

Role of monocytes in the pathogenesis of antiphospholipid syndrome and potential therapeutic targets (Review)

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Abstract. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized primarily by arterial and/or venous thrombosis, obstetric complications and persistent positivity for antiphospholipid antibodies (aPLs). It has been proposed that the pathogenesis of APS is closely associated with vascular endothelial cell activation, complement activation and platelet activation. Notably, APS may be key to understanding the relationship between innate immune cells, and thrombosis and obstetric complications. Monocytes are activated by aPLs, adopting a pro-inflammatory and pro-coagulant phenotype, and producing inflammatory cytokines; however, the exact mechanisms of action of monocytes in APS remain unclear. Monocytes may act as an intermediary, triggering immune dysregulation, closely linking them to thrombosis and obstetric complications. Therefore, a better understanding of the potential pathogenic role of monocytes in APS is required, which could assist clinicians in gaining deeper insights into the pathogenesis of APS and identifying new therapeutic targets. This may provide new options for the management of APS. Therefore, the present study aimed to review monocytes and their role in APS.

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1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by arterial and/or venous thrombosis, obstetric complications and persistently positive antiphospholipid antibodies (aPLs) (1). The aPLs include lupus anticoagulants, anticardiolipin antibodies and anti- β -2-glycoprotein-I (β_2 GPI) antibodies (2). Thrombosis can be present in any tissue or organ, such as the skin, eyes, heart, lungs, kidneys and the micro-vessels of other organs, with the deep veins of the lower extremities and the cerebral arteries being the most commonly affected. Notably, APS can cause damage and endanger life, thus imposing a considerable health burden (3,4). Furthermore, pregnancy-related complications associated with APS, such as fetal death and eclampsia, have a notable impact on health and quality of life (5).

The mechanisms underlying thrombosis and obstetric complications in APS have not yet been fully elucidated. At present, various pathogenic mechanisms underlying this disorder have been proposed, including activation of vascular endothelial cells (6), activation of complement and complement-mediated injury (7,8), activation of platelets (9), activation of the coagulation coupling system, inhibition of the fibrinolysis system (10,11) and activation of neutrophils (12), T cells (13) and extracellular vesicles have pro-coagulant effects (14,15).

In addition to the aforementioned pathogenic immune cells, current studies have shown that monocytes are involved in thrombosis and obstetric complications (16,17), but evidence regarding their role in the development of APS is limited (17). Monocyte activation can be induced in patients with APS

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through different pathways, including the direct binding of aPLs to monocytes and activation through the complement pathway. Monocytes can differentiate into other forms of immune cells by themselves, and secrete pro-inflammatory and pro-coagulant factors, thus disrupting the balance of the immune system, which is closely related to thrombosis and obstetric complications in APS (18,19). However, further related studies are required. Therefore, the aim of the present study was to review the role of monocytes in APS, thereby providing further understanding of the pathogenesis of APS and to potentially identify therapeutic targets for the treatment of APS. Fig. 1 shows a schematic diagram summarizing how monocytes can act as potential therapeutic targets for APS.

2. Epidemiology of APS

At present, based on recently summarized data, the estimated annual incidence rate of APS is 1-2 cases/100,000 individuals within the global population, and the prevalence rate is 40-50 cases/100,000 individuals (20). Notably, there are differences in these rates among countries and regions (21-23). According to different regional studies (including the United States, South Korea, Argentina, Northwest Italy and Spain), the peak age of onset of APS in men is 55-79 years and it is 30-39 years in women (20,21), and the ratio of female to male patients with primary APS is 2-4:1 (20,21). Secondary APS is mainly related to systemic lupus erythematosus, with a ratio of 1:7. Catastrophic APS (CAPS) accounts for <1% of all patients with APS (20,24). The 10-year survival rate of APS ranges between 80 and 90.7%, and the standardized mortality rate is 1.61-1.8/100,000 individuals (23,25).

3. Diagnosis of APS

In 1999, an expert panel formulated the classification criteria for APS (1), and the classification criteria were revised in 2006 in Sydney, Australia (1). Regarding the clinical manifestations of APS, thrombosis and obstetric complications are predominant, and the main serological manifestation is positivity for aPLs (Table I) (26). In addition to the aforementioned typical clinical manifestations, some patients are persistently positive for aPLs and present only with 'non-standard' manifestations. Non-standard manifestations occur in other organs; for example, when the kidneys are involved, APS can present as hypertension and proteinuria (27). When the skin and corresponding blood vessels are involved, APS may present as reticular blue spots (1). When the cardiovascular system is involved, APS manifests as myocarditis, valvular heart disease or diastolic dysfunction (28). Neurological diseases can manifest as dementia, epilepsy, migraine, myelitis and chorea (28). In addition to the standard aPLs listed in Table I, non-standard aPLs, such as antiphosphatidylserine/prothrombin, anti-dome-specific anti- β_2 GPI, anti-annexin A5 and immunoglobulin A antibodies (29), serve an important role in supplementing the diagnosis of APS; however, more studies are required for further confirmation. In the latest APS classification criteria (1), which were jointly developed in 2023 by the American College of Rheumatology and the European League Against Rheumatism, clinical manifestations such as heart valve and hematological (thrombocytopenia) pathologies

