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Review Article

Dysregulated haemostasis in thrombo-inflammatory disease

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Inflammatory disease is often associated with an increased incidence of venous thromboembolism in affected patients, although in most instances, the mechanistic basis for this increased thrombogenicity remains poorly understood. Acute infection, as exemplified by sepsis, malaria and most recently, COVID-19, drives 'immunothrombosis', where the immune defence response to capture and neutralise invading pathogens causes concurrent activation of deleterious prothrombotic cellular and biological responses. Moreover, dysregulated innate and adaptive immune responses in patients with chronic inflammatory conditions, such as inflammatory bowel disease, allergies, and neurodegenerative disorders, are now recognised to occur in parallel with activation of coagulation. In this review, we describe the detailed cellular and biochemical mechanisms that cause inflammation-driven haemostatic dysregulation, including aberrant contact pathway activation, increased tissue factor activity and release, innate immune cell activation and programmed cell death, and T cell-mediated changes in thrombus resolution. In addition, we consider how lifestyle changes increasingly associated with modern life, such as circadian rhythm disruption, chronic stress and old age, are increasingly implicated in unbalancing haemostasis. Finally, we describe the emergence of potential therapies with broad-ranging immunothrombotic functions, and how drug development in this area is challenged by our nascent understanding of the key molecular and cellular parameters that control the shared nodes of proinflammatory and procoagulant pathways. Despite the increasing recognition and understanding of the prothrombotic nature of inflammatory disease, significant challenges remain in effectively managing affected patients, and new therapeutic approaches to curtail the key pathogenic steps in immune response-driven thrombosis are urgently required.

Haemostatic response to vessel injury

Blood coagulation is activated in response to blood vessel injury (Figure 1). Traumatic disruption of the endothelial cell layer causes the recruitment of platelets to the site of vessel injury, either via platelet glycoprotein 1b receptor interaction with plasma von Willebrand factor (VWF) bound to sub-endothelial tissue, or via direct platelet collagen receptor binding to exposed collagen. Adherent platelets become activated, prompting extensive morphological changes and secretion of granular contents to encourage further platelet recruitment to the growing clot and provide a cellular surface to amplify procoagulant enzymatic reactions. Activated platelets also secrete VWF and express P-selectin, an important cell adhesion receptor, which binds to P-selectin glycoprotein ligand 1 (PSGL-1) expressed by monocytes and neutrophils. In parallel, vessel injury causes the exposure of tissue factor (TF), expressed extensively within the sub-endothelial tissue, to blood (for detailed review, see [1]). TF bound to activated FVII (FVIIa) triggers the formation of the extrinsic tenase complex (TF, FVIIa, and factor X, FX). Activated FX (FXa), bound to its cofactor activated factor V (FVa), promotes the conversion of zymogen prothrombin to thrombin. Thrombin, in turn, activates several coagulation proteases and cofactors, including FV, FVIII, and FXI, to

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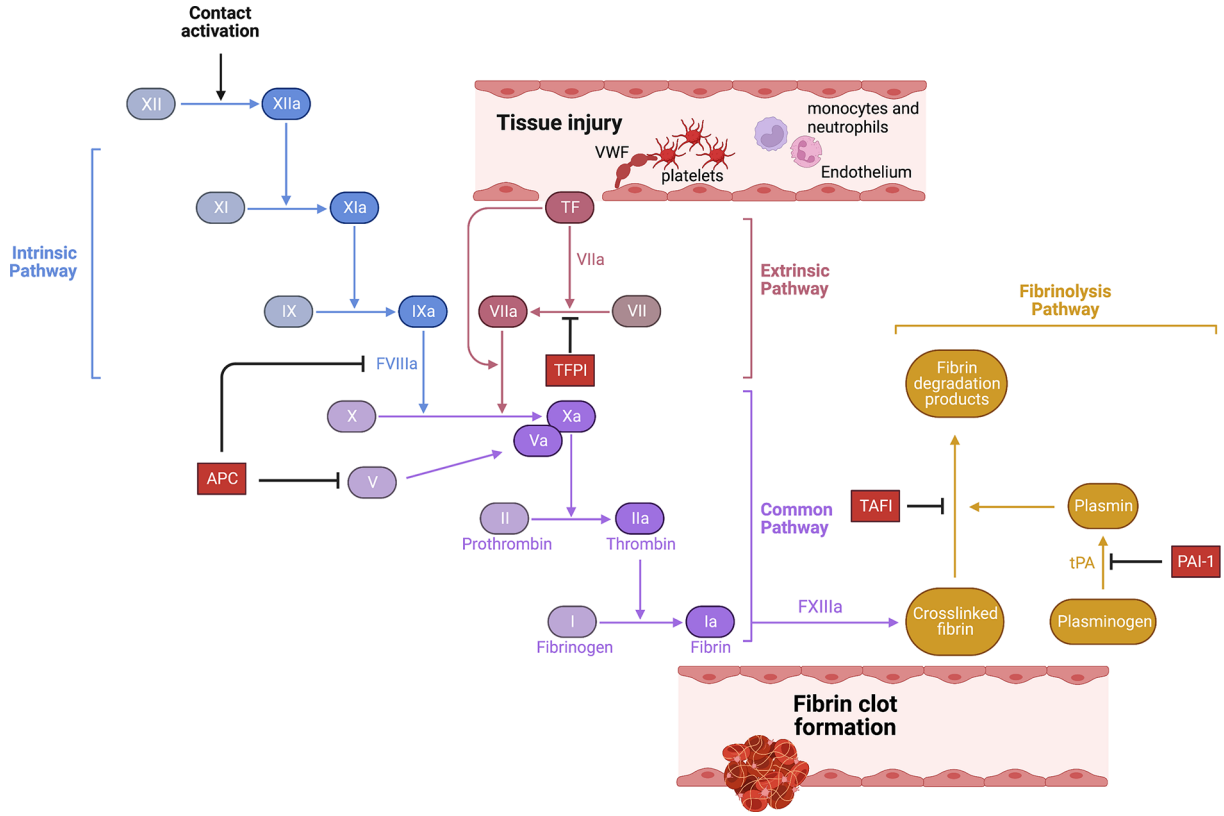

Figure 1. Mechanisms of blood clot formation

Blood coagulation is triggered by vessel injury and TF exposure. This triggers extrinsic pathway activation, leading to thrombin generation via the shared pathway and fibrin generation. Alternatively, contact pathway activation via FXII activation by polyP also leads to intrinsic pathway activation, thrombin generation and fibrin deposition in the absence of vessel damage, leading to pathological thrombus formation. Clot growth and size is regulated at multiple stages by endogenous anticoagulants, including tissue pathway inhibitor, the PC pathway and antithrombin. Once the vessel repair is underway, proteolytic clot lysis is orchestrated by plasmin, which breaks down cross-linked fibrin into fibrin degradation products.

amplify the procoagulant response and overwhelm counteractive anticoagulant mechanisms such as tissue factor pathway inhibitor (TFPI). FXIa activation of FIX prompts intrinsic tenase complex formation (FIXa, FVIIIa, and FX) that promotes sufficient FXa generation to drive prothrombinase activity, allowing generated thrombin to convert soluble fibrinogen in the blood into an insoluble fibrin mesh clot. Thrombin also further activates platelets and endothelial cells via protease-activated receptor (PAR1) signalling [2]. Endogenous anticoagulant mechanisms, such as antithrombin and the protein C (PC) pathway, regulate clot size and spread. In addition, fibrinolytic factors, such as tissue-type plasminogen activator (tPA) and plasmin, coordinate clot resolution by enzymatic fibrin degradation.

