The dual role of innate immunity in the antiphospholipid syndrome

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Abstract

The antiphospholipid syndrome (APS), as both a primary syndrome and a syndrome in association with systemic lupus erythematosus (SLE), can be a devastating disease. It is unclear what factors (genetic and/or environmental) lead to the generation of antiphospholipid antibodies (aPL). It is equally unclear why only certain individuals with aPL develop clinical events. We hypothesize that innate immune activation plays a critical role at two distinct stages of APS, namely, the initiation phase, in which aPL first appear, and the effector phase, in which aPL precipitate a thrombotic event. According to the model we propose, aPL alone are insufficient to cause thrombosis and a concomitant trigger of innate immunity, e.g. a toll-like receptor (TLR) ligand, must be present for thrombosis to occur. Here, we discuss our findings that mice immunized with β_2 -glycoprotein I (β_2 GPI) and lipopolysaccharide (LPS), a TLR ligand, produce high levels of aPL and other SLE-associated autoantibodies, and develop lupus-like glomerulonephritis. We also discuss our data showing that autoantibodies to heat shock protein 60 (HSP60), an 'endogenous TLR ligand', promote thrombus generation in a murine model of arterial injury. Thus, both pathogen-derived TLR ligands (e.g. LPS) and endogenous TLR ligands (e.g. HSP60) may contribute to the pathogenesis of APS. This putative dual role of innate immunity provides new insight into the generation of aPL as well as the enigma of why some individuals with aPL develop APS, while others do not.

Keywords

antiphospholipid syndrome; β_2 -glycoprotein I; heat shock protein 60; innate immunity; lipopolysaccharide; toll-like receptor ligands

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Introduction

The antiphospholipid syndrome (APS) is classified clinically by the presence of: (1) a laboratory abnormality (antiphospholipid antibodies, aPL); and (2) a clinical event (vascular thrombosis and/or complication of pregnancy).¹ aPL are found in approximately 20–30% of patients with systemic lupus erythematosus (SLE), and are the major autoantibodies in patients with primary APS.^{2,3} APS, both as a primary syndrome and as a syndrome secondary to SLE, can be a devastating disease with significant morbidity and mortality. It remains unclear what factors (genetic and/or environmental) lead to the generation of aPL. Equally unclear is the reason only certain individuals with aPL develop clinical events.

The major evidence that aPL are pathogenic comes from murine models in which passive transfer of aPL results in an adverse event, such as fetal resorption.⁴ These models, however, often lack physiological relevance and fail to address the question whether aPL are the sole etiological factor in causing the clinical event. Moreover, most current APS models provide little insight as to how and why aPL arise in the first place. We have recently developed a murine model of SLE, in which mice produce high levels of aPL and other SLE-associated autoantibodies.⁵ These mice develop lupus-like glomerulonephritis, but, despite high aPL titers, do not develop overt thrombotic events. This SLE-like model not only replicates the sequential emergence of autoantibodies observed in human SLE,⁶ but also approximates the prevalent clinical scenario of an SLE patient who manifests high-titer aPL without thrombotic events.^{2,3} This scenario (in both human and murine disease) begs the question of what additional factors are necessary to induce thrombotic events.

Several studies support an important role for innate immune activation in the pathogenesis of APS. *In vitro*, antibodies to β_2 -glycoprotein I (β_2 GPI) were shown to bind to endothelial cells and induce MyD88-dependent nuclear factor- κ B (NF- κ B) translocation, resulting in an endothelial cell phenotype similar to that elicited by lipopolysaccharide (LPS).⁷ Similarly, in monocytes, anti- β_2 GPI antibodies triggered NF- κ B translocation, leading to a proinflammatory and procoagulant monocyte phenotype.⁸ β_2 GPI has been shown to interact with annexin A2 on both endothelial cells^{7,9} and monocytes.^{8,10} In the case of monocytes, at least, membrane association of β_2 GPI is with both annexin A2 and toll-like receptor 4 (TLR4), and it appears to occur within lipid rafts.⁸ *In vivo*, in a rat model of mesenteric arterial thrombosis, human polyclonal anti- β_2 GPI antibodies lacked a procoagulant effect, while anti- β_2 GPI antibodies combined with LPS resulted in thrombotic occlusion.¹¹ The latter findings are consistent with another *in vivo* model of thrombosis, which showed that mice receiving aPL antibodies produced thrombi only if subjected to a physical ‘pinch injury’. Together, these data suggest that innate immune activation may be required for aPL to exert their pathogenic effects.¹²

