Under crossfire: thromboembolic risk in systemic lupus erythematosus

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ABSTRACT

Cerebral and cardiovascular ischaemic events are frequent complications of systemic lupus erythematosus (SLE) and constitute primary causes of permanent damage. However, the pathogenic determinants of an increased thromboembolic risk in patients with SLE are only partially understood. Atherosclerosis constitutes a fertile soil for the development of thrombosis and shows disproportionately high prevalence and progression rates in patients with SLE. Antiphospholipid antibodies are independent risk factors for acute thrombosis, but can also prompt long-term vascular inflammation. Aberrant interactions among immune cells and dysfunctions in the deployment of the coagulation cascade have historically less been explored in SLE, but recent evidence suggests they can also play a critical role at the crossroads between inflammation and haemostasis. In this review, we discuss how different pro-thrombotic mechanisms can be prompted by and synergise with SLE-specific pathogenic events and speculate about novel potential directions for research and drug development.

KEYWORDS: systemic lupus erythematosus, thrombosis, thromboembolism, ischaemia, cardiovascular risk, antiphospholipid antibodies, coagulation, protein C, atherosclerosis, innate immunity

KEY MESSAGES

- Patients with SLE have an increased thromboembolic risk
- Antiphospholipid antibodies and accelerated atherosclerosis constitute established risk factors for thrombosis in patients with SLE
- Dysfunctional coagulation cascade and innate immune responses may also promote thrombophilia and inflammation in SLE

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifactorial, autoimmune rheumatic disease with a peak incidence in females during early adulthood. From a pathogenic perspective, SLE results from a wide range of inherited and acquired factors, which combine to disturb the physiological immune response at different levels. Clinically, this complexity is evident from the significant phenotype heterogeneity, which in turn impairs the capacity to develop effective treatments for large numbers of patients. Thus, despite significant advances in the control of the inflammatory manifestations, that are usually identified as hallmarks of the disease, we still lack knowledge of key individual pathogenic mechanisms that link SLE to increased overall mortality and reduced quality of life [1, 2].

Cerebral and cardiovascular ischaemic events are major causes of irreversible damage and death in patients with SLE [3-5]. SLE-associated pregnancy complications and non-cerebrovascular neurological features constitute additional major causes of morbidity and, interestingly, potential manifestations of vascular dysfunction [6, 7]. Patients with SLE show an increased cardiovascular risk and develop thromboembolic events earlier [8-10], compared to age-matched controls from the general population and to patients with other immune-mediated diseases [11, 12]. Furthermore, SLE constitutes an independent risk factor for mortality and impaired recovery after an ischaemic event [4, 13]. Cerebral and cardiovascular events can complicate the underlying inflammatory disease at any time, but the early stages of the disease seem to be associated with a higher age-adjusted risk of vascular complications [14-16]. Nonetheless, the excess prevalence of ischaemic manifestations in patients with SLE increases with time in comparison to control subjects [17]. Arterial ischaemic events are more frequent [18] and occur with an estimated probability of 5.1-8.5% within five years from diagnosis [19]. In addition, venous events are relatively frequent in patients with SLE (five-year probability 3.7-10.3% according to ethnicity [19]), who show a 4.5-12.7-fold increased risk of deep venous thrombosis and a 3.0-19.7-fold increased risk of pulmonary embolism, compared to the general population [20, 21]. The reasons for a disproportionate thromboembolic risk in patients with SLE are only partially understood, but seem to involve different pathogenic mechanisms such as accelerated atherosclerosis, antiphospolipid antibodies (aPL), abnormal interactions between platelets, leukocytes and the endothelium and aberrant activation of the coagulation cascade (**Figure**

1). Aseptic endocarditis and, in particular, Libman-Sacks' endocarditis can affect up to 31% of patients with SLE and constitute additional potential causes of embolism [22]. In this review, we discuss the most recent evidence describing the susceptibility of patients with SLE to the development of thromboembolic ischemic events and speculate about possible future directions for investigation of pathogenic mechanisms and therapeutic intervention.

ACCELERATED ATHEROSCLEROSIS

The rupture of an atherosclerotic plaque is a major cause of thromboembolism and subsequent cardiac, cerebral or limb ischemia. Atherosclerosis has a high prevalence in patients with SLE, according to clinical and post-mortem studies [16, 23]. Potential factors accounting for an increased atherosclerotic risk in patients with SLE include inflammation-induced vessel dysfunction and increased prevalence of conventional cardiovascular risk factors (**Figure 2**) [24, 25]. Disease-specific inflammatory events probably synergise with traditional drivers of atheroma formation and with the side effects of corticosteroids and other treatments.