were included in the classification criteria. Compared with the Sapporo classification criteria revised in 2006 (30), the specificity was 99 vs. 86%, and the sensitivity was 84 vs. 99% (1). CAPS is rare; however, due to microvascular thrombosis, it can lead to multiple organ failure and is life-threatening. The diagnosis of CAPS should meet the following four classification criteria: Clinical manifestations of damage to at least three organs and systems; clinical manifestations developed simultaneously and rapidly within 1 week; laboratory-confirmed presence of aPLs; and histopathological evidence of small-diameter vascular obstruction (31).

4. Monocytes

Monocytes are an important immune cell, accounting for ~10% of total nucleated cells in circulating blood (32,33), and they are the main components in autoimmune responses. When entering tissues, monocytes trigger endogenous inflammatory processes (34), and in response to damage or infection, monocytes rapidly participate in regulating the inflammatory response and promoting the repair of damaged tissues (35). Monocytes are not only heterogeneous but they can also self-renew. Their membranes express various molecular markers, such as lipopolysaccharide (LPS)-related receptors [Toll-like receptors (TLRs)], complement receptors and cytokine receptors, and perform multiple functions, including participating in thrombosis and destroying pathogens (36). Monocytes can be classified into the following three subgroups based on their expression of CD14 (LPS-related receptor) and CD16 (Fc γ III receptor) (37,38): i) Classical monocytes, which express the surface markers CD14⁺⁺CD16⁻ and C-X-C chemokine receptor 2⁺CX3CR1⁻, and account for 80-95% of monocytes; this subgroup mainly performs phagocytosis and tissue repair functions, and secretes cytokines, such as IL-1, IL-10, IL-12 and TNF- α (39,40). ii) Intermediate monocytes, which express the surface markers CD14⁺⁺CD16⁺ and C-C chemokine receptor (CCR)2⁺CX3CR1⁺, and account 2-11% of monocytes; this subgroup has a highly pro-inflammatory cellular effect, generates a high level of reactive oxygen species (ROS) and inflammatory mediators, and can secrete cytokines, such as IL-1 β , IL-6 and TNF- α (40,41). iii) Non-classical monocytes, which express the surface markers CD14⁺⁺CD16⁺ and CCR2⁺CX3CR1⁺, and account for 2-8% of monocytes; this subgroup mainly serves roles in patrolling, clearing debris, eliminating apoptotic cells and in the antiviral response, and can secrete cytokines, such as IL-1 β , IL-6 and TNF- α (40,42). Among patients with APS, the classic and intermediate types of monocytes are dominant, and at the same time, their surface adhesion is enhanced (43), participating in activation of complement and endothelial cell injury, and thus they are related to the pathogenesis of thrombosis and adverse pregnancy outcomes in APS.

5. Role of monocytes in normal coagulation

As aforementioned, monocytes have receptors that enable sensing of vascular damage, inflammation or infection, leading to activation. They can then migrate into tissues and differentiate into dendritic cells and macrophage subtypes. In addition to serving a role in innate immune responses

Table I. Sydney classification criteria for antiphospholipid syndrome.

Criteria	Description
Clinical criteria	
Vascular thrombosis	Including arterial, venous and microvascular thrombosis
Obstetric complications	i) One or more fetal losses after week 10 of gestation; ii) one or more premature births due to eclampsia, severe preeclampsia or placental insufficiency (<34 weeks); iii) at least three consecutive spontaneous abortions occurring before 10 weeks gestation; iv) maternal or paternal anatomic, hormonal or chromosomal causes excluded
Laboratory criterion	
aPL titer levels	i) Lupus anticoagulant present in plasma in ≥ 2 samples; ii) anticardiolipin antibody IgG and/or IgM present in medium or high titer on ≥ 2 occasions at a distance of 12 weeks; iii) anti- $\beta 2$ glycoprotein-I antibody IgG and/or IgM present in medium or high titer on ≥ 2 occasions at a distance of 12 weeks

aPL, antiphospholipid antibody.