Pathological venous clot formation, typically in the absence of traumatic injury, requires factor FXII (XII) activation rather than solely TF-dependent fibrin generation (for detailed review, see [3]). FXII can be activated by negatively charged synthetic materials such as glass, silica or nanoparticles [4]. Recently, however, potential endogenous FXII activators have been identified, such as misfolded protein aggregates, free collagen, glycosaminoglycans and circulating nucleic acids [5]. Of particular importance is inorganic polyphosphate (polyP) [6], which is released from activated platelets to rapidly activate FXII and drive thrombus development [7].

What is ‘immunothrombosis’?

Clot development likely evolved in part as an ancient anti-bacterial response to enable localisation and neutralisation of various bloodborne pathogens. Aberrant clot formation, however, that arises from infection or excessive inflammatory response during disease is now commonly termed ‘immunothrombosis’ (Figure 2). Whereas this primitive response represents an effective strategy to slow pathogen spread during infections, this may come at the cost of immune-driven pathological thrombus formation. Currently, therapeutic approaches to control immunothrombotic

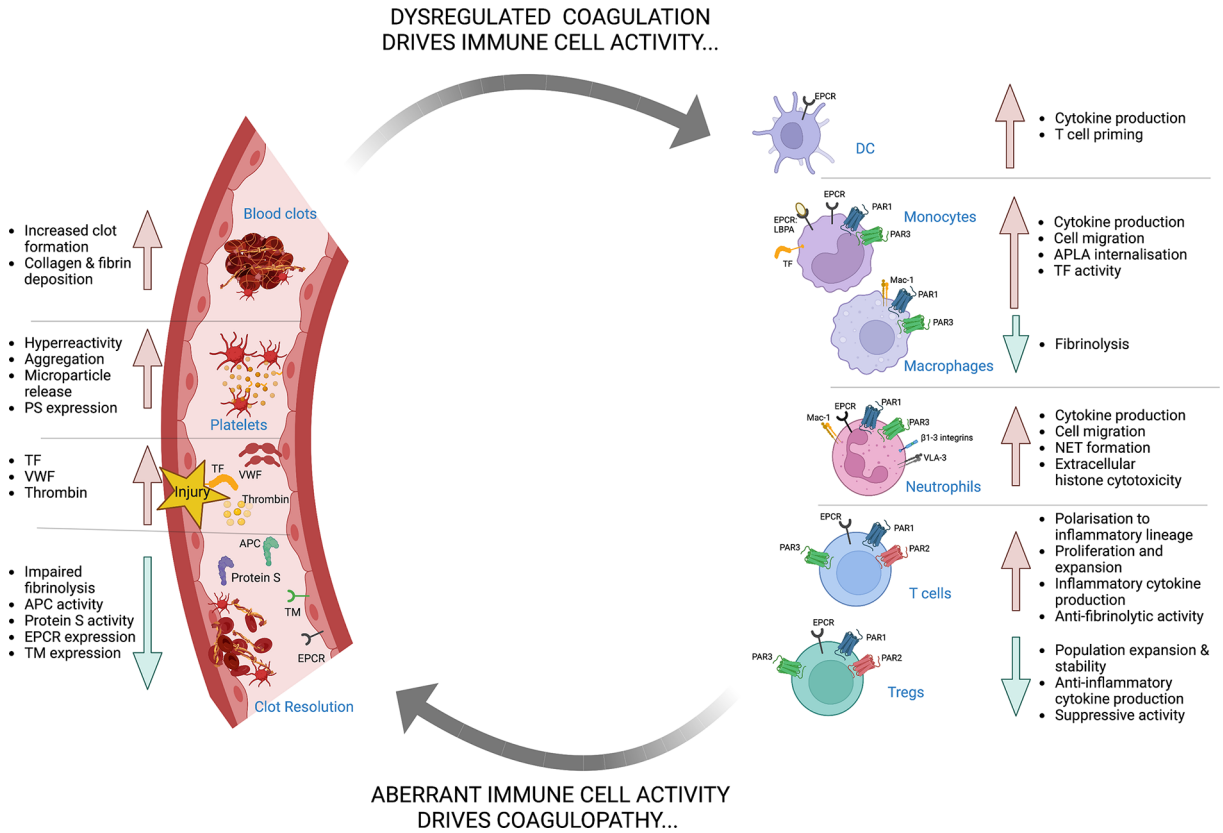

Figure 2. Molecular and cellular mechanisms of immunothrombosis

Both acute and chronic inflammatory diseases, including autoimmune diseases, allergies, and infections, promote dysregulation of haemostasis, leading to immunothrombosis. Inflammatory mediators such as enhanced pathogenic immune cell populations, increased proinflammatory cytokines and chemokines levels, and diminished tolerogenic Treg cell responses coincide with and promote aberrant coagulation. This enhanced procoagulant state feeds back to amplify inflammation, inducing further expansion of proinflammatory immune cells, enhanced TF expression in myeloid cells, NET production and inhibition of tolerogenic Treg responses that impair thrombolysis and clot resolution.

disease are limited by our nascent understanding of how proinflammatory and procoagulant pathways intersect. In this review, we describe the convergent mechanisms that determine how inflammatory events precipitate an increased risk of venous thromboembolism (VTE).

Activation of the immune response

Innate immune cells, such as monocytes, macrophages, granulocytes and dendritic cells (DCs), classically perform sentinel roles in immunosurveillance and antigen presentation to cells of the adaptive immune system, thereby inducing a robust immune response and generating immune memory [8]. These innate cells recognise intra- and extra-cellular pathogens via pathogen recognition receptors (PRRs). PRRs are sub-classified as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (Nod) like receptors (NLRs), C-type lectin receptors (CLRs), and RIG I-like receptors (RLRs). Macrophages and DCs recognise extracellular pathogens by sensing components of their cell wall such as LPS, bacterial lipopeptides, lipoteichoic acids, glycolipids, flagellin, and β-glucans via TLR1, TLR2, TLR4, TLR5, TLR6, and CLRs, such as dectin-1 and dectin-2, which are expressed on their plasma membrane [8]. TLR3, TLR7, TLR8, and TLR9, are expressed in the cell endosomes and sense intrinsic pathogens, such as viral nucleic acids [8]. RLRs, NLRs, and cytosolic DNA sensors detect viral RNA and DNA, and invading bacteria in the cytosol [8–12]. In the bloodstream, monocytes and neutrophils recognise invading bacterial, fungal and protozoan pathogens via TLRs, NLRs, and CLRs and facilitate phagocytosis, degranulation, and killing of these microorganisms [8,13]. Following pathogen recognition, innate immune cells also secrete inflammatory cytokines and chemokines

Clinical Science (2022) **136** 1809–1829
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into the vicinity, recruiting both other innate and adaptive cells to the site to amplify the inflammatory response. Furthermore, antigen-loaded DCs migrate to the draining lymph nodes to prime an adaptive T-cell response. The type of T-cell response induced depends on several factors including, the location of the site of injury or infection, the class of antigen being presented and the presence of other instructive cytokines and chemokines in the milieu [8]. Typically, bacteria, protozoa and fungi elicit a type 1 immune response via TLRs, RLRs, and CLRs, involving CD4+ Th1 and Th17 cells, and CD8+ cytotoxic lymphocytes (CTLs) [14–19], whereas helminths, allergens, and venoms elicit a type 2 immune response, involving CD4+ Th2 cells [20–22]. CTL induction of type 1 immunity is also required to clear viral infection via RLRs, TLR3, and CLRs [23–25]. Recent studies have highlighted the role of both adaptive and innate immune cell responses in dysregulated haemostasis.

