, platelet-leukocyte aggregate formation, and TF expression, which are all inhibited by the IL-6 receptor neutralizing antibody tocilizumab [79]. Therefore, proinflammatory and procoagulant factors generated in COVID-19 contribute to platelet activation platelet-leukocyte aggregate formation and hypercoagulability, indicating an interplay between coagulation and inflammation in severe COVID-19.

Conclusion

Emerging insights on platelet biology have highlighted platelets as dynamic cells playing substantial roles in the inflammatory and immune continuums. Through complex interactions with leukocytes, platelets can reprogram the immune network orchestrating inflammatory and prothrombotic responses in a diversity of infectious diseases, including those caused by viruses. Pathophysiological mechanisms involving platelet–leukocyte interactions have been reported in HIV infection, dengue, influenza, and recently in COVID-19. Platelets interact with leukocytes in different viral infections through mechanisms involving similar and distinct pathways and responses (Figure 1). Platelets signaling to leukocytes participate in major features of viral infections including inflammatory infiltration into target tissues, cytokine storm, hypercoagulability, and virus transfer or restriction in target cells as described above. Even though these features are majorly described as contributing to injurious thromboinflammatory mechanisms in viral infections, they also participate in beneficial immune response and virological control. Increasing our understanding of the immunoregulatory functions of platelet–leukocyte interactions will certainly increase our knowledge of disease mechanisms triggered by viruses, improving clinical management and therapeutic options.

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Authorship

ACQ-T, LBM, MBMP, SVR, and EDH wrote the manuscript. EDH, PTB, and FAB designed the review article, edited and revised the manuscript. All authors discussed the concepts.

Disclosure Statement

The authors declare no conflict of interest.

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