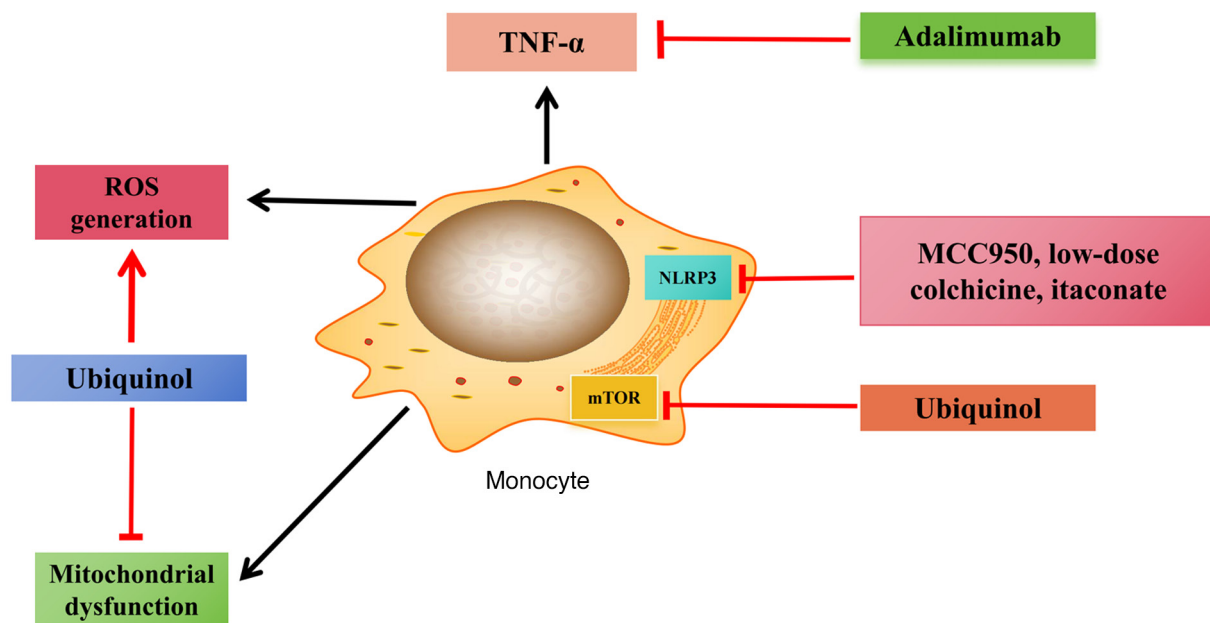


Figure 1. Monocytes as potential therapeutic targets for APS. Various drugs target distinct components of monocytes, such as TNF- α , ROS, NLRP3 and mTOR, thereby suppressing monocyte activation in APS, reducing the production of inflammatory cytokines and concurrently decreasing the secretion of procoagulant factors. This approach is anticipated to effectively inhibit thrombosis and address obstetric complications. APS, antiphospholipid syndrome; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor family pyrin domain containing 3; ROS, reactive oxygen species.

and tissue repair, monocytes are actively involved in hemostasis (44). When blood vessels are damaged, platelets are recruited and they interact with monocytes, thus activating each other. Simultaneously, cytokines (such as TNF- α , IL-8 and IL-1 β) are released, and the two form heterogeneous cell complexes (45). After platelets are activated, they can express P-selectin (CD62P) on their surface, which binds to the related receptors expressed by monocytes. Meanwhile, platelets can also adhere to monocytes through bridging molecules, such as fibrinogen and thrombomodulin, thereby contributing to the formation of more complexes (46,47). Under the mediation of CCR1, this complex increases the binding of platelet factor 4 to the surface of monocytes and markedly enhances the arrest of monocytes on endothelial cells induced by CCL5, thereby

recruiting more platelets to aggregate at the site of injured endothelial cells (48-50), which is conducive to hemostasis. Furthermore, under normal circumstances, the activity of tissue factor (TF) expressed by monocytes is low and can be transformed into fully pro-coagulant TF through specific inflammatory agonist pathways. For example, when CD162P binds to its receptor, it can rapidly increase TF exposure and TF-dependent coagulation activity in monocytes, even in the absence of protein synthesis. This may be related to the conformation or orientation changes of the extracellular domain of the protein when exposed to anionic phospholipids on the surface of monocytes (51). In this scenario, monocytes roll on the surface of blood vessels and adhere in large quantities to the luminal surface of the affected blood vessels. Simultaneously,

they deposit together with other white blood cells under the mediation of CD62P to initiate thrombosis (52). The TF formed by monocytes also initiates *in vivo* coagulation through factor VII, promotes the release of thrombin, and converts fibrinogen into fibrin. Activation of coagulation factor XIII is beneficial for maintaining the stability of fibrin clots, and the coagulation process is further amplified by the activation of factors V, VIII and XI (53), thereby exerting hemostasis. Notably, a previous study has shown that in monocytes of healthy individuals, when platelets and CD62P are co-cultured, there is a marked upregulation of the expression of TF. Meanwhile, monocytes can further enhance the activation of platelets, thereby enabling the secretion of more platelet-derived growth factors and soluble CD62P (54). When platelets and CD62P combine with polystyrene beads, they effectively increase the exposure of TF in monocytes, thereby unlocking potential TF activity (54) and participating in hemostasis.