Immune cell contribution to pathological thrombus formation

Platelets represent the classical bloodborne haemostatic cell, and their prothrombotic activity is critical for normal haemostasis. In addition to platelets, recent data have highlighted the roles played by various innate immune cells in thrombus development via distinct and often cell-specific mechanisms. Post-mortem studies and preclinical deep vein thrombosis (DVT) mouse models suggest an essential contribution of myeloid cells to VTE. Neutrophils have a crucial role in response to infection and subsequent resolution of inflammation but have recently also been identified to be critical for DVT formation. Neutrophils release neutrophil extracellular traps (NETs), which represent a last-ditch 'damage-limitation' approach to kill microbes during infection [26] but can also induce toxic collateral damage within the vasculature. As such, NET formation is implicated in the pathogenesis of numerous autoimmune and inflammatory diseases [26–29]. Furthermore, NETs have been demonstrated to contribute to aberrant thrombus development via multiple mechanisms [30,31]. DNA strands within NETs have been reported to capture and contribute to FXII activation [32]. Notably, NET formation can be regulated by different plasma DNAses [33]. Moreover, neutrophil enzymes, including elastase and cathepsin G, can cleave and inactivate plasma TFPI, removing a vital anticoagulant regulator from the proximity of the developing thrombus [32]. Extracellular histones within NETs promote activation of platelets [34] and interact with NET-bound VWF [35]. In addition, extracellular histones inhibit the PC anticoagulant pathway by attenuating activated protein C (APC) generation by the thrombin–thrombomodulin complex on endothelial cells [36]. Therapeutic strategies to inhibit or degrade NETs have also been reported. For example, NET inhibitors that target protein arginine deiminases (PAD4) critical for NET formation exert beneficial activity in preclinical models of arthritis, shifting the T-cell balance from a proinflammatory Th1/Th17 response to a pro-resolution Th2 response [37].

Monocytes and tissue-resident macrophages also contribute to VTE development and monocyte count have recently been reported to correlate with thrombus size and growth in murine thrombosis models [38]. Myeloid cells typically express TF on their surface, and TF expression and activity are up-regulated by exposure to either pathogen-associated molecular patterns or proinflammatory cytokines [39]. In a mouse model of stasis-induced DVT, monocyte TF was critical for initiating DVT formation [40], highlighting the complex and multi-faceted role played by innate immune cells in pathological clot formation.

Coagulopathy during acute infection

Sepsis develops due to a systemic dysregulated immune response to acute infection and accounts for ∼20% of global deaths [41]. The case fatality rate of sepsis has steadily decreased in the past 20 years; however, its incidence is the same or increasing [42–44]. Sepsis is characterised by excessive cytokine production in response to infection, leading to tissue and organ dysfunction [45]. A prominent feature of sepsis is haemostatic dysregulation, thrombocytopenia, and disseminated intravascular coagulation (DIC) [46]. DIC is associated with a worse outcome and higher mortality rate compared with sepsis patients without DIC [47–49].

Aberrant up-regulation of TF expression on circulating innate immune cells and the endothelium upon exposure to proinflammatory stimuli has long been considered an important trigger for DIC [50–52]. Moreover, recent studies have provided a mechanistic basis for cell surface TF release into the blood during bacterial infection, highlighting the crucial role of non-canonical inflammasome formation in modulating TF-rich microparticle release from activated myeloid cells. This mechanism may also be partially conserved in other cell types, such as tumour cells, which also actively release TF-containing microparticles and are associated with increased thrombgenicity [53]. Activation of the canonical or non-canonical inflammasome in macrophages following exposure to *Escherichia coli* EprJ type-III-secretion system rod proteins or LPS, respectively, results in the release of TF-rich microparticles [54]. In this process, pathogen exposure triggers gasdermin D (GSDMD) cleavage by activated caspase-1 and -11 to drive pyroptosis and interleukin-1β (IL-1β) release [54]. It has also been reported that a GSDMD-dependent increase in TF activity

following non-canonical inflammasome activation occurs independently of cell death via increased phosphatidylserine (PS) exposure, aiding in the assembly of the extrinsic tenase complex [55]. By labelling PS on mouse splenic and peripheral blood leukocytes with lactadherin, the study showed increased PS on mouse leukocytes following transfection of LPS and a reduction in exposed PS in *Gsdmd*$^{-/-}$ leukocytes [55]. Furthermore, myeloid cell inflammasome formation has been shown to contribute to VTE development in a mouse inferior vena cava (IVC) stenosis model [56]. Mice with caspase-1 or GSDMD deficiency exhibited smaller and fewer thrombi formation following IVC stenosis compared with wild-type mice, underscoring the potential importance of canonical and non-canonical inflammasomes in immunothrombosis.

Similarly, pathogen and cytokine activation of the endothelium also contributes to a prothrombotic milieu during sepsis. Various cytokines promote the release of long, multimeric chains of ultra-large von Willebrand factor (UL-VWF) on to the endothelial cell surface. UL-VWF binds circulating platelets via platelet glycoprotein Ibα [57] and is typically broken down by the plasma metalloproteinase ADAMTS13 into smaller multimers, reducing VWF thrombogenicity [58]. UL-VWF can act as an adhesive surface to monocytes and polymorphonuclear leukocytes by binding PSGL-1 and β2-integrin [59]. VWF strings decorated with platelets and other immune cells have been suggested to contribute to microthrombi development in DIC. Notably, sepsis patients have lower levels of circulating ADAMTS13 and ADAMTS13 activity [60,61], contributing to sustained VWF strings in the intravascular space. In support of an essential role for ADAMTS13 in regulating VWF thrombogenicity during infection, low ADAMTS13 activity in patients with *Staphylococcus aureus* infections is associated with increased disease severity [62]. NETs formed during sepsis contribute to widespread organ damage [63] and DIC development [64,65] and their presence is reported to be especially deleterious in infant sepsis [66].

Many endogenous plasma anticoagulant proteins and cell receptors are depleted during sepsis, leading to unregulated thrombin activity and fibrin generation. For example, low levels of circulating PC, protein S and antithrombin have been associated with worse sepsis outcomes [67]. To address this, various anticoagulant therapies have been tested to mitigate sepsis-associated coagulopathy, with limited success. Most recently, recombinant APC (Xigris, Eli Lilly) was shown to reduce mortality in severe sepsis patients and was licensed on this basis [68]. Subsequent trials, however, raised questions about the efficacy and safety of APC in this setting and Xigris was eventually voluntarily withdrawn for patient use [69]. Important anticoagulant receptors, such as thrombomodulin (TM) and the endothelial PC receptor (EPCR), are cleaved from the endothelial cell surface under inflammatory conditions. Soluble forms of both receptors are elevated in the plasma of individuals with sepsis [70]. Depleting endothelial cell surface EPCR and TM restricts PC activation, skewing the haemostatic balance towards thrombin generation. Interestingly, individuals with the rs2239562 single-nucleotide polymorphism in the promoter region of the thrombomodulin (*THBD)* gene have been suggested to be more susceptible to sepsis and experience worse outcomes [71].