Based on the literature and our own data, we hypothesize that innate immune activation plays a dual role in the pathophysiology of APS, and that innate immune activation is necessary both for initiating the production of aPL and for precipitating a thrombotic event. According to the model we propose, aPL alone are insufficient to cause thrombosis and, for a thrombotic event to occur, there must be a concomitant trigger of innate immunity (e.g. a

TLR ligand). This review will address the dual role of innate immune activation in both the 'initiation' and 'effector' phases of APS.

Overview of innate immunity

TLRs and TLR ligands

The discovery of TLRs and their respective ligands has been critical in elucidating the mechanisms by which microbes and their products activate innate immunity.¹³ Ten (human) and 13 (murine) TLRs have been identified, along with their respective ligands. TLRs recognize their ligands by binding to a number of highly conserved pathogen-associated molecular patterns (PAMPs). These include a variety of microbial peptides, LPS, lipoteichoic acids, bacterial DNA, and viral single- and double-stranded RNA. TLR recognition of PAMPs triggers intracellular signaling pathways that result in activation of several key transcription factors, especially NF- κ B, activator protein 1 (AP-1), and members of the interferon regulatory factor (IRF) family. Much signaling occurs through the adapter protein MyD88, but some TLRs (e.g. TLR4) also trigger MyD88-independent pathways.¹³

TLR signaling leads to innate immune activation, which can, in turn, result in an inflammatory response. Upon activation, tissue-resident macrophages release proinflammatory cytokines (tumor necrosis factor- α [TNF- α], interleukin-1 beta [IL-1 β], and interleukin-6 [IL-6]) that coordinate both local and systemic inflammatory responses.¹⁴ TNF- α and IL-1 β activate the local endothelium, inducing vasodilation and increased vascular permeability. The activated endothelium expresses increased levels of tissue factor, leading to local activation of the coagulation cascade. Together, IL-1 β and IL-6 activate hepatocytes to produce a number of acute phase proteins, including complement, that further amplify the innate immune response.

Endogenous TLR ligands

There is increasing evidence that TLRs may also be involved in sterile injury (i.e. injury in the absence of infection). Certain TLRs, especially TLR4, respond to endogenous molecules that are released from injured or stressed tissues.¹⁵ Moreover, TLR4-deficient animals exhibit reduced inflammation in *in vivo* models of injury, suggesting that TLR4-mediated signaling results from sterile injury.¹⁵ Endogenous TLR4 ligands that could result from tissue injury include heat shock proteins (HSPs), fibrinogen, and heparan sulfate.^{15,16} Together, these data indicate that TLR activation may occur in the absence of overt infection and support an emerging paradigm for TLR4 as a sentinel to detect tissue damage.¹⁵

Link between innate and adaptive immunity

TLRs are expressed on multiple cells of the innate immune system, including macrophages, dendritic cells (DCs), neutrophils, mucosal epithelial cells, and endothelial cells. These receptors not only alert the immune system to infection but also initiate and facilitate adaptive immune responses. Among its many effects, TLR signaling induces up-regulation of both major histocompatibility complex class II (MHC II) and costimulatory (CD80/CD86) molecules on DCs, and promotes migration of DCs to the nearest lymph node.

Through these and other activities, the innate immune response provides a link between innate and adaptive immunity.

Hypothesis: dual role of innate immunity in APS

We hypothesize that innate immunity contributes critically to the pathogenesis of APS in two distinct phases: (1) an ‘initiation (or immunologic) phase’ and (2) an ‘effector (or pathologic) phase’ (Figure 1). During the ‘initiation phase’, the role of innate immunity is to amplify the adaptive immune response (e.g. to phospholipid-binding [PL-binding] proteins such as β_2 GPI), resulting in the long-lived production of aPL and other SLE autoantibodies. Subsequently, during the ‘effector (or pathologic) phase’, the role of innate immunity is to enhance the prothrombotic effects of aPL via priming of the vascular endothelium (e.g. cellular activation and/or disruption) at the site of eventual thrombosis. During both phases, innate immunity may be triggered by events such as injury, infection, inflammation, infarction, or ischemia.