6. Role of monocytes in normal pregnancy

During pregnancy, the innate immune response usually changes. Compared with monocytes in non-pregnant individuals, the monocytes in pregnant individuals exhibit increased expression of CD14 and CD64, increased number and activation, and functional changes, indicating phenotypic activation of monocytes during pregnancy (55). During a healthy pregnancy, intermediate monocytes increase in number, while classical monocytes decrease in number and release inflammatory cytokines such as TNF- α and interferon (IFN)- γ . In a normal pregnancy, an appropriate amount of TNF- α can not only protect the placental unit, but also change the adhesion of trophoblast cells to laminin and inhibit their mobility, thereby regulating the invasion of trophoblast cells (56). IFN- γ not only downregulates protease activity and increases apoptosis in extravillous trophoblasts (EVTs), thereby preventing excessive invasion of EVT, but also contribute to vascular remodeling during implantation, improving nutrient delivery to the implanted cells (57,58). Therefore, IFN- γ serves a key role in early placental development and trophoblast invasion. After the implantation period ends, the T helper (Th)1-dominant immune advantage in the decidua gradually shifts toward a Th2-dominant profile (59). This advantage is related to IL-4 released by monocytes, which can bias T-cell subsets towards Th2, and Th2 cells can induce a local Th2 advantage by releasing Th2 cytokines after infiltrating into the decidua basalis (60). For example, the release of IL-4, IL-10 and IL-13 inhibits the development of Th1 and Th17 immunity, and promotes allograft tolerance, thus facilitating pregnancy (61).

In addition, trophoblasts express and secrete chemokines, and recruit monocytes into the decidua, where monocytes differentiate into dendritic cells and can be functionally reprogrammed by decidua stromal cells under the action of IL-1 β and granulocyte colony-stimulating factors, thus altering the cytokine profile secreted by monocyte-derived dendritic cells. The secretion of IL-1 β , IL-6 and IL-10 is increased, and the secretion of IL-8 and TNF- α is decreased, thus differentiating lymphocytes to the Th2 spectrum (62,63). IL-1 β activity is positively associated with the enzyme activities of matrix metalloproteinase (MMP)2 and MMP9, thereby enhancing the phagocytic ability of macrophages and degrading the

extracellular matrix to promote trophoblast invasion (64). In addition, monocyte-derived decidua macrophages secrete vascular endothelial growth factor (VEGF) and placental growth factor, which are considered to serve an important role in the early stage of spiral artery remodeling (65). Therefore, monocytes have an important role in normal pregnancy.

7. Relationship between monocytes and thrombosis in APS

In vitro studies of APS have revealed that, compared with controls (anti- β_2 GPI peptide-treated monocytes that were isolated from the venous blood of 30 healthy, age and sex-matched subjects), monoclonal aPLs isolated from patients with APS (that were then co-cultured with mononuclear cells from healthy donors), result in elevated TNF- α levels (66,67). When aPLs bind to the β_2 GPI protein on monocytes, TLR-4 activates the myeloid differentiation primary reactive protein signaling pathway, thus leading to the release of various pro-inflammatory cytokines, including IL-1, IL-6, IL-8 and TNF- α (68,69). Studies using monoclonal aPLs co-cultured with healthy mouse monocytes have revealed that aPLs activate the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in monocytes, inducing expression of caspase-1 and increasing its enzymatic activity. This simultaneously upregulates IL-1 gene expression and IL-1 protein production, thereby increasing TF expression and activity in monocytes (62,70,71). Through monocytes, APS induces inflammation, particularly when monocytes adhere to endothelial cells, causing chronic endothelial inflammation and damage. This process recruits more monocytes, which roll along, firmly adhering to the injured vessel wall, migrating into tissues and differentiating (72). After differentiation into M1 macrophages, they can phagocytize excessive oxidized low-density lipoproteins and other immune complexes, leading to apoptosis, necrosis, lipid deposition, and the release of numerous inflammatory cytokines and TFs that further recruit circulating monocytes (72). Inflammatory cytokines produced by M1 macrophages, such as IL-12, promote differentiation of T cells into Th1 cells. Locally produced IFN- γ and TNF- α by activated Th1 cells increase the expression of class II major histocompatibility complex molecules on endothelial cells, enabling these cells to present β_2 GPI to T cells. This process further amplifies differentiation into Th1 effector cells (73), exacerbating endothelial cell damage. Moreover, anti- β_2 GPI antibodies can activate the mammalian target of rapamycin (mTOR) pathway in monocytes, thereby upregulating the expression of TF and IL-8, which is closely related to the formation of pro-inflammatory and pro-coagulant phenotypes in monocytes (74).

Normally, when the vascular endothelium is damaged, collagen is exposed to the circulation under high shear flow, and platelet-rich thrombosis is formed under the action of monocytes (64). The activation of monocytes, platelets and endothelial cells under the interaction of various receptors and ligands can lead to increased expression of adhesion molecules, such as E-selectin, increased inflammatory response, and a pro-coagulant effect by reducing the expression of anti-coagulant molecules, such as thrombomodulin (64). In addition, endothelial cells can transfer related substances, such as microRNA (miR)-125a-5p and miR-222, to monocytes via