Recent studies indicate that immune cross-talk has a role in the immunothrombotic state observed in malaria infection. Coagulation dysregulation is commonly observed among malaria patients and represents an often fatal complication of the disease [72]. A recent clinical trial revealed that healthy volunteers injected with low levels of *Plasmodium falciparum* sporozoites exhibited a hypercoagulable state. At detection of parasitaemia, the thrombin generation potential of plasma isolated from infected subjects was 17% higher compared with their baseline measurements [73]. In addition, malaria patient studies and preclinical malaria animal studies support the role of increased endothelial cell activation and UL-VWF secretion, in sequestering infected red blood cells in the microvasculature to promote cerebral vascular occlusion [74]. Taken together, these findings indicate that coagulopathy driven by acute infection arises from aberrant activation of multiple procoagulant mechanisms that are further amplified by inflammation-induced endothelial damage and diminished systemic anticoagulant activity.

The Coronavirus Disease in 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection represents an exemplar model of immunothrombotic disease driven by viral infection. VTE rates among COVID-19 patients are increased compared with healthy individuals [75,76], and COVID-19 causes a unique coagulopathy that can promote microvascular thromboses in the lung vasculature. Retrospective studies indicate that the severity of COVID-19 symptoms and the level of proinflammatory biomarkers in patients with COVID-19 positively correlated with the patient's risk of experiencing VTE [77]. For instance, in a dataset containing 6153 COVID-19 patients, only 0.09% of non-hospitalised COVID-19 patients developed VTE [77], whereas 3.1% of hospitalised patients experienced a VTE, rising to 7.2% of COVID-19 patients who required ventilation [77]. Similarly, in a cohort of 1114 COVID-19 patients, only a small number of thrombotic events were reported in COVID-19 outpatients, whilst the highest rates of thrombotic complications appeared in those COVID-19 patients admitted to ICU [78]. Numerous studies have highlighted potential mechanisms of prothrombotic activity

Clinical Science (2022) **136** 1809–1829
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associated with COVID-19 pathobiology. In severely ill patients, dysregulated inflammatory cytokine release promotes endotheliopathy and innate immune cell dysfunction, driving formation of a prothrombotic milieu [79]. Neutrophils play a critical role in COVID-19-associated coagulopathy. Plasma biomarkers of NET formation correlate with COVID-19 disease severity [80], and neutrophil-platelet aggregates may also contribute to enhanced platelet reactivity in COVID-19 patients [81,82]. Interestingly, patients with severe COVID-19 often exhibit thrombocytopenia, despite having increased generation of megakaryocytes and proplatelet formation. This disproportionate platelet count is likely due to thrombus deposition in multiple vessel beds [29,81].

A persistent immunothrombotic state in COVID-19 patients may also contribute to post-viral syndrome or 'long-COVID', a common feature in COVID-19 patients characterised by fatigue and chronic disease symptoms that can last for weeks and months post-infection [83]. The underlying cause of this fatigue is unclear but may arise in part due to damage to the endothelium arising from chronic hypoxia and inflammation [84]. In support of this, recent data indicate that individuals with 'long-COVID' exhibit a persistent endotheliopathy characterised by dysregulated VWF proteolysis, endothelial dysfunction and the persistence of activated monocyte and T-cell populations [85]. Anticoagulant and anti-inflammatory strategies targeting the inflamed endothelium may therefore provide a novel approach to mitigate symptoms associated with long COVID.

Does the adaptive immune system contribute to immunothrombosis?

Although adaptive immune system cells do not appear to contribute to normal haemostasis, recent work has highlighted a new role for T effector memory (T_{EM}) cells and regulatory T cells (Tregs) in modulating venous clot lysis. Unexpectedly, $CD44^{high}CD62L^{low}CD4^{+}$ and $CD8^{+}$ T_{EM} cells infiltrate the thrombus and vessel wall during DVT in a murine thrombosis model [86]. Infiltrating T_{EM} cells secrete IFNγ, independent of antigen stimulation, and recruit monocytes and neutrophils to the injury site, delaying thrombus resolution. Deficiency in T_{EM} cells enhanced thrombolysis and promoted increased matrix metalloproteinase-9 (MMP-9) expression by monocytes [86]. Previous studies have shown that suppression of MMP-9 in macrophages by T cell, NK cell and innate lymphoid cell-derived IFNγ delays clot resolution [87]. Tregs also play an unanticipated role in mediating efficient clot degradation, and their depletion results in delayed thrombolysis [88]. Furthermore, Treg population dynamics were found to influence monocyte recruitment and differentiation. Following TGFβ stimulation, a Treg subpopulation was found to produce secreted protein acidic and rich in cysteine (SPARC), a matricellular protein involved in cell turnover, tissue remodelling, and ECM repair. $SPARC^{+}$ Tregs were reported to recruit more CD11c+ monocytes to the thrombus with enhanced MMP and fibrinolytic activity [88]. Interestingly, cancer patients undergoing T cell targeted immunotherapies, such as immune checkpoint inhibitors (ICIs), exhibit an increased VTE risk (1.5- to 6.5-fold) [89] and cumulative incidence of VTE (5–10% at 12-month follow-up) [90], which may be due to the increased activity of effector T cells. These data demonstrate an unexpected but potentially important role for T cell sub-populations in modulating clot lysis and resolution.

Why do autoimmune disorders cause an increased VTE risk?

Current estimates report a global prevalence of autoimmune disease in 3–5% of the general population [91], with a recent report highlighting an increasing incidence of 3–9% per year [92]. Notably, increased VTE risk is characteristic of many autoimmune diseases, such as inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and graft versus host disease (GvHD), and often represents a fatal disease complication.

IBD

IBD represents an expanding global healthcare burden affecting many adults and children. Approximately 0.3% of the worldwide population are diagnosed with IBD, with 25% of these cases arising in childhood and adolescents [93–95]. Notably, thromboembolic disease represents the most significant cause of mortality among IBD patients [96], with adult and paediatric IBD patients exhibiting a 3- and 6-fold increased risk of VTE development compared with the general population [97,98]. Yet, the mechanism(s) underlying this prothrombotic state remains unknown. Individuals with IBD are characterised by increased levels of proinflammatory immune cells, such as T cells, innate lymphoid cells, monocytes and macrophages, and cytokines, such as TNFα, IFNγ, IL-1β, IL-17a, IL-36α, IL-18, IL-6 and IL-8 [99–102]. Several plasma procoagulant and anti-fibrinolytic proteins, including PAI-1, fibrinogen, and prothrombin, are elevated during an IBD 'flare', in which symptoms are acutely increased [103–106].

In murine IBD models, TF inhibition is associated with reduced immunothrombotic activity [107]. In addition, increased numbers of procoagulant TF^+ MPs are shed by platelets and leukocytes in IBD patients [108,109]. Interestingly, these MPs also can stimulate neutrophil NETosis [110,111]. As NET density correlates with disease severity [27], targeting NET formation and MP interactions may represent a potential strategy to mitigate against immunothrombosis in IBD patients. Platelet dysregulation and hyperactivity also contribute to the prothrombotic state observed in IBD. Increased platelet activation in IBD patients has been observed, with platelet activation status correlating with disease severity [112,113].