T-cells are major drivers of SLE pathogenesis [26]. Imbalances between effector and regulatory T-cell functions can account for disease flares and for accelerated vascular injury [27]. However, growing evidence supports a role of innate immunity in impairing the vascular response to flow-related or metabolic stressors in patients with SLE. Interferon alpha (IFNα), in particular, is a hallmark of the antiviral-like inflammatory response that drives disease flares at least in a subset of patients with SLE [28, 29]. IFNα impairs the maintenance tasks of endothelial progenitor cells and favours the local differentiation of macrophages into foam cells [30, 31]. Complement activation may also be associated with endothelial inflammation and subsequent leukocyte recruitment at sites of vascular atherogenic inflammation. Furthermore, complement deposition can be detected in vascular atherosclerotic lesions from patients with SLE [32].

The significance of traditional cardiovascular risk factors seems to vary among different SLE cohorts, possibly reflecting differences in lifestyles among different populations and/or historical changes in treatment strategies. More consistently, patients with SLE show a higher prevalence of hypertension [17], which in turn associates with cardiovascular events, pregnancy complications and

mortality [16, 33, 34]. Diabetes and sedentary habits are also more frequent in patients with SLE, although their specific role in SLE as clinical predictors of atherosclerosis is less clear [16, 17]. Quantitative data on lipid profile in SLE are conflicting and do not clearly support a disproportionate prevalence of hyperlipidaemia in patients with SLE [17, 34]. In contrast, qualitative data indicate a sinister increase in pro-atherogenic oxidised lipoproteins during active disease [35-37], pointing to a major role for inflammation-induced oxidative stress in perturbing lipid metabolism and causing subsequent vascular injury in SLE [38]. In accordance with a unique pathophysiological background, patients with SLE show a distinctive pattern of vascular injury characterised by focal, rapidly growing and highly unstable lesions rather than generalised vessel wall thickening [39-42]. Plaque formation in SLE may represent an accelerated mis-repair response to a primary vascular injury, possibly favoured by concomitant “surges” in cellular and humoral inflammatory mediators (perhaps linked to disease flares) as well as in oxidative stress [27, 40, 43]. In addition, the vascular damage in SLE not only involves large arterial vessels, but also the microcirculation, thus further enhancing the risk of ischemic events [44].

ANTIPHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies are part of the spectrum of SLE-related serological abnormalities and detectable in up to 40% of patients [19]. Clinically significant aPL are those that are persistently positive, i.e. present on two occasions at least 12 weeks apart. Antiphospholipid syndrome (APS) is defined as persistent aPL associated with thrombosis (arterial, venous or microvascular) or pregnancy morbidity according to the International consensus criteria [45]. Catastrophic APS (CAPS) is defined as the simultaneous occurrence of APS manifestations in three or more organs, systems or tissues and confirmed by finding microthrombosis at biopsy [46]. APS occurs in approximately 15% of SLE patients [47] and can also be found in other inflammatory diseases or as a stand-alone disorder (primary APS). CAPS has a 1% prevalence in patients with APS [46]. Routine aPL screening conventionally [45] involves testing for lupus anticoagulant (LA) and measuring the titres of IgG and IgM anticardiolipin (aCL) and anti-beta2-glycoprotein I (aβ2GPI) antibodies. Beta2-glycoprotein I constitutes the main antigenic counterpart of aPL, although other potential ligands

have been identified (**Figure 3**). The physiological role of β2GPI is only partially understood and includes scavenging microparticles and pyrogens from the circulation, trimming the activation of the coagulation cascade and interacting with the endothelium and circulating cells [48, 49]. In particular, *in vitro* studies suggest that Toll-like receptor (TLR) 4 and annexin A2 (a phospholipid-binding protein involved in endothelial activation and in the regulation of the coagulation cascade), possibly through reciprocal interactions, behave as β2GPI cell surface receptors and promote activation of the endothelium as well as of circulating leukocytes and platelets [50]. TLR 1, 2, 6 and apolipoprotein E receptor 2 might also redundantly recognise β2GPI on the cell surface [50-52].