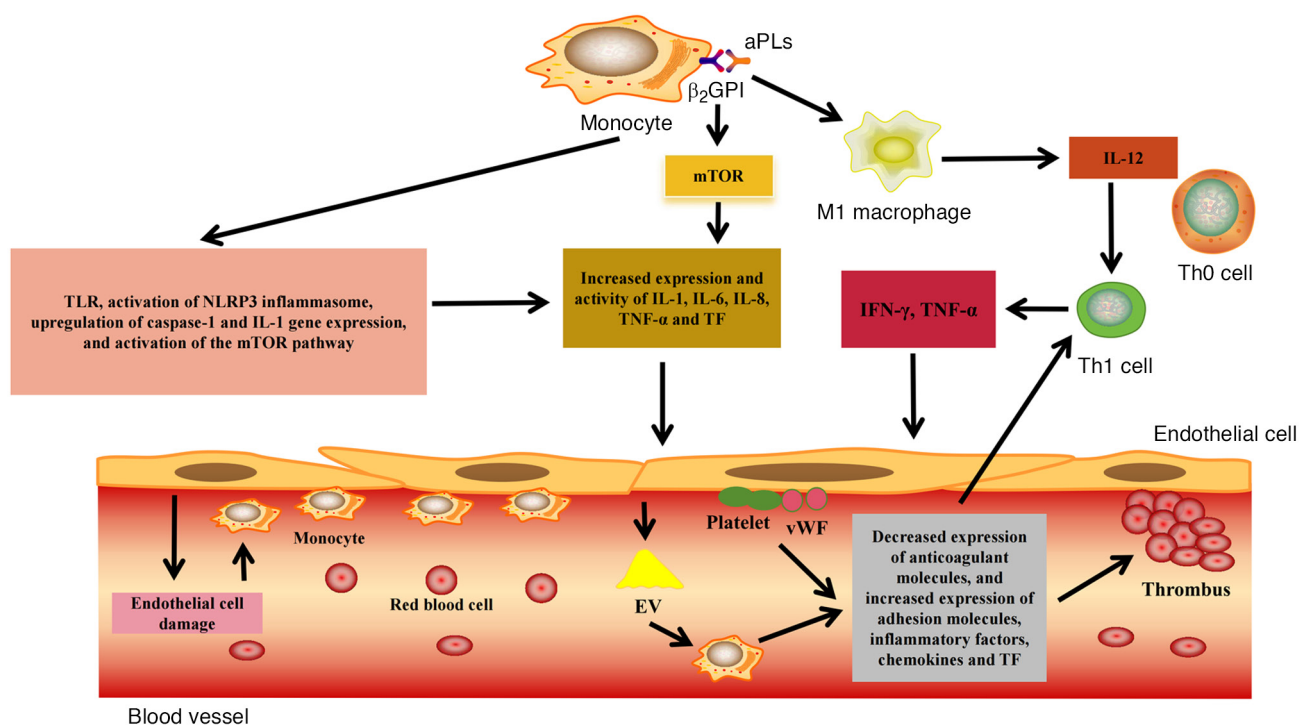


Figure 2. Potential pathogenesis of thrombosis in monocytes in APS. In APS, aPLs binds to the TLR of monocytes through the β_2 GPI protein and activates NLRP3 and mTOR, which can activate monocytes, and secrete pro-inflammatory and pro-coagulant factors. Pro-inflammatory factors can damage endothelial cells, thereby secreting EVs and transferring microRNAs to monocytes, causing monocytes to release cytokines, chemokines and TF, and eventually form a thrombus. β_2 GPI, β -2-glycoprotein-I; aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; EV, extracellular vesicles; IFN, interferon; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor family pyrin domain containing 3; Th, T helper; TLR, Toll-like receptor; vWF, von Willebrand factor.

extracellular vesicles, while releasing cytokines, chemokines and TF (75). Since anti- β_2 GPI antibodies hinder clearance of extracellular vesicles, they can further trigger the immune complex to induce monocyte activation, resulting in the secretion of inflammatory cytokines and triggering a coagulation cascade (64). In patients with APS (67), and in an *in vitro* study simulating CAPS (43), it has been reported that monocytes express heterodimers of CD49d that can bind to ligand vascular cell adhesion molecule 1, causing monocytes to adhere to damaged endothelial cells (76), which is associated with thrombosis. Fig. 2 summarizes the potential role of monocytes in thrombosis in APS, as aforementioned.

8. Relationship between monocytes and obstetric complications in APS

In APS, monocytes evolve into dendritic cells and secrete cytokines, such as IL-4, to induce activation of autoreactive B cells, thereby producing aPLs (35,77). After binding with an autoantigen, these antibodies form immune complexes, and their deposition can induce the activation of complement. Meanwhile, activation of monocytes can reduce complement regulatory proteins, resulting in the production of the allergic toxin C5a (78,79). After C5a binds to the C5a receptor on monocytes, it not only leads to the release of inflammatory mediators, such as chemokines, cytokines and C3, but it also attracts a large number of monocytes to infiltrate the decidua. This results in a substantial inflammatory response, which enhances the activation and deposition of C3, leading