Whereas chronic inflammation disrupts haemostatic balance to promote thrombosis, the ability of many coagulation proteases to modulate cell function, particularly the inflammatory response directly via cell signalling, suggests an additional mechanism by which aberrant coagulation protease activation, or loss of protective anticoagulant signalling responses, can modulate the mucosal immune response. The PC pathway has been implicated as an important regulator of mucosal immunity, regulating the inflammatory responses in the endothelium, epithelium, and innate and adaptive immune cells [114,115]. Transgenic mice with low plasma PC (<5% normal levels) display a constitutively enhanced proinflammatory and prothrombotic phenotype [116], and in the context of IBD, have been shown to develop spontaneous colitis due to increased TNF-mediated intestinal barrier permeability [114]. Colitogenic mice display a reduced capacity for PC activation [115] likely due to decreased EPCR and TM expression in the inflamed microvasculature [114,115]. Accordingly, EPCR-deficient mice exhibit exacerbated disease in DSS-induced colitis compared to wild-type mice [117]. Chronic inflammation may contribute to the increased VTE risk experienced by IBD patients. Interestingly, IBD patients receiving anti-TNF biologics exhibit a reduced risk of VTE compared with those on traditional corticosteroids [118], implicating TNFD-mediated inflammation as a critical feature of increased VTE risk in IBD patients. In contrast, however, other targeted immunobiologics, including ustekinumab, a monoclonal antibody targeting the p40 subunit of IL-12/23, and vedolizumab, a monoclonal antibody targeting the $\alpha_3\beta_7$ integrin, confer a potential risk of severe cardiovascular events to patients, including stroke [119], thrombocytopenia [120] and reduced clot formation time [121].

Graft versus host disease

Incidence of VTE among haematopoietic stem cell transplant (HSCT) patients ranges from 0.5 to 13%, and the occurrence of VTE is typically associated with the development of Graft versus Host Disease (GvHD) [122–129]. In those who develop VTE post-transplant, there is a 65% incidence in GvHD [122]. Furthermore, there is a higher risk of other thrombotic events associated with GvHD severity and donor blood group, with non-O-donor to recipient ABO match exhibiting a 2.7-fold higher hazard ratio of thrombotic complication compared to O-donor to O-recipient match [130]. Transplant-associated thrombotic microangiopathy (TA-TMA) is a common complication of HSCT and is associated with complement activation following an endothelial injury during GvHD [131]. The association between severity of inflammation exposure and risk of thrombosis in GvHD patients is exemplified by the lowered threshold for neutrophil NETosis in GvHD patients and the consequent role in increased plasma hypercoagulability. Paediatric recipients post-HSCT have elevated levels of plasma double-stranded DNA (dsDNA), a surrogate marker for NETs, alongside an increased risk of TA-TMA, onset of gastrointestinal GvHD and mortality [132].

SLE

VTE is a common co-morbidity in patients with systemic lupus erythematosus (SLE), and the risk of its development is commonly associated with the presence of antiphospholipid antibodies (APLA). To date, the most critical APLAs identified to confer thrombotic risk are anticardiolipin antibodies (ACA), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (anti-β2-GPI) [133,134]. Despite this, 40% of SLE patients diagnosed with thrombotic complications are negative for APLAs [133], indicating a multifactorial mechanism for VTE in these patients. SLE patients display endothelial dysfunction, characterised by increased expression of fibrinogen and cell adhesion molecules, ICAM, VCAM, VEGF, and VWF [135].

Furthermore, SLE patients exhibit a reduced capacity to clear neutrophil NETs [136] and an enhanced adaptive proinflammatory cytokine and immune cell profile [137]. Interestingly, β2GPI-reactive $CD4^+$ T cells are hypothesised to drive auto-antibody production in SLE [138], thus amplifying the immunothrombotic environment. Recent work has identified an EPCR-lysophosphatidic acid (LBPA) complex expressed on monocyte cell surfaces as a receptor for APLAs that facilitates their internalisation and subsequent proinflammatory and procoagulant activities [139]. APLAs binding to EPCR-LBPA activate TF-FVIIa-FXa-PAR2 signalling via acid sphingomyelinase TF decryption to promote coagulation. APLA-mediated TF activation also induces IFN production from DCs, promoting the expansion of APLA-producing B1a cells, creating an immunothrombotic loop. Studies using EPCR-deficient transgenic

Clinical Science (2022) **136** 1809–1829
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mice and EPCR-blocking antibodies revealed that EPCR-LBPA deficiency protects against APLA-induced thrombosis and foetal loss, murine SLE and APS [139]. Therefore, therapeutic targeting of this pathway holds promise in regulating APLA autoimmunity and thrombosis.

Allergies

Dysregulation of haemostatic and fibrinolytic activity is evident in many allergic diseases, including chronic spontaneous urticaria (CSU), asthma and dermatitis [140–143]. Still, the inflammatory mechanisms underlying this haemostatic dysregulation, such as elevated soluble TF levels, PAI-1 and thrombin activatable fibrinolysis inhibitor (TAFI) [143] found in asthma patient sputum, are poorly understood. Interestingly, there is a significantly increased risk of pulmonary embolism in asthma patients compared to the general population, linked to the frequency of asthma exacerbation and hospitalisation [144]. In the airways, TF expression is induced by IL-13, one of the major cytokines involved in asthma pathogenesis [145]. In parallel, FX is also implicated in airway dysfunction, and FXa signalling increases airway fibroblast proliferation via the production of autocrine platelet-derived growth factor (PDGF) and procollagen synthesis through PAR1 activation, resulting in airway fibrosis and reduced lung compliance. Accordingly, FXa inhibition with fondaparinux has been shown to alleviate airway pathology in a mouse asthma model [146,147]. Enhanced thrombin activation and reduced levels of APC are also reported in asthma patients [148–150]. Platelet hyperactivity and fibrin deposition all exacerbate asthma, contributing to bronchial hyperresponsiveness, constriction, airway remodelling and inflammation [151]. Similarly, fibrin degradation products (FDPs) contribute to airway dysregulation, promoting leukocyte infiltration, proinflammatory cytokine and PAI-1 release [151–154].

Allergies in the skin, such as atopic dermatitis and contact dermatitis, are chronic inflammatory disorders of the epidermis, affecting up to 10% of adults and 20% of children globally [155]. These conditions are triggered by skin exposure to potential allergens [156], which can induce an exaggerated T cell-mediated immune response [157]. The infiltrating T cells exert cytotoxic effector mechanisms on nearby keratinocytes, thus disrupting the skin barrier and allowing the further invasion of allergens [157]. Like airway inflammation, increased myeloid cell TF expression and activity are associated with skin allergy pathogenesis, and monocytes isolated from CSU patients express significantly more TF activity than healthy controls [158]. Coagulation proteases can also induce degranulation of human skin mast cells and basophils via complement C5a and C5aR, causing edema [159]. Similarly, thrombin and fibrinogen have been shown to play a pathological role in contact dermatitis. Children with contact dermatitis show a correlation between disease severity, transepidermal water loss (TEWL), and total thrombin generation. Inhibition of either thrombin or fibrinogen in preclinical dermatitis models alleviates disease [160], as does treatment with recombinant APC [142]. APC signalling through PAR2 helps clinical signs of disease by inhibiting CD4+ T cell generation and proinflammatory responses [142]. Collectively, these studies highlight an emerging role for dysregulated haemostatic protease signalling function in the development and persistence of allergic skin disease.