Antiphospholipid antibodies can bind to different epitopes on the pentameric tridimensional structure of β2GPI. Domain I of β2GPI contains the immunodominant epitope for clinically relevant aPL. However, this epitope is only exposed when β2GPI binds to anionic surfaces, losing its default closed circular conformation and enabling antibody binding [49]. Among the non-criteria aPL, anti-annexin A5 (AnxA5) antibodies have also been detected in patients with APS [53]. AnxA5 forms organised structures on surface phospholipids, providing an anticoagulant shield against tissue factor (TF)-dependent coagulation progression [50]. Anti-AnxA5 antibodies might interfere with this mechanism, thus favouring thrombosis, but their clinical significance is controversial [54]. Antibodies targeting prothrombin or the phosphatidylserine-prothrombin complex (aPS/PT) may show better promise as diagnostic and prognostic markers in APS. In particular, aPS/PT appear to be associated with increased thrombotic risk [55-58], SLE-related neuropsychiatric manifestations [59] and pregnancy morbidity [57, 60, 61]. The pathogenic mechanism underlying these clinical manifestations is also unknown. Recently, following previous evidence of impaired protein C activity in association with aPL positivity and APS [62-66], anti-protein C antibodies have been added to the APS serological repertoire [67].

Thromboembolic events do not occur in all persistently positive aPL patients. In fact, though aPL induce a prothrombotic environment, additional factors are required to trigger and sustain activation of the coagulation cascade leading to thromboembolic events. Constitutional variables include congenital abnormalities in coagulation factors or acquired pro-thrombotic conditions such as neoplasia. Situational, environmental or host-related factors such as infections, traumas, ongoing

surgery, pregnancy, exogenous estrogens, smoking and flares of an underlying inflammatory disease can provide the so-called *second hit* for aPL-mediated progression to thrombosis. Endothelial priming plays a crucial role in the recruitment of clotting factors. Inflammatory stimuli such as lipopolysaccharide (LPS) are able to provide this initiating input. Interestingly, LPS-induced upregulation of TLR4 favours β2GPI docking to the vessel walls, possibly also enhancing aPL/β2GPI binding [50]. Linearization of β2GPI and exposure of domain I is another rate limiting step in the pathogenesis of aPL-induced thrombosis. Oxidation might play a role in this setting [68] as oxidised β2GPI is bound more strongly by aβ2GPI *in vitro* [69]. Accordingly, patients with APS at higher clinical risk show increased levels of oxidised β2GPI, higher titres of anti-domain I antibodies and higher markers of oxidative stress [70]. Complement is also crucial to foster endothelial as well as platelet and leukocyte activation towards thrombosis [71]. Thrombotic microangiopathy (TMA), characterised by extensive endothelial injury, decreased coagulation factors and platelet levels, traumatic haemolysis and multi-organ injury, constitutes an extreme phenotype in the spectrum of deranged complement activation and can be part of the clinical manifestations of APS [72].

Acute thrombosis represents the most devastating manifestation of aPL in patients with APS, with or without SLE. However, mechanistic studies suggest that aPL also promote long-term vessel remodelling [55, 73]. These pathogenic events have a prominent role in aPL-related nephropathy [73, 74], which can account for up to 14% of cases of SLE with renal involvement and eventually cause nephrovascular hypertension [75]. Furthermore, chronic aPL-induced vascular injury is a potential co-factor in the development of atherosclerosis in patients with SLE [31]. Similar to patients with SLE [76], patients with APS also show an IFN-mediated impairment of endothelial turnover which might promote plaque destabilisation [77].

PLATELETS, LEUKOCYTES AND THE ENDOTHELIUM

Endothelial cells, leukocytes and platelets interact productively to ensure vessel integrity. These first line innate immune cells sense the presence of potential septic or non-septic threats within the circulating blood and activate a complex set of stereotyped responses, which in turn promote inflammation and thrombosis [78, 79]. Platelets, in particular, are involved in a wide range of

inflammatory tasks beyond their most obvious role in haemostasis (**Figure 4**). After recognition of invading pathogens through innate (TLR) or adaptive (Fcγ,εR) immune receptors, platelets promote endothelial and leukocyte activation locally, through direct cell-cell interactions, or systemically, due to release of microparticles. Platelet-derived microparticles (PMP) are shed from platelet cell surface following activation and constitute the bulk of circulating microparticles in humans [80]. Constitutive activation of platelets and persistently high levels of PMP are thought to characterise autoimmune diseases and affect disease activity, vessel integrity and thrombotic risk [81-84]. Platelets further contribute to long-term vessel remodelling by releasing growth factors and mitogens [85].