Innate immunity in the ‘initiation phase’ of APS

We have recently reported a murine model of SLE that produces high levels of aPL and other SLE autoantibodies, and develops lupus-like glomerulonephritis.⁵ Healthy non-autoimmune mice (C57BL/6 or BALB/c) were immunized with human β_2 GPI in the presence of the TLR4 ligand LPS. In addition to being a PL-binding protein and major target of aPL, β_2 GPI binds readily to the surface of apoptotic cells¹⁷ and appears to be one of the first autoantigens targeted in SLE.⁶ Mice developed a long-lived, potent immune response to β_2 GPI, which, over time, led to epitope spread to multiple SLE autoantigens. Remarkably, autoantibodies appeared in a sequential manner that recapitulates the order seen in human SLE.⁶ These findings demonstrate that immunization with an apoptotic cell-binding protein (β_2 GPI), together with a TLR4 ligand (LPS) that triggers innate immune activation, can induce aPL and SLE-like disease in mice.

Our studies were motivated by the following considerations (Figure 2). First, we required an immunogen that could take advantage of apoptotic cells as a scaffold for epitope spread, but avoid the immunosuppression associated with administration of apoptotic cells. Most SLE- and APS-associated autoantigens are found on the surface of apoptotic cells, suggesting that these cells may constitute the cellular platform or ‘scaffold’ upon which epitope spread occurs in this disease.^{5,18,19} In SLE, epitope spread is defined as a sequential spread of the autoimmune response, leading to the ordered emergence of autoreactivity to multiple autoantigens. Epitope spread can be both intermolecular (epitopes on different molecules that are physically associated) and intramolecular (epitopes on the same molecule). In general, intermolecular epitope spread occurs between molecules whose physical association permits their simultaneous uptake by an antigenpresenting cell (APC). This type of epitope spread provides an elegant explanation for how autoantibodies to non-protein antigens (e.g. DNA and PL) can occur. For example, uptake of an apoptotic cell by an APC should result in presentation of all antigens derived from that apoptotic cell. In this way, the apoptotic cell serves as a ‘scaffold’ physically linking multiple autoantigens that are individually targeted by the autoimmune response. Consistent with epitope spread, autoantibodies in human SLE

appear in a remarkably consistent order, and precede the development of clinical disease by up to 9 years.⁶ As aPL are one of the earliest autoantibody specificities to emerge in SLE,⁶ we chose β_2 GPI, a prominent APS-associated autoantigen, as our immunogen. Importantly, to minimize the well-described, potent anti-inflammatory effects of apoptotic cells, we used soluble β_2 GPI, which should interact with endogenous apoptotic cells.

Second, we needed a potent activator of innate immunity in order to generate a strong and persistent T-cell response to the inciting immunogen. To generate a strong innate immune, and subsequent, T-cell response, we co-immunized with LPS, a known TLR ligand. As described above, activators of the innate immune system, such as LPS, enhance MHC-associated antigen presentation and induce up-regulation of co-stimulatory molecules like CD80 and CD86. LPS also has additional immunogenic effects, such as promoting survival of memory T-cells.²⁰

In accordance with our hypothesis, repeated co-immunization of β_2 GPI with LPS led to a potent β_2 GPI-specific T helper cell response, with subsequent production of anti- β_2 GPI antibodies and other aPL, as well as intermolecular epitope spread to other apoptotic cell-associated autoantigens. Notably, immunized mice not only produced aPL and SLE autoantibodies, but also developed SLE-like glomerulonephritis.⁵

