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REVIEW ARTICLE

Exosomal-complement system activation in preeclampsia

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Abstract

Aim: Preeclampsia (PE) is a severe pregnancy-related disorder characterized by hypertension and multi-organ failure, primarily affecting the maternal vasculature and placenta. The aim of this review is to explain the molecular mechanisms behind PE by investigating the relationship between exosome release and complement activation, which could provide insight into potential therapeutic targets.

Methods: This review analyzes existing literature on the role of the complement system and exosomes in the pathophysiology of PE. The focus is on how abnormal complement activation contributes to inflammation and vascular dysfunction, particularly in the placenta, and the role of trophoblast-derived exosomes carrying pathogenic molecules such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng).

Results: Findings from recent studies indicate that during PE, abnormal complement activation leads to severe inflammation and vascular dysfunction in the placenta. Additionally, exosomes, particularly those derived from trophoblasts, are present in higher concentrations in maternal circulation during PE and carry molecules that disrupt endothelial function. These factors contribute to the development of hypertension and other maternal complications.

Conclusions: Understanding the interaction between complement activation and exosome release in PE may open avenues for novel therapeutic approaches. Targeting complement regulation and exosome-mediated signaling could potentially improve maternal and fetal outcomes, offering new strategies for managing this complex condition.

KEYWORDS
complement, exosomes, immunological mechanisms, maternal health, preeclampsia

INTRODUCTION

Preeclampsia (PE) is a grave pregnancy-related condition that affects both maternal and fetal health and is characterized by new-onset hypertension and multi-organ failure. It is a major cause of maternal death, morbidity, and poor perinatal outcomes, especially in low- and middle-income countries.[1] Despite its global frequency, the specific pathophysiology of PE is unknown; however, it is universally recognized as a placental condition marked by inadequate trophoblastic invasion and aberrant placentation. The condition is divided into two types: early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE), with EOPE being more severe and associated with abnormal placentation, leading to increased maternal and fetal morbidity and mortality.[2,3]

Relatively recent research has revealed the intricate relationship between immunological dysregulation, inflammation, and vascular dysfunction in the development of PE. One of the immunological processes implicated in PE is the complement system, which is an essential component of innate and adaptive immunity.[4] The complement system is the body's first line of defense against pathogens, removing foreign bodies, apoptotic cells, and tissue debris while also controlling inflammation. The complement system can be activated by the classical, lectin, and alternative pathways, all of which lead to the production of C3 and C5 convertases, which

then form the membrane attack complex (MAC), which causes cell lysis.[5]

In addition, to complement system dysfunction, exosomes have emerged as important participants in the pathogenesis of PE. Exosomes are small extracellular vesicles that transport proteins, lipids, and nucleic acids between cells. These vesicles participate in a variety of physiological processes, including immunological regulation, inflammation, and angiogenesis.[6] In PE, trophoblast-derived exosomes are released in high concentrations into the maternal circulation, contributing to endothelial dysfunction, immunological dysregulation, and placental disease. These exosomes contain chemicals such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which impede endothelial proliferation and migration, resulting in vascular dysfunction and hypertension in PE patients.[7,8]

This review will examine the complex interaction between exosomes and the complement system in preeclampsia. This review will shed light on how complement activation and exosome function contribute to the pathogenesis of PE by analyzing the molecular pathways involved. Understanding these interactions could lead to new treatment targets for preeclampsia management and prevention, ultimately improving maternal and fetal outcomes in afflicted pregnancies.