Platelets may have a fundamental role as inflammatory partners of neutrophils [86]. In fact, platelets can trigger neutrophil activation, extend neutrophil lifespan and prompt the generation of neutrophil extracellular traps (NETs) [87, 88]. These aggregates of decondensed chromatin concentrate high amounts of crucial autoantigens for the pathogenesis of SLE and coagulation triggers such as TF or von Willebrand factor (vWF) [89]. NETs further contribute to thrombosis by neutralising tissue factor pathway inhibitor (TFPI) and activating factor XII [90]. Recently, a non-canonical mechanism of vascular occlusion due to uncontrolled NET formation has been described [91]. Interestingly, this phenomenon was dependent on DNAses, which are preferential SLE autoantigens [92]. Neutrophils from patients with SLE have also been shown to undermine endothelial integrity under inflammatory conditions and to contribute to atherosclerosis by enhancing cholesterol-induced innate responses and by promoting IFNα production [31, 93-95]. Deranged platelet-leukocyte interactions and/or NETosis are also detectable in rheumatoid arthritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, APS and even diabetes, which all share an enhanced thrombotic risk [96-98]. Intriguingly, aPL induce NETs, which in turn are also able to promote thrombin generation. This phenomenon is apparently more evident with aβ2GPI and is dependent on the formation of reactive oxygen species and on platelet/endothelial TLR4 [99]. Conversely, heparin contrasts the formation of NETs [100]. NETs have also been detected within coronary thrombi and can contribute to plaque destabilisation in atherosclerosis [101].

The activation of the endothelium is a pivotal pathogenic event at the crossroads between inflammation and thrombosis, as it involves the expression of leukocyte adhesion molecules such

as P-selectin and, later on, E-selectin, vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecules (ICAMs) as well as coagulation triggers such as TF and vWF. Furthermore, similar to platelets and other circulating cells, the endothelium is endowed with the ability to release signalling quanta through microparticles and has a major role in the control of the vascular tone. Endothelial activation and vasomotor dysfunction, possibly favoured by IFNα-prominent responses, are hallmarks of SLE and may account for part of the SLE-related cardiovascular risk [76]. Moreover, endothelium-derived microparticles (EMP) constitute the prevalent microparticle subset in patients with SLE and can promote dendritic cell activation and NETosis [83, 102].

DYSFUNCTIONAL COAGULATION CASCADE

Clinical and biological evidence suggests the existence of extensive connections between haemostasis and inflammation [90]. Thus, not surprisingly, alterations in the deployment of the coagulation cascade constitute a distinctive feature of patients with inflammatory diseases such as SLE (**Figure 5**) [81, 103-105]. Enhanced activation of TF pathway can, intuitively, be linked to increased inflammation-induced TF expression on endothelial cells, neutrophils, eosinophils and other cells [89, 101] and has been consistently detected in SLE [106]. However, impaired TFPI function has also been proposed as a potential pro-thrombotic mechanism in patients with SLE and in patients with APS. Circulating TFPI levels are affected by disease activity [105, 107] and by the generation of NETs [90]. In addition, TFPI can be inhibited by aβ2GPI [108]. Nonetheless, conflicting results have been reported on TFPI concentrations in SLE under resting conditions in comparison to healthy subjects [105, 107, 109]. In addition to TFPI, the plasmin system and the thrombomodulin/protein C/protein S system concur to physiologically regulate the coagulation cascade. Activation of protein C during the coagulation cascade is crucial to counterbalance the prothrombotic effects of thrombin generation, with factor Va and VIIIa inactivation by activated protein C (APC) effectively preventing thrombin formation [110]. Interestingly, in addition to its role as an anticoagulant, protein C is also an anti-inflammatory mediator. APC exerts an endothelial protein C receptor (EPCR)-dependent cytoprotective effect on the endothelium (as well as on

glomerular podocytes), through cleavage of protease activated receptor 1 [111]. Furthermore, it inhibits the formation of NETs [112].

Thrombin generation (TG) via the TF pathway is integral to the blood coagulation process and TG analysis provides a global measure of coagulation dynamics and an individual's thrombogenic potential [113-115]. Two studies reported that generation of thrombin in SLE patients under platelet-free conditions was either delayed [103] or less extensive [104] than in controls, which apparently contrasts with the increased thrombotic risk of these patients. Notably, in the latter study the results were not affected by the aPL profile, thus ruling out an exclusive LA effect and supporting the idea that multiple biological factors might account for the unique SLE haemostatic phenotype [104]. By contrast, Pereira et al. took into consideration the amount of PMP in platelet-free plasma and found that TG was dependent on PMP. In addition, the levels of PMP correlated with the ability of plasma to generate thrombin. Since patients with SLE had higher concentrations of circulating PMP, they also showed a higher endogenous thrombin potential (ETP) [81]. More recently, Arachchillage et al. demonstrated that high-avidity anti-protein C antibodies were associated with greater resistance to both endogenous and exogenous protein C and with a severe APS thrombotic phenotype (defined as the development of recurrent VTE while patients were receiving therapeutic anticoagulation or both venous and arterial thrombosis), suggesting their potential use as prognostic markers in APS [67].