to activated monocytes entering the placenta and causing placental inflammation (75,80); this eventually leads to fetal damage. In the decidua, monocytes not only participate in the expression of TF, but also produce a large number of ROS, and the induction of oxidation can cause fetal membrane injury and fetal death (64). Activated monocytes can also secrete monocyte chemoattractant protein 1 (MCP-1), which binds to CCR2 when there is an immune imbalance, and mediates the transformation of T cells to Th1 and the production of Th1 cytokines, such as TNF- α and IFN- γ (81). Activated monocytes in the placenta secrete cytokines, such as IL-1, causing T cells to differentiate into Th17 cells. This further activates natural killer cells and secretes IFN- γ , TNF- α , perforin and granzyme, mediating their cytotoxic activity against target cells (82); this may damage placental vascular endothelial cells and lead to micro-thrombotic events in the placenta. This subsequently leads to obstetric complications. Excess Th17 cells and their secreted cytokines may also lead to uncontrolled infiltration of neutrophils at the maternal-fetal interface (83), which can lead to a further elevated local TNF- α level, decreased essential angiogenic factors and VEGF, and ultimately abnormal placenta formation and fetal death.

TNF- α increases the plasminogen activator inhibitor-1 level from trophoblastic cells, reduces the invasive capability of trophoblastic cells, activates endothelial cells, induces the expression of MMP-9 in the decidual membrane and destroys the decidual extracellular matrix, thus interfering with normal EVT invasion (81). TNF- α can also increase the expression of MCP-1. With an increase in MCP-1 levels, more M1-type

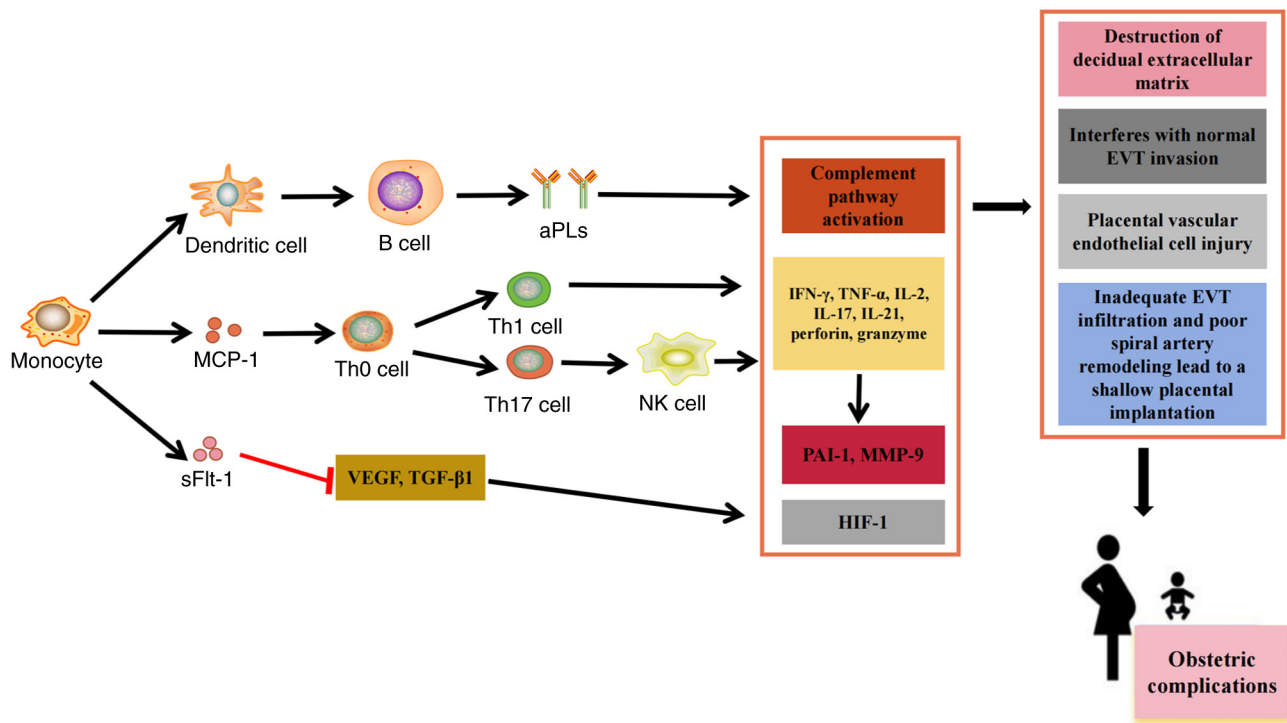


Figure 3. Potential pathogenesis of obstetric complications in APS mediated by monocytes. In APS, aPLs activate the complement pathway, leading to the formation of inflammatory fragments such as C3a and C5a. These fragments not only deposit in the placenta but also bind to receptors on monocytes, thereby inducing the secretion of inflammatory cytokines (such as IFN- γ and TNF- α), TF, large amounts of reactive oxygen species, MCP-1, sFlt-1, PAI-1 and other mediators. This cascade can result in damage to placental vascular endothelial cells, inhibit the remodeling of uterine spiral arteries, interfere with normal EVT invasion, and ultimately lead to abnormal placental development and fetal loss. APS, antiphospholipid syndrome; aPL, antiphospholipid antibody; EVT, extravillous trophoblast; IFN, interferon; Th, T helper; MCP-1, monocyte chemoattractant protein-1; sFlt-1, soluble fms-like tyrosine kinase-1; PAI-1, plasminogen activator inhibitor-1; MMP, matrix metalloproteinase; HIF-1, hypoxia-inducible factor 1.