THE COMPLEMENT SYSTEM

The complement system is part of our innate immune response and is the first line of defense against pathogens, including bacteria and viruses.[9] The complement system's functions include the removal of infections, antigen–antibody complexes, dead/foreign cells, and tissue debris, as well as the regulation of responses mediated by antibodies and the adaptive immune system.[10] Furthermore, it defends the host by systemically removing apoptotic cells, wounded tissue, and immune complexes, thereby maintaining the balance between pro-inflammatory and anti-inflammatory cytokines to facilitate homeostasis.[11]

Complement activation

The complement system is mediated through three primary pathways: the classical pathway (CP), the lectin pathway (LP), and the alternate pathway (AP), all of which result in one common pathway.[12] The CP is activated by the binding of complement component recognition molecules C1q to IgG or IgM immune complexes attached to the surface of microorganisms or other structures.[13] This results in a configuration modification that activates C1r and C1s. Following that, C1s cleaves C4 and C2 to generate a C4bC2a complex, which is a C3 convertase.[14] The LP is activated by recognition molecules, viz., mannose-binding lectin when they bind to mannose and sugar molecules on the surface of microorganisms.[12,15] This causes the mannan-binding lectin serine proteases (MASP-1) and MASP-2 to become active. MASP-1 and MASP-2 subsequently cleave C4 and C2 to create the C3 convertase, or C4bC2a complex.[16] The AP differs from the CP and LP in that it is always active in the body at low levels. The spontaneous hydrolysis of C3 to create C3(H_2O) facilitates activation, causing factor B to bind and factor D to cleave to form C3 convertase, or C3bBb.[17,18]

All complement system pathways lead to C3 convertase, which is subsequently divided into C3a and C3b. C3b attaches to its target's activating surface and helps activate the C5 convertase. C5 convertase converts C5 into C5a and C5b. C5b, along with C6, C7, C8, and C9, creates MAC (as seen in Figure 1) that causes cell lysis.[4,19,20]

Complement component C1q

The complement system relies heavily on the first subcomponent of the CP, C1q. C1q is synthesized locally by monocyte-lineage cells such as macrophages, immature DCs, and microglia, with minor contributions from other cell types.[21] C1q, a 460 kDa glycoprotein, has a hexameric structure with globular heads at the C-terminus. The N-terminal contains a collagen-like triple-helix tail that binds the subunits together.[22] C1q binds to its targets, activating the enzymes C1r and C1s. Complement activation can activate effector processes, including opsonization, anaphylatoxin release, and MAC formation.[23]

Complement component C2

C2 plays a crucial role in both the CP and LP, preventing microbial infections and eliminating immunological complexes. MBL or ficolin, coupled with MASP-1, binds to carbohydrate molecules. Cleaving C2 and C4 activates MASP-2 and creates a C3 convertase similar to the CP.[24] Chromosome 6 has a short arm called human leukocyte antigen (HLA) class III, which contains complement component C2. When C1 is activated, this precursor protein is produced, together with the C2b and C2a components. C2 and serine proteinase have identical sequences, but the former has a catalytic chain with an extended N-terminus of 60 amino acids. Furthermore, the essential structures of Factor B and C2 are similar. C2a, along with C4b, creates C3 convertase (C4b2a).[25]

Complement component C3

Complement component C3 is the central component of the complement system. The C3 protein comprises 13 structural domains that can be split into tiny peptides