Besides APS, acquired APCr has also been reported in SLE. In particular, Oosting and colleagues described the ability of some aPL extracted from patients with SLE to dampen APC-mediated inactivation of activated factor V with variable dependency on the presence of protein S [62]. Nojima et al. later reported a 34.4% prevalence of acquired APCr in patients with SLE and found a strong association with venous thromboembolism and with coexisting LA and anti-prothrombin antibodies [65]. The same group also described additional associations with aPS/PT, aβ2GPI and anti-protein S antibodies [63, 64]. Little is known about the role of anti-protein C antibodies and APCr in SLE.

Besides being favoured by inflammation, the generation of thrombin, in turn, affects the activation state of a wide range of cells involved in inflammation, such as the endothelium, circulating

platelets and even mast-cells [116-118]. Thrombin is also able to bypass the conventional ways of initiation of the complement cascade and to favour the generation of C5a and C5b [119]. High levels of anaphylotoxins, such as C5a, affect the activation status of the endothelium, platelets and leukocytes, ultimately promoting thrombosis through the expression of TF and increasing vascular permeability. Thrombin-induced shredding of C5 also leads to the formation of the complement membrane attack complex, which either causes direct endothelial damage or promotes long-term inflammation through its inactive form [120]. Accordingly, anticoagulation prompts substantial changes in complement activation status [121]. Similarly, C1 inhibitor (C1INH), one of the main physiological regulators of the complement cascade can also inhibit the coagulation system [122]. Patients with SLE and thrombotic events constitutionally show reduced C1INH – activated factor XII complexes, suggesting the presence of disease-related alterations in the activation of the contact system [123]. The presence of shared activation pathways between the coagulation cascade and other key cellular of humoral players in the pathophysiology of SLE suggests that imbalances in haemostasis could, epiphenomenally, represent or pathogenically affect SLE-related manifestations other than overt thrombosis.

CLINICAL IMPLICATIONS

Tools for ischaemic risk assessment in SLE

The Framingham risk equations are widely used to estimate the 10-year risk for coronary artery disease, stroke or cardiovascular disease in the general population. With respect to the general cardiovascular outcome, age, gender, history of smoking or diabetes, systolic blood pressure and antihypertensive treatments, total cholesterol and high-density lipoprotein levels constitute relevant predictive variables [124]. However, cardiovascular risk estimate according to traditional factors fails to capture the whole population of patients with SLE that will eventually develop a cardiovascular event [125]. Accordingly, attempts have been undertaken to integrate SLE-specific clinical parameters of potential relevance for thromboembolic diseases into the Framingham core of risk factors. A score combining antiphospholipid-related with conventional cardiovascular risk factors has been developed in APS and validated in small cohorts of patients with SLE and APS. In

particular, the Global Anti-Phospholipid Syndrome (GAPSS) score takes into consideration the presence of arterial hypertension, hyperlipidaemia and positive serology for aCL, anti-β2GPI, LA and/or anti-PS/PT [126]. Similar algorithms, which also consider disease activity markers, have been developed retrospectively in large SLE cohorts, but only partially validated [127, 128]. Recently, Urowitz et al. reported that assigning double values to each Framingham item, consistently predicts the development of coronary artery disease in patients with SLE [129]. Currently, there is no SLE-specific score for assessing the risk of venous thromboembolism [130]. Genetic determinants of increased thrombotic risk seem to affect the risk of venous events independently [131], while acquired factors such as cancer, renal failure or aPL (especially LA) might play a synergistic role in SLE, suggesting that patients with those comorbidities should be assigned to a high-risk category [21, 130, 132].