macrophages are recruited and stimulated to secrete more pro-inflammatory factors, thus further promoting the expression of MCP-1, forming a positive feedback loop and a vicious cycle (17,84), which can result in miscarriage. When MCP-1 levels increase, the number of CD14⁺CD11c⁺CD163⁺ monocytes is markedly increased, which enhances Fas-mediated EVT cell apoptosis and interferes with placental implantation (85,86). In addition, MCP-1 and IL-8 attract circulating monocytes to the wall of the placental blood vessels and damage the vascular endothelium in a manner similar that seen in atherosclerotic lesions, resulting in hypoxia caused by insufficient blood supply to the placenta, thereby reducing the expression of atypical chemokine receptor 2, and promoting MCP-1 upregulation and trophoblast apoptosis through negative feedback. This is associated with pre-eclampsia (87,88). Soluble fms-like tyrosine kinase 1 (sFlt-1) is an anti-angiogenic factor, which has an association with the development of pre-eclampsia. In mouse models with an inducible form of human sFlt-1, the expression of this protein in the early stage of pregnancy triggers fetal growth restriction, a finding accompanied by serious defects in placental formation (89). Furthermore, increased levels of anti-angiogenic factors (such as sFlt-1) cause maternal endothelial dysfunction (89). Excessive release of sFlt-1 selectively binds to VEGF, thereby inhibiting the binding of VEGF to its membrane receptors, while inhibiting TGF- β 1 signaling, which can lead to reduced production of nitric oxide, endothelial cell dysfunction and vasodilatory disorders. In this scenario, a hypoxic environment causes placental cells to

activate hypoxia-inducible factor-1 (90). In patients with APS, the aforementioned pathways may lead to fetal resorption by continuously amplifying the inflammatory response, inhibiting uterine spiral artery remodeling, damaging the placenta and reducing the number of fetal capillaries. Fig. 3 summarizes the potential role of monocytes in obstetric complications of APS, as discussed in the present study.

9. Potential therapeutic targets for monocyte-induced immune disorders in APS

The pathogenesis of APS is complex, and the specific, targeted treatment remains unclear. Currently, heparin, aspirin and hydroxychloroquine (HCQ) are considered key therapeutic agents in managing APS (91). The mechanism by which these drugs act in APS has been explored in previous studies. For example, aspirin may exert its effect by modulating lipoproteins and blocking the impact of aPL on human trophoblast migration and endothelial cell interactions (92). Heparin has been shown to prevent APL-induced fetal loss by inhibiting the activation of complement and regulating the balance between T-cell subsets (93). HCQ can not only reduce the production of inflammatory cytokines, such as TNF- α , IFN- γ and IL-6, by peripheral blood monocytes, but also reduce TF expression, and the plasma levels of soluble cell adhesion molecules, such as E-selectin, and vascular cell adhesion molecules, while improving the formation of endothelial nitric oxide synthase (94-97). As aforementioned, monocyte-induced

Table II. Potential role of different drugs in antiphospholipid syndrome.

Name of drug	Target of action	Potential therapeutic effect	(Refs.)
Adalimumab	TNF- α -blockade	Inhibits anti- β_2 GPI-induced TF expression, has favorable effects on endothelial dysfunction and fetal resorption	(98,99)
Rapamycin, sirolimus	Mammalian target of rapamycin blockade	Decreases anti- β_2 GPI-induced IL-8 and TF mRNA expression and activity, preserves kidney function	(99-100)
MCC950, low-dose colchicine, itaconate	NLRP3 inflammasome	Decreases multi-organ failure, decreases thrombo-inflammatory organ injury, inhibition of NLRP3 inflammasome formation, targets ROS production by blocking proinflammatory mediators such as TNF- α and IL-6	(101-104)
Ubiquinol	ROS generation, mitochondrial dysfunction	Decreases IL-1 β and TNF- α mRNA, decreases the production of IL-6 and IL-8, reduces TF expression and activity	(105,106)

β_2 GPI, β -2-glycoprotein-I; NLRP3, NOD-like receptor family pyrin domain containing 3; ROS, reactive oxygen species; TF, tissue factor.

immune dysregulation serves a notable role in the development and progression of APS, contributing to both obstetric complications and thrombotic events. Therefore, pharmacological strategies aimed at correcting monocyte-related immune abnormalities, particularly their pro-inflammatory and pro-coagulant phenotypes, are essential for improving patient outcomes. Identifying new therapeutic targets to address monocyte-driven immune dysfunction is urgently needed and may provide valuable insights for advancing APS treatment (Table II) (74,98-106).