Neurodegenerative disease and ageing

Aberrant coagulation pathway activity and signalling have been implicated in the pathogenesis of several neurological disorders. Multiple sclerosis (MS) is an immune-mediated demyelinating and degenerative disease of the central nervous system (CNS) [161]. MS patients have a 2-fold higher VTE risk compared with the general population [162]. Histopathological studies by Putnam in the 1930s reported an increased incidence of thrombi in plaques surrounding the CNS vasculature of MS patients that did not form in response to vessel wall injury but instead due to 'abnormal lability in blood plasma' [163,164]. Since then, MS patients have exhibited increased fibrin deposition around active MS lesions, impaired fibrinolytic activity, high soluble TF levels in the CNS, circulating soluble TM and elevated VWF activity reflective of endotheliopathy [165–169]. These studies indicate that proinflammatory and coagulation pathways are co-activated during MS pathogenesis, and dual targeting of both systems may be beneficial in this setting. In support of this, recent work selectively targeting a cryptic fibrin epitope ($\gamma_{377\text{-}395}$) with a monoclonal antibody (5B8) was beneficial in preventing amyloid-driven neurodegeneration and CNS autoimmunity in preclinical models of MS and Alzheimer's disease (AD) [170]. 5B8 inhibited fibrin binding to CR3, thus suppressing fibrin-induced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, subsequent reactive oxygen species (ROS) release and innate immune-driven neurotoxicity. 5B8 down-regulated expression of genes involved in immune cell recruitment and proinflammatory responses in fibrin-treated bone marrow-derived macrophages and reduced axonal damage, ROS generation, demyelination and $CD11b^+$ cell innate-driven inflammation in EAE [170]. Furthermore, inhibiting fibrin/CD11b interactions with 5B8 reduced loss of cholinergic neurons and microglia activation around plaques in 5XFAD mice and down-regulated critical pathways involved in neurodegeneration and oxidative stress, complement pathway, lysozyme, antigen presentation, cytokine response, and ROS pathway signalling. Significantly, this antibody

did not interfere with normal haemostasis, with no differences reported in fibrin polymerisation *in vitro*, clotting time, or partial thromboplastin time (aPTT) in human plasma treated with 5B8 reported compared to IgG2b-treated plasma controls [170].

Elevated levels of FXII have also been observed in the plasma of MS patients and may contribute to the thrombo-inflammatory state observed in the CNS of affected individuals [171,172]. EAE mice display significantly elevated FXII levels in the plasma, cerebrospinal fluid (CSF), and lymph nodes compared with control mice. FXII deficiency ameliorates disease via inhibition of DC-mediated priming of Th17 cell pathogenic responses [171]. Importantly, mechanistic studies have revealed that FXIIa inhibition inhibits thrombus formation but does not affect haemostasis [4,173,174]. Therefore, inhibiting contact activation may prove a safe method to break the immunothrombotic loop observed in neuro-inflammatory and neurogenerative diseases, without enhancing the risk of bleeding.

The risk of thrombosis increases with age. This is probably influenced by 'inflammaging', which describes the chronic low-grade and systemic inflammation that accelerates during biological ageing and occurs through various mechanisms, including immunosenescent cell generation, increased intestinal barrier permeability, bacterial dysbiosis, and leakage [175,176]. Collectively, these processes combine to induce increased levels of proinflammatory cytokines, chemokines, and immune cells in the vasculature, creating a lower threshold for pro-thrombotic events.

For example, older mice are reported to exhibit higher levels of TNFα in their plasma compared with young mice [177,178] and inflammaging contributes to age-related platelet hyperactivity via exposure to enhanced constitutive levels of proinflammatory cytokines such as TNF in the blood. Following stimulation, platelets from older mice also express increased levels of αIIbβ3 and PS and display an enhanced capacity to form thrombi *ex vivo*. Furthermore, TNF levels are heightened in the bone marrow compartment of older mice [179], suggesting local megakaryocytes will be more susceptible to inflammaging. Interestingly, monocytes have been proposed as the cellular source of TNF in this environment [180]. Monocyte-derived TNF is implicated in the increased platelet count and reactivity observed in older patients with myeloproliferative disorders [181,182]. Enhanced platelet–monocyte interactions result in proinflammatory cytokine production [183], which may be exacerbated by platelet derived-MPs that are also increased in older individuals [184].

Elevated fibrin levels have been observed in AD patient brains post-mortem, and signalling by this protein is linked to Aβ and tau deposition, vascular dysfunction, inflammation, and neurodegeneration [185]. In an open-label study of patients with mild to moderate AD, treatment with the thrombin inhibitor hirudin with donepezil significantly reduced the rate of cognitive decline among patients [186], suggesting that coagulation inhibition may be a novel strategy for mitigating neurodegenerative and neuroinflammatory disease. Furthermore, there is emerging evidence for the role of neutrophils and NETosis in AD pathology. Neutrophils, NETs and NET-associated MPO have been found in plaques surrounding the microvasculature in post-mortem AD patient brains and murine AD models [187,188]. The contact pathway is also implicated in AD pathogenesis. FXII has been detected in Aβ plaques [188], increased plasma kallikrein activity has been observed in the AD brain parenchyma [189], and enhanced levels of HK cleavage in the cerebrospinal fluid in AD patients compared with non-disease controls [190]. *In vitro* studies have found that Aβ can trigger FXIIa-dependent kallikrein activity and kallikrein-mediated cleavage of HK [191–193]. *In vivo* studies have supported these findings, suggesting Aβ plaques can mediate the upregulation of contact activation [194]. Notably, FXII inhibition was beneficial in AD mice, which displayed improved cognitive functioning compared with untreated controls. Furthermore, FXII depletion in AD mice resulted in diminished plasma HK cleavage and reduced fibrinogen deposition, neurodegeneration and neuroinflammation compared with untreated controls [195]. Collectively, these studies indicate that activation of the contact pathway contributes to the vascular and inflammatory dysfunction observed in AD.

Stress and circadian rhythm disruption

Stress is a risk factor for neurodegenerative disease [196,197], metabolic disease [198], cancer [199] and, with particular relevance to this review, thromboembolic disease [200]. Both acute and chronic stress causes a change in the distribution of immune cells between the circulation and tissue [201,202]. Assessment of the effect of stress on hypercoagulability is challenging, and several studies have generated disparate results. Following induction of acute stress by a public speaking task and a mock job interview, individuals exhibited increased plasma levels of D-dimer and VWF [203,204]. A comprehensive acute stress test study analysed multiple plasma coagulation parameters before and after stress. They found significant increases in FVII and FVIII activity and increased VWF and D-dimer levels in acutely stressed individuals compared to unstressed individuals. No significant changes were seen in fibrinogen and soluble TF levels [205]. These studies indicate that acute stress may promote transient changes in plasma hypercoagulability.