Current status and perspectives for therapeutic interventions

Taken together, the data so far presented confirm that heterogeneity is a hallmark of the pathogenic events that underlie the development of SLE and in particular of its cardiovascular complications. There is a notable lack of prospective trials aimed at assessing the potential benefit of specific interventions for preventing the development of ischemic complications in SLE. A trial on the role of pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, in vascular prevention in SLE is ongoing (NCT02338999). More consistent evidence has been acquired on the role of anticoagulants in patients with APS. In particular, according to the available data, patients with thrombotic APS generally require lifelong anticoagulation [133-135]. Warfarin has long been the mainstay of treatment in this setting. However, the recent RAPS trial reported that in APS patients with venous thromboembolism and a target INR range of 2.0-3.0, rivaroxaban, a direct oral anticoagulant (DOAC), might offer the potential to be an effective, safe and convenient alternative to warfarin [136]. However, since the RAPS study employed a surrogate laboratory marker of pharmacological efficacy and did not met the primary endpoint (less than 20% inferiority in reduction of the endogenous thrombin potential, compared to warfarin), further clinical trials with clinical end points would aid in defining the role of DOACs in APS. Despite the advances in the setting of APS,

there is still a significant area of uncertainty with respect to the treatment of both criteria as well as non-criteria APS manifestations such as aseptic endocarditis [133]. In addition, little is known about the optimal strategies to combat the most severe manifestations of APS, such as CAPS and TMA [46, 137]. In the acute phase of CAPS, removal or neutralisation of pathogenic autoantibodies can be achieved by plasma exchange or intravenous immunoglobulins in addition to glucocorticoids and alternatively to conventional immunosuppressants [137]. Rituximab could play a role in maintaining remission and improving survival in the long-term [138]. Similar strategies can be employed for refractory thrombotic APS [134]. Intravenous immunoglobulins, or the anti-C5 antibody eculizumab, can be useful in complement-driven conditions such as TMA. Novel therapies including decoy β2GPI domains have also been proposed [50, 134]. According to a recent meta-analysis, aspirin has a clinically relevant prophylactic role in patients with SLE who are asymptomatic carriers of aPL [139].

Anti-malarials such as hydroxychloroquine constitute the backbone treatment for patients with connective tissue diseases and have a robustly established role in SLE to increase overall survival and prevent disease flare. In addition, anti-malarials might reduce low-density lipoprotein levels [140] and (especially in combination with low-dose aspirin [141]) have a protective effect against thrombosis in SLE and APS although the evidence at this regard is at least in part conflicting [142, 143].

Given the increased prevalence of traditional cardiovascular risk factors in SLE, aggressive control of hypertension, lipid profile, diabetes, smoking and other lifestyle habits might be rewarding. Preliminary data from large inception cohorts apparently confirm this idea [17]. Statins constitute the mainstay of treatment in dyslipidaemic patients at increased risk of atherosclerosis. Furthermore, statins might also exert non-metabolic, immunoregulatory effects such as enhanced T-regulatory function or reduced oxidative stress in monocytes besides protection from atherosclerosis [144-147]. Statins may also behave in synergy with anti-malarials to dampen IFNα-related responses [148]. Similar pleiotropic effects have also been observed with metformin, a widely used antidiabetic drug [149].

However, these agents have probably limited effect on the main pathogenic drivers of the disease [150], which also probably comprise a constellation of possible concurring events. The

presence of pathogenically-distinct subsets of patients in the clinical landscape of SLE [28], highlights the need for individualised treatment approaches.

CONCLUSION

Patients with SLE have a disproportionate thromboembolic risk throughout their life. Deranged intravascular and systemic immune homeostasis probably synergise with the side-effects of drugs and with traditional cardiovascular risk factors to promote long-term vascular injury and acute thrombosis. The spectrum of potentially concurring factors in this setting is extremely broad and only partially understood as each patient with SLE represents a unique combination of multiple pathogenic events. Therefore, individualised patient-tailored treatments, possibly based on the prevalent pathogenic profile, constitute the most promising strategy for the future.

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FIGURE 1: main pathogenic determinants of thromboembolic risk in SLE

Accelerated atherosclerosis, antiphospolipid antibodies (aPL), abnormal interactions between platelets, leukocytes and the endothelium and aberrant activation of the coagulation cascade account for increased thromboembolic risk in patients with SLE.