TNF- α blockers can completely inhibit β_2 GPI-induced TF expression in monocytes, while improving endothelial dysfunction and preventing fetal resorption. A previous study evaluated their efficacy in 18 women with persistent aPL positivity and recurrent adverse pregnancy outcomes despite treatment with low molecular weight heparin (LMWH) combined with low-dose aspirin (LDA) and HCQ. Of these patients, 16 initiated adalimumab and 2 initiated certolizumab in addition to the original regimen; 12 women achieved successful pregnancy outcomes, including 9 term deliveries and 3 preterm births. This suggests that the combination of LMWH, LDA and TNF- α blockers may be a promising therapeutic approach for refractory obstetric manifestations associated with aPL, with good tolerability and no reported adverse reactions (107). However, the limited sample size in this previous study necessitates larger-scale trials to further evaluate the efficacy and safety of this regimen.

Activation of the mTOR pathway is associated with vascular injury. In the renal context, the vascular endothelium of proliferative intrarenal vessels in patients with APS nephropathy has demonstrated evidence of mTOR complex pathway activation (100). The use of the mTOR inhibitor sirolimus has been associated with preserved renal function in aPL-positive renal transplant recipients (100). In addition, a previous study revealed that patients with APS nephropathy treated with sirolimus exhibited no recurrence of vasculopathy, with biopsy findings showing reduced vascular proliferation.

Among 10 patients receiving sirolimus therapy, 7 (70%) maintained normal renal allograft function at 144 months post-transplantation, compared with only 3 of the 27 untreated patients (11%) (100). These findings hold notable implications for aPL-induced mTOR activation in monocytes. *In vitro* studies have also demonstrated that rapamycin completely blocks anti- β_2 GPI antibody-induced monocyte activation, resulting in notable reductions in IL-8 expression, TF mRNA levels and TF activity (74,98). Notably, rapamycin fails to inhibit anticardiolipin antibody-mediated signaling, suggesting potential needs for aPL subtype stratification when utilizing these agents (98). However, further large-scale investigations are required to validate these observations.

The NLRP3 inflammasome in monocytes represents another potential therapeutic target. MCC950, a highly selective NLRP3 inhibitor, significantly reduces TNF- α and IL-6 levels in endotoxemic mice while markedly decreasing extracellular vesicle TF activity and thrombin-antithrombin complexes, demonstrating dual anti-inflammatory and anticoagulant properties (108). A previous study also identified the anti-inflammatory effects of endogenous Krebs cycle metabolites, such as itaconate, which suppresses inflammasome activation through NLRP3 modification (102). Colchicine additionally blocks NLRP3 and improves thromboinflammation (98). These agents represent promising therapeutic candidates for APS; however, these interventions remain unexplored in the context of APS and require systematic investigation.

ROS may represent another potential therapeutic target in APS, being closely associated with inflammation-driven thrombosis. Adequate ubiquinol levels serve crucial roles in protecting cells against protein oxidation and lipid peroxidation (109). *In vitro* experiments have demonstrated that ubiquinol supplementation to peripheral blood cells from patients with APS can not only reduce oxidative stress, but also improve mitochondrial dysfunction, revealing notable anti-inflammatory properties (105). A randomized double-blind controlled trial involving 36 patients with APS showed that

ubiquinol (200 mg/day) for 1 month enhanced vascular endothelial function, decreased monocyte expression of prothrombotic and proinflammatory mediators (IL-1 β , TNF- α , IL-6 and IL-8), inhibited phosphorylation of thrombosis-associated protein kinases, and reduced peroxides along with the proportion of depolarized mitochondria in monocytes (106). These findings suggest the potential therapeutic benefits of ubiquinol in APS, possibly serving as adjuvant therapy to standard APS treatment.

10. Conclusion

In recent years, the role of monocytes in the pathogenesis of APS has been continuously studied; however, their role in the underlying pathogenic mechanisms of thrombosis and obstetric complications is still unresolved, because the signaling pathways and molecular-level specific mechanisms of action have not been clearly elucidated. In addition, interactions between monocytes and other immune cells, such as endothelial cells, platelets and T cells, can further complicate the situation. aPLs induce pro-inflammatory and pro-coagulant states in monocytes. Monocytes are activated by different pathways and are the most important source of TF in APS, and exposure to TF on monocytes is associated with pathways that promote coagulation and inflammatory responses, indicating that these pathways may be promising therapeutic targets. Therefore, the role of monocytes in APS may be an important area of study, and further studies are required to investigate the specific molecular mechanisms of the association between the activation of monocytes, and thrombosis and obstetric complications, as a reference for the development of new targeted interventions for APS.

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Authors' contributions

RXH, CCW and YTY wrote the manuscript. YY, XCH, BQW, DLM, RJH and YJH acquired and interpreted the data. RXH conceptualized and designed the study. JYL and XXH edited the manuscript for intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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