Innate immunity in the 'effector phase' of APS

Murine models of APS—Among the few existing murine models of APS, most have used passive transfer of human polyclonal or murine monoclonal β_2 GPI-dependent anticardiolipin antibodies (aCL) to produce experimental APS.⁴ Moreover, these models have evaluated pregnancy loss rather than thrombotic events as their major outcome. Other models have used less physiological immunizations, such as human and murine monoclonal aCL in complete Freund's adjuvant (CFA), to induce APS. To date, two models have been used to study aPL-associated thrombosis *in vivo*.^{11,12,21} In one model, a pinch injury of the femoral vein was required to induce thrombosis.¹² Mice injected with aCL (both polyclonal and monoclonal) developed larger clots and more persistent thrombi.²¹ A role for TLR4 activation in this model was suggested by the finding that aCL-induced thrombi were smaller in LPS-non-responsive (C3H/HeJ) than in LPS-responsive (C3H/HeN), mice.²² In the other model, the effects of aPL, with or without LPS, were studied.¹¹ aPL alone had no effect, while aPL with LPS resulted in platelet-leukocyte aggregates and thrombotic occlusions. It is noteworthy that in our induced model of SLE-like disease, careful histological evaluation of multiple tissues (including kidney, liver, spleen, heart, lung, brain, pancreas, and bone marrow) failed to reveal any thrombotic lesions despite high titers of aPL.⁵ These findings beg the question of what additional factors are necessary to induce aPL-associated thrombosis. They also suggest that models of the 'initiation phase' of APS may not be suitable for investigating the 'effector phase' of APS.

Murine model of thrombosis induced with autoantibodies to HSP60, an endogenous TLR ligand—Based on our hypothesis that the presence of aPL alone is insufficient for thrombosis, we and our collaborators (Y Merhi and E Thorin) elected to use a ferric chloride (FeCl₃)-induced murine model of carotid artery injury.²³ In this model,

application of FeCl₃ to the outside of the carotid artery leads to endothelial cell injury and resultant thrombus formation. Mice can be treated prior to injury with autoantibodies or other agents that promote or inhibit thrombus formation. Using this model, we have recently shown that autoantibodies to HSP60 (anti-HSP60) promote endothelial dysfunction and thrombus generation in healthy non-autoimmune mice.²³ Occlusion of the carotid occurred significantly faster in anti-HSP60-treated than in control IgG-treated mice. The most striking effect of anti-HSP60 IgG was on thrombus stabilization. Pretreatment with anti-HSP60 led to complete and stable occlusion (blood flow = $1.7 \pm 0.6\%$) in all animals by 12 min, while the minimum blood flow achieved in control IgG-treated mice was $34.0 \pm 12.6\%$ ($p = 0.0157$). Furthermore, thrombi were significantly larger in anti-HSP60-treated mice and contained four-fold more inflammatory cells, as compared to controls. Notably, uninjured contralateral arteries in anti-HSP60-treated, but not control IgG-treated, mice were also affected, with abnormal endothelial cell morphology and significantly increased surface expression of von Willebrand factor (vWf) and P-selectin. These data demonstrate that passive transfer of anti-HSP60 not only results in altered endothelial cell morphology and increased vWf and P-selectin expression, consistent with innate immune activation, but also promotes arterial thrombosis and inflammatory cell recruitment.

Mammalian HSP60 is an intracellular protein that is generally thought to be expressed on the surface only of cells that have been activated or stressed. However, endothelial cells in culture have been shown to express surface HSP60 that can be recognized by anti-HSP60.²⁴ It is possible that surface HSP60 expression occurs on morphologically intact endothelial cells during normal turnover. This would explain the effect of anti-HSP60 treatment on uninjured contralateral carotid arteries in our mice. As HSP60 appears to bind to innate immune cells, and through interaction with LPS promotes proinflammatory responses, it has been called an 'endogenous TLR ligand'.²⁵ Circulating anti-HSP60 may arise during infection or as part of an autoimmune response. In either case, anti-HSP60 could amplify the innate immune response through their ability to induce endothelial dysfunction.