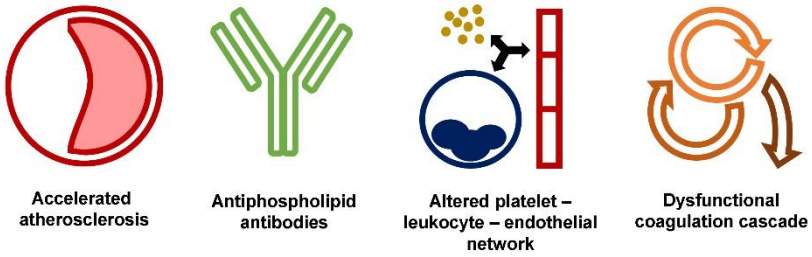


FIGURE 2: factors involved in accelerated atherosclerosis in SLE

Deranged immune responses promote endothelial activation and facilitate the extravasation of leukocytes. Monocytes respond to the accumulation of oxidised lipid products within the vessel walls and disrupt the physiological architecture of their inner layers. This process is potentially favoured by unbalanced T cell activation as well as by an interferon-enriched environment and can occur over short periods of time during disease flares. Interferon responses also account for impaired endothelial turnover and endothelial dysfunction in patients with SLE. Conventional cardiovascular risk factors further promote the development of atherosclerosis in SLE. Antiphospholipid antibodies (aPL) also promote chronic atherosclerotic lesions besides prompting thrombosis.

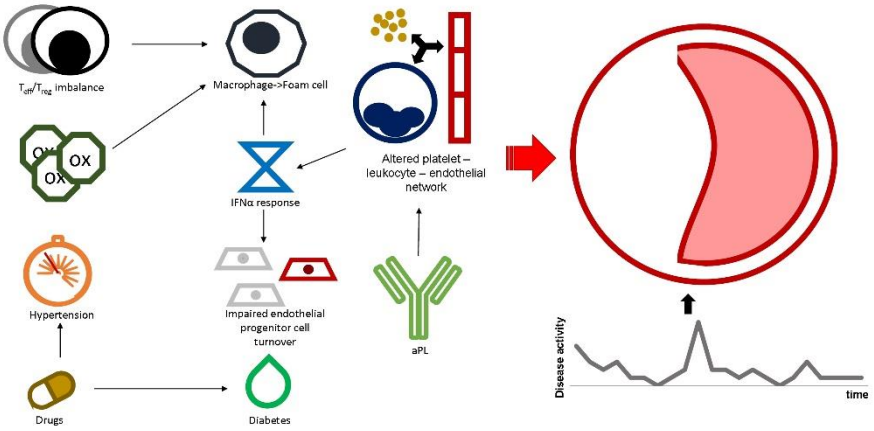


FIGURE 3: pathogenic effects of antiphospholipid antibodies

Antiphospholipid antibodies (aPL) jeopardise physiological haemostasis through several mechanisms, which include facilitation of the coagulation cascade, activation of the endothelium and promotion of long-term vessel remodelling, complement activation, recruitment of inflammatory cells and inhibition of the scavenger, antinflammatory or antithrombotic properties of their antigenic targets. Most aPL recognise the linearised form of beta 2 glycoprotein I (β2GPI) as their ligand and affect cellular activation through Toll-like receptor (TLR)1,2,4 and 6, annexin (Anx) A2, apolipoprotein E receptor 2 (ApoER2) and other yet unknown receptors. Nonetheless, other antigens such as phosphatidylserine/prothrombin complexes or annexin A5 (AnxA5) might be relevant target for aPL.