Clinical Science (2022) **136** 1809–1829
https://doi.org/10.1042/CS20220208

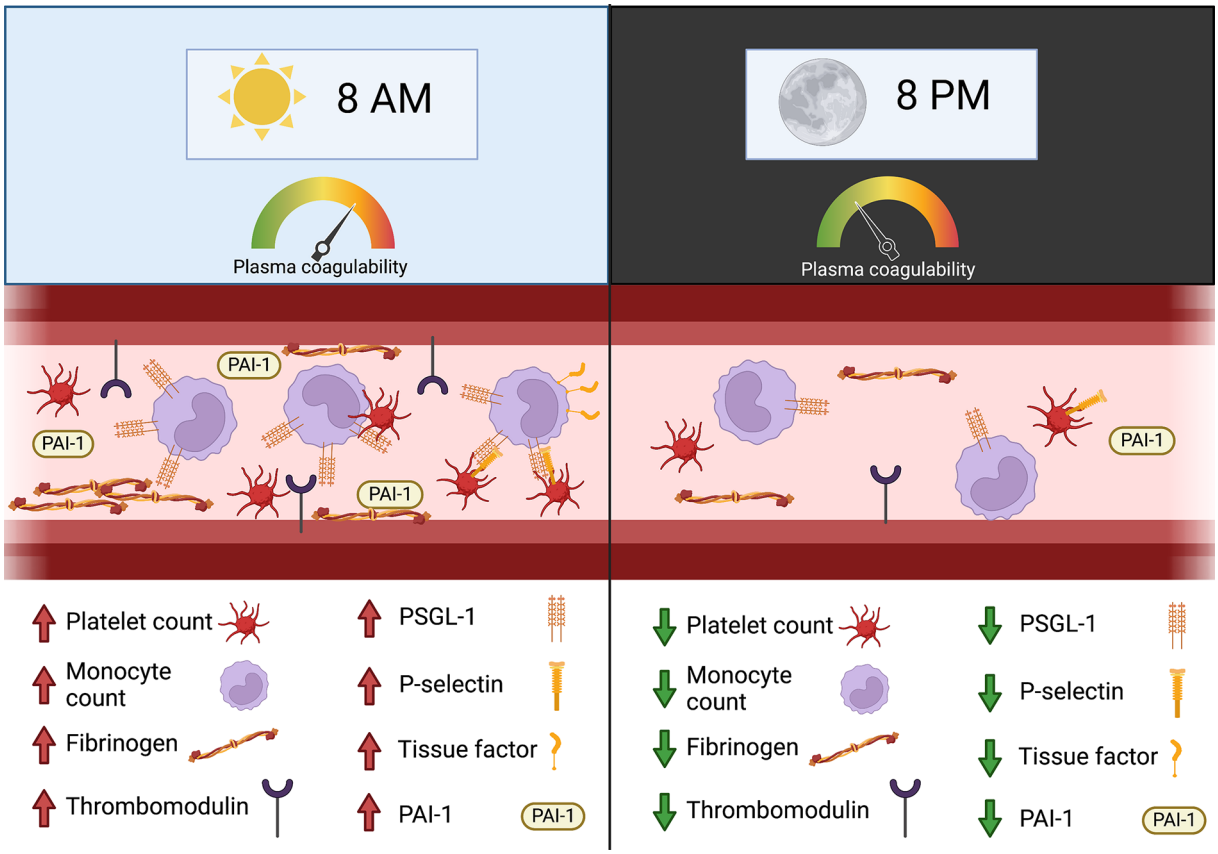

Figure 3. The role of circadian variation in modulating haemostatic activity

Levels of various procoagulant proteins, including fibrinogen and thrombomodulin, as well as fibrinolysis inhibitor PAI-1, vary with time of day, skewing the plasma and vessel surface environment in the morning towards procoagulant activity. Similarly, platelet and monocyte count increase in the morning, as is the expression of pro-adhesive cell surface receptors, such as PSGL-1. This can facilitate monocyte binding to platelet P-selectin to form aggregates, triggering increased TF activity on the monocyte surface. Collectively, circadian variation in plasma coagulation protein levels, innate immune cell number and activity, and vessel surface receptor composition may contribute to observed time-of-day effects on acute cardiovascular disease manifestation.

However, more extensive studies are required to assess the mechanistic basis for these biological changes and their potential long-term impact on other haemostatic parameters [206].

According to the 2021 edition of 'Living and working in Europe' [207] 19% of the EU population worked at least once during the night every month, and 21% were shift workers. Other sources of circadian disruption are social and travel-related jet lag, as well as light pollution. Circadian disruption is now well-established to disrupt normal immune cell function, and emerging data suggest a shared role in the dysregulation of haemostasis (Figure 3). The rhythmic expression of genes associated with coagulation may also contribute to the increased incidence of acute cardiovascular disease in the morning hours of the day [208,209].

Circadian rhythms are controlled by a transcriptional-translational feedback loop present in almost all cell types (for detailed review, see [210]). The positive arm of the loop is controlled by transcription factors BMAL1 and CLOCK, which heterodimerise and drive the transcription of *Per* and *Cry* genes. Once phosphorylated, PER and CRY can re-enter the nucleus and act as transcriptional repressors of the BMAL1/CLOCK heterodimer, making up the negative arm of the loop. This prevents transcription of *Per* and *Cry*, reducing production of the repressors and allowing BMAL1/CLOCK to function again. Another part of the loop is formed by RORα and REV-ERBα. Their transcription is under the control of BMAL1/CLOCK and they drive or repress *Bmal1* transcription, respectively. BMAL1 and CLOCK are active during daytime, while PER, CRY, RORα and REV-ERBα are active during night-time. The complete feedback loop takes 24 h to complete, giving rhythmicity to the cell and any genes under the control of these clock transcription factors, termed clock-controlled genes (CCGs). BMAL1/CLOCK bind to E-box sequences while RORα and REV-ERBα bind to RORE sequences.

Bmal1$^{-/-}$ mice age prematurely and lack the characteristic rhythmic expression of clock target genes [211]. Notably, several coagulation and haemostasis-related genes are CCGs, including *Serpine1* [212], *F7* [213,214], *F12* [214] *and Thbd* [215]. *Bmal1*$^{-/-}$ mice exhibit a prothrombotic phenotype and clot more rapidly in a $FeCl_3$ treatment model [216]. A shifted light schedule in mice also decreased prothrombin time, plasma fibrinogen concentration, and increased bleeding time, illustrating how coagulation changes can be driven by circadian rhythm disruption [214]. It is important to consider that mice and humans exhibit opposing circadian schedules, where mice are nocturnal and humans are diurnal, making human studies important for fully elucidating the role of circadian rhythms in coagulation. In humans, PAI-1, tPA and fibrinogen concentrations in the blood vary over 24 h [217]. PAI-1 is subject to diurnal fluctuation, independent of any day- or night-time associated behaviours [218], suggesting the capacity for thrombus formation and clearance will vary with time of day. Mouse and human neutrophils have been shown different propensities to form NETs based on time of day [219]. Mouse neutrophils isolated at night-time form more NETs than day-time neutrophils, while the opposite is seen in human neutrophils (in keeping with their opposite circadian rhythms [219]. Inflammatory (Ly6C^{hi}) monocytes also contribute to venous thrombus formation [220] and their number is also subject to diurnal oscillations [221]. Platelet aggregation and interactions between neutrophils and monocytes is an integral arm of immunothrombosis, and their activity and distribution are also circadian. Platelet expression of activation surface markers, including GPIIb-IIIa, GpIb and P-selectin, is highest in the morning (8–9 AM). In contrast, the threshold for platelet aggregation is lowest in the evening (8 PM) [222]. Interestingly, the efficacy of the platelet inhibitor Ticagrelor (Brilinta, AstraZeneca) also varies modestly with time of day, with the lowest effectiveness at 1 PM [223]. Circadian nuclear receptor Rev-Erbα has recently been shown to have a role in platelet activation and aggregation [224]. Platelet-specific deletion of Rev-Erbα in mice and pharmacological inhibition of Rev-Erbα in human platelets showed decreased activation and aggregation by light aggregometry assays compared with untreated platelets [224]. The proposed mechanism involves GTPase activating protein Oligophrenin-1 (OPHN1), which is protected from degradation following binding to Rev-Erbα in platelets [224] and the brain [225]. Activated OPHN1 binds and activates GTPase RhoA, which is required for actin remodelling upon platelet activation [226]. Furthermore, mice whose circadian rhythms were disrupted were found to develop larger atherosclerotic lesions using a murine atherosclerotic model in which the mice were exposed to a reversed light/dark schedule. Subsequently, it was found that *Bmal1* expression is altered in the foam cells in those lesions, and foam cells experience increased ER stress compared with mice in normal light conditions [227]. Collectively, these studies highlight the variance in clotting proteins and cellular components at different times of day. These studies also highlight a potential role for time of day in the effectiveness of anticoagulant and antithrombotic drugs.