Innate immunity and the 'effector phase' of human APS—We (with P Fortin and coworkers) have recently completed an epidemiological study of anti-HSP60 in a cohort of SLE and non-SLE patients with and without aPL. Preliminary analyses indicate that anti-HSP60 are an important predictor of vascular events, in particular when found concomitantly with aPL.²⁶ These data are consistent with a broadening role for TLR activation in multiple non-infectious diseases, including autoimmune disease (e.g. APS), cardiovascular disease, allergy, and cancer. Although infection is sometimes associated with APS²⁷ and triggers the disease in as many as 24% of patients with catastrophic APS, it is unlikely that infection initiates APS in most patients. Other factors (including surgical trauma, withdrawal of anticoagulation, and carcinoma) also likely play a role,²⁷ and may, like infection, result in activation of innate immunity. Innate activation appears to be the common denominator across a broad spectrum of triggers to thrombosis, with infection and tissue injury or death at one end of the spectrum, and cellular stress or malfunction at the opposite end.²⁸ Innate immune activation may, in turn, lead to increased expression of tissue factor by the endothelium and peripheral blood cells, with initiation of the coagulation cascade (Figure 3).

Conclusions and future perspectives

We have discussed how innate immunity can play a role in both the ‘initiation phase’ and the ‘effector phase’ of APS. Pathogen-derived TLR ligands (e.g. LPS) may trigger the initial production of aPL, while endogenous TLR ligands (e.g. HSP60) may be important in local endothelial changes that enable circulating aPL to activate the coagulation cascade. The occurrence of autoantibodies to endogenous ligands, such as HSP60, may contribute to the pathophysiology of APS, not only amplifying the innate immune response, but also modulating endothelial cell morphology and function. This dual role of innate immunity in the pathogenesis of APS, as put forth in this review, provides new insight not only into the generation of aPL but also the enigma of why some individuals with aPL develop APS, while others do not.

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Figure 1.

Proposed dual role of innate immunity in the antiphospholipid syndrome (APS). The model proposes two phases in the development of APS, both dependent on innate immune activation: (1) an 'initiation (or immunologic) phase', in which the role of innate immunity is to amplify the adaptive immune response (e.g. to a phospholipid/apoptotic cell-binding protein such as β_2 -glycoprotein I [β_2 GPI]), leading to the long-lived production of antiphospholipid antibodies (aPL) and other SLE-related autoantibodies; and (2) an 'effector (or pathologic) phase', in which the role of innate immunity is to enhance the prothrombotic effects of aPL via priming of the vascular endothelium (e.g. activation and/or disruption) at the site of eventual thrombosis. Innate immunity may be triggered by local or systemic events, such as injury, infection, inflammation, infarction, or ischemia. TLR4: toll-like receptor 4.

Figure 2.

Role of innate immunity in the 'initiation phase' of antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). This figure outlines a minimal, but sufficient, model by which immunization of mice with human β_2 -glycoprotein I (β_2 GPI) (a phospholipid-binding protein and target of antiphospholipid antibodies [aPL]) and lipopolysaccharide (LPS) (a toll-like receptor [TLR4] ligand) leads to aPL production, followed by a break in tolerance and epitope spread to multiple SLE autoantigens. We propose 3 stages: (1) activation of antigen-presenting cells (APCs) and human β_2 GPI-specific T-cells; (2) activation of human β_2 GPI-specific B-cells; and (3) generation of B-cell autoimmunity. In this setting, the human β_2 GPI-specific T-cell can provide help to any B-cell that internalizes an apoptotic cell having human β_2 GPI bound to its surface. In this manner, multiple autoreactive B-cells can be activated by a single human β_2 GPI-specific T-cell and lead to multiple SLE autoantibodies and SLE-like disease. h β_2 GPI: human β_2 GPI; m β_2 GPI: murine β_2 GPI. *Source:* reproduced with permission from Levine et al.⁵ (copyright 2006. The American Association of Immunologists, Inc.)

Figure 3.

Role of innate immunity in the ‘effector phase’ of APS. This figure outlines the interplay between innate immunity and antiphospholipid antibodies (aPL). A stimulus of innate immunity (e.g. injury, infection, or ischemia) induces the exposure of negatively charged phospholipid (PS), i.e. phosphatidyl-serine, and tissue factor (TF) on the surface of vascular cells, resulting in binding of coagulation proteins and other phospholipid-binding proteins (e.g. β_2 -glycoprotein I) and subsequent recognition of cells by circulating aPL. aPL have been proposed to affect a number of steps in this process, including cellular activation, activation of the coagulation and kinin cascades, and up-regulation of adhesion molecules, all resulting in enhanced thrombogenicity.