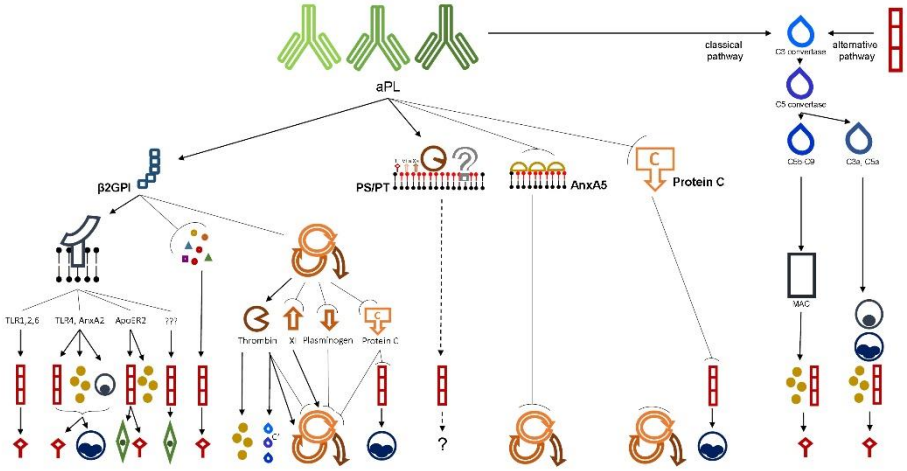


FIGURE 4: platelet-leukocyte-endothelial interactions in SLE

Upon activation, neutrophils are able to promote thrombosis by expressing tissue factor and by generating neutrophil extracellular traps (NETs). The activation of neutrophils can be induced by several stimuli, including interactions with activated platelets by cell-cell contact or by microparticles (yellow dots). Interferon alpha can also promote NETosis and affect endothelial turnover. The endothelium also plays a crucial role in triggering coagulation through tissue factor and by providing leukocytes with the access to tissues. Besides exerting a role in the control of local inflammation and haemostasis, the endothelium can also extend its functions systemically, through microparticles (red dots).

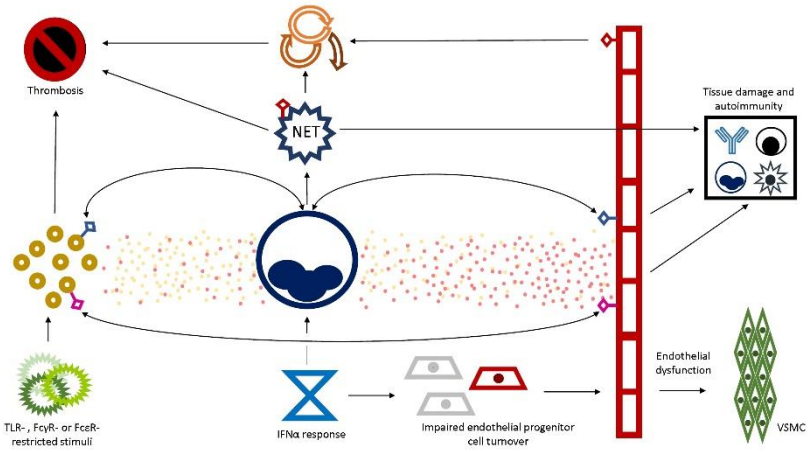
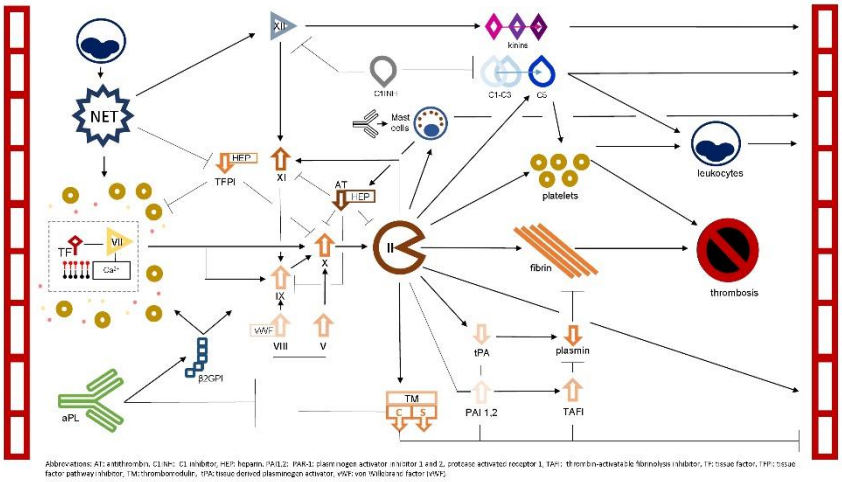


FIGURE 5: the coagulation cascade in SLE

An active interplay links the coagulation cascade with inflammation in SLE. Inflammation induces the expression of TF on the endothelium and on circulating platelets, leukocytes, platelet-derived and endothelial-derived microparticles (yellow and red dots respectively). NETting neutrophils constitute additional sources of TF, activate factor XII and neutralise TFPI. TF, in combination with phospholipids (provided by activated cells), activated factor VII and calcium, constitutes the main trigger of the coagulation cascade *in vivo*. Thrombin can interact with multiple cellular and humoral immune mediators, including complement. SLE can impair the regulation of the coagulation cascade at different levels including TFPI and protein C.



Abbreviations: AT: antithrombin, C1-INH: C1 inhibitor, HEP: heparin, PAI1,2: PAR-1: plasminogen activator inhibitor 1 and 2, protease activated receptor 1, TAFI: thrombin-activatable fibrinolysis inhibitor, TF: tissue factor, TFPI: tissue factor pathway inhibitor, TM: thrombomodulin, tPA: tissue derived plasminogen activator, vWF: von Willebrand factor (vWF).