New anti-immunothrombotic therapies? APC beyond sepsis

APC demonstrates potent anti-inflammatory and cytoprotective signalling properties on multiple cell types [115,228–235]. Nevertheless, APC signalling primarily occurs via activation of protease-activated receptor 1 (PAR1) when APC when bound to the EPCR [236]. Despite the failure of recombinant APC (Xigris, Eli Lily) in the treatment of severe sepsis, multiple studies have demonstrated that APC cytoprotective and anti-coagulant mechanisms can be targeted independently [237], and a variety of APC mutants altered to possess no anticoagulant activity but with cytoprotective signalling-specific activity could prove therapeutically beneficial in several inflammatory disease states. APC has been shown in many preclinical models to modulate thrombo-inflammation via regulation of both innate and adaptive immune cell signalling. For example, administration of exogenous APC ameliorates disease and induces mucosal healing by promoting barrier integrity, inhibiting leukocyte adhesion, a proinflammatory cytokine, and chemokine release in murine colitis models [114,115]. APC administration to a preclinical mouse model of asthma significantly attenuated airway inflammation via decreased neutrophil, DC and eosinophil influx, reduced type 2 cytokine levels, and IgE concentration in BAL fluid. Interestingly, these effects occurred independently of APC anticoagulant activity, indicative of a critical role for its signalling function [232,238,239]. Attempts to treat airway inflammation via FXa inhibition or by limiting TF activity resulted in severe bleeding episodes or haemorrhagic events [240–242], highlighting the challenge of traditional anticoagulant strategies to restrain the proinflammatory signalling activity of procoagulant proteases. In contrast, non-anticoagulant, signalling-selective recombinant APC variants may represent a useful strategy to address allergic airway inflammation. Administration of recombinant APC to DCs *in vitro* alters their population dynamics, shifting the cells from a proinflammatory conventional DC phenotype towards an anti-inflammatory plasmacytoid DC phenotype while simultaneously reducing IL-6 and IL-10 secretion [239]. As such, APC-mediated DC reprogramming renders these cells less effective in priming Th1 and

Clinical Science (2022) **136** 1809–1829
https://doi.org/10.1042/CS20220208

Th2 cells *in vitro* and diminished hyperresponsiveness in an allergic airway challenge *in vivo*. Mice adoptively transferred with APC-treated ovalbumin-pulsed DCs exhibited significantly decreased lung concentrations of Th1 and Th2 cytokines, IFNγ and IL-5, respectively, and lower levels of immunoglobulin E (IgE) in the plasma [239].

APC can also regulate the differentiation and pathogenicity of Th17 cells. Administration of recombinant APC or PROCR deficiency inhibits the generation of Th17 cells *in vitro* and ameliorates Th17 mediated EAE *in vivo* [165,243]. Aside from inhibiting proinflammatory T-cell responses, APC also enhances anti-inflammatory Treg generation and suppressive functioning. Interestingly, administration of recombinant APC ameliorates disease in MS-like experimental autoimmune encephalomyelitis (EAE) [165,168] and APC mutants with either cytoprotective or anticoagulant mechanisms both alleviated EAE disease in mice [165]. Similarly, 3K3A-APC, a recombinant non-anticoagulant APC mutant, exerts therapeutic benefits in clinical models of AD, with reduced Aβ deposition, improved cerebrovascular integrity, and diminished neuroinflammatory responses reported [244]. 3K3A-APC also promotes BBB integrity and prevents neuronal damage during ischemic stroke in pericyte-deficient mice [228]. These studies indicate that APC treatment may benefit neurological conditions associated with pericyte loss, such as AD, dementia, and ageing.

In murine GvHD, pre-incubation of pan T-cell populations with APC before transplantation prevented the induction of disease via PAR-2/PAR-3 signalling, resulting in significantly lower levels of IFNγ, TNFα, and IL-17a plasma cytokines and reduced accumulation of IFNγ, TNFα, and IL-17^{+}CD4^{+} splenic T cells when compared to non-APC treated T cell-recipient mice. Furthermore, APC-treated mice exhibited an enhanced regulatory phenotype with significantly increased numbers of FOXP3^{+}CD4^{+} Treg cells in the periphery, alongside elevated levels of TGFβ and IL-10 in the plasma, compared with control mice. Mechanistic studies *in vitro* revealed a similar trend in human T cells, with APC incubation enhancing Treg generation and expansion, inhibiting Th1 and Th17 differentiation [233]. These studies indicate the potential use of APC in T cell immunotherapy, inhibiting T cell-mediated pathology and associated immunothrombotic effects.

Conclusions

Proinflammatory pathways overlap with and trigger many prothrombotic molecular and cellular activities, including myeloid cell activation, neutrophil NETosis, enhanced platelet reactivity and the release of procoagulant microparticles. Although well-established in sepsis, increased thrombogenicity is increasingly recognised as a common feature in disparate acute and chronic inflammatory disease settings. In addition, dysregulation of immunity caused by standard features of modern lifestyles, such as chronic stress and circadian disruption also unbalances haemostasis and understanding the biological processes underlying these changes represents a significant new challenge. Similarly, whereas an increased risk of VTE in the elderly is well-established, the growing appreciation that this may arise as a by-product of 'inflammaging' epitomises the emerging paradigm of immunothrombosis. Despite the increasing recognition of the prothrombotic nature of inflammatory disease, significant challenges remain in managing affected patients and new therapeutic approaches to curtail the key pathogenic steps described are urgently required.

Data Availability

NA

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRediT Author Contribution

Paula A. Klavina: Conceptualization, Writing—original draft, Writing—review & editing. **Gemma Leon:** Conceptualization, Writing—original draft, Writing—review & editing. **Annie M. Curtis:** Conceptualization, Writing—original draft, Writing—review & editing. **Roger J.S. Preston:** Conceptualization, Writing—original draft, Writing—review & editing.

Abbreviations

AD, Alzheimer's disease; APC, activated protein C; CLR, C-type lectin receptor; CSF, cerebrospinal fluid; DC, dendritic cell; DVT, deep vein thrombosis; EAE, experimental autoimmune encephalomyelitis; IgE, immunoglobulin E; NLR, Nod-like receptor;

Nod, nucleotide-binding oligomerization domain; PAR1, protease-activated receptor 1; PRR, pathogen recognition receptor; PSGL-1, P-selectin glycoprotein ligand 1; RLR, RIG I-like receptor; ROS, reactive oxygen species; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue-type plasminogen activator; VTE, venous thromboembolism; VWF, von Willebrand factor.

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