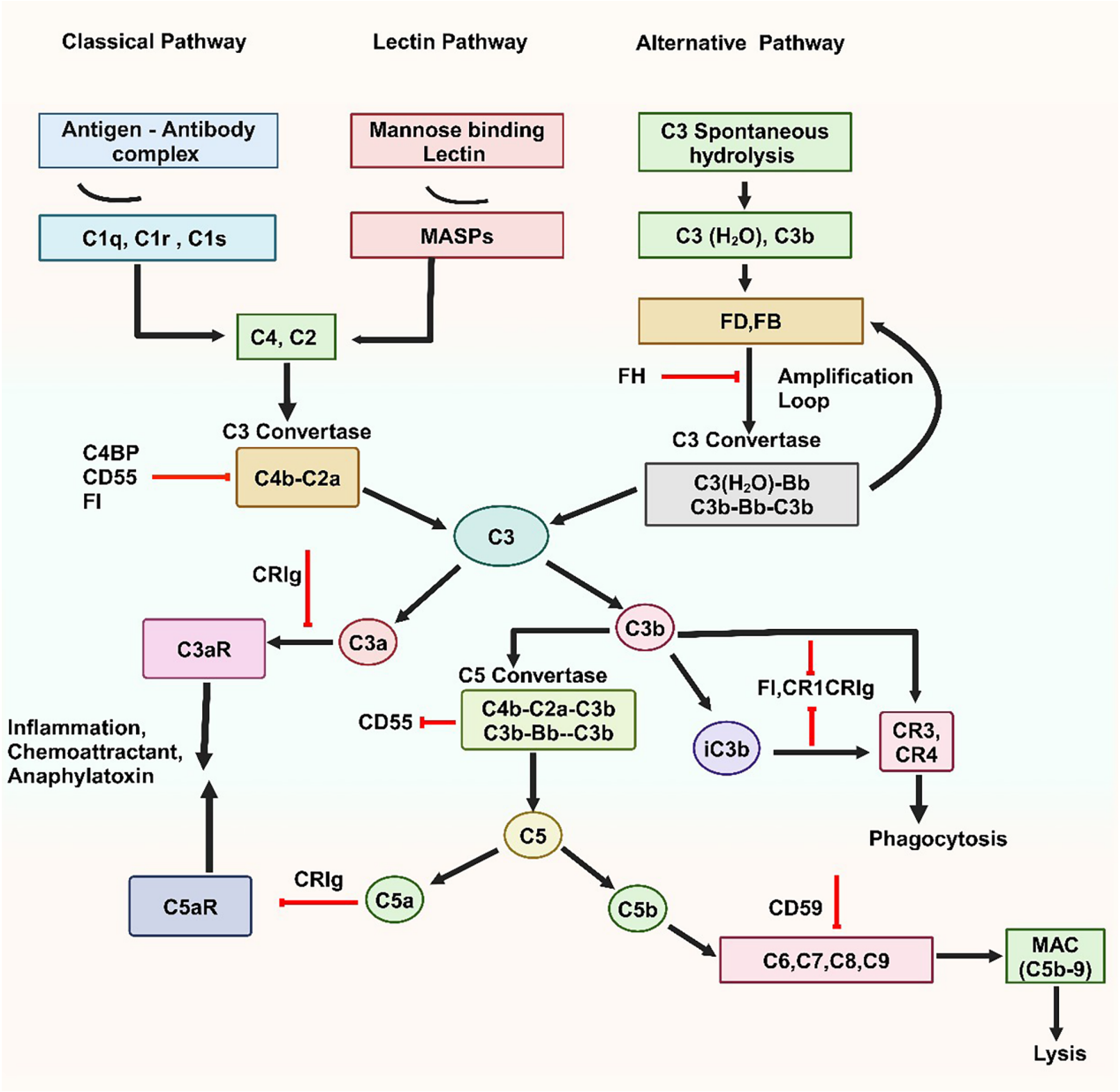

FIGURE 1 Schematic overview of the complement system, illustrating the three pathways.

or complete domains through proteolytic processes, resulting in changes in composition, structure, and function.[26] The most prevalent proteolytic event is the cleavage of C3 into two tiny chemotactic fragments, C3a (~9 kDa) and C3b (~176 kDa). These are crucial for the production of C convertase in the complement pathway and are vital effectors of increasing inflammation and opsonization.[27]

Complement component C4

Complement C4 has up to 30% of its sequence identity with complement proteins C3 and C5, which are descended from the same ancestor gene. Nevertheless, C4 maturation is more intricate than that of C3 and C5.[28] It involves the introduction of posttranslational modifications, such as four N- and one O-linked glycosylation and the sulfation of three tyrosine residues, as well as the synthesis of three chains from the precursor: α (95 kDa), β (75 kDa), and γ (30 kDa).[29] C4 has two isotypes generated by the genes C4A and C4B. C4A and C4B differ by only four amino acids (P1120PCPVLD1125 vs. L1120LSPVIH1125), yet they have significantly different hemolytic activity and substrate affinities. Complement C4 activates CP and LP, synthesizes C3 convertase, and strengthens the MAC against infections and foreign substances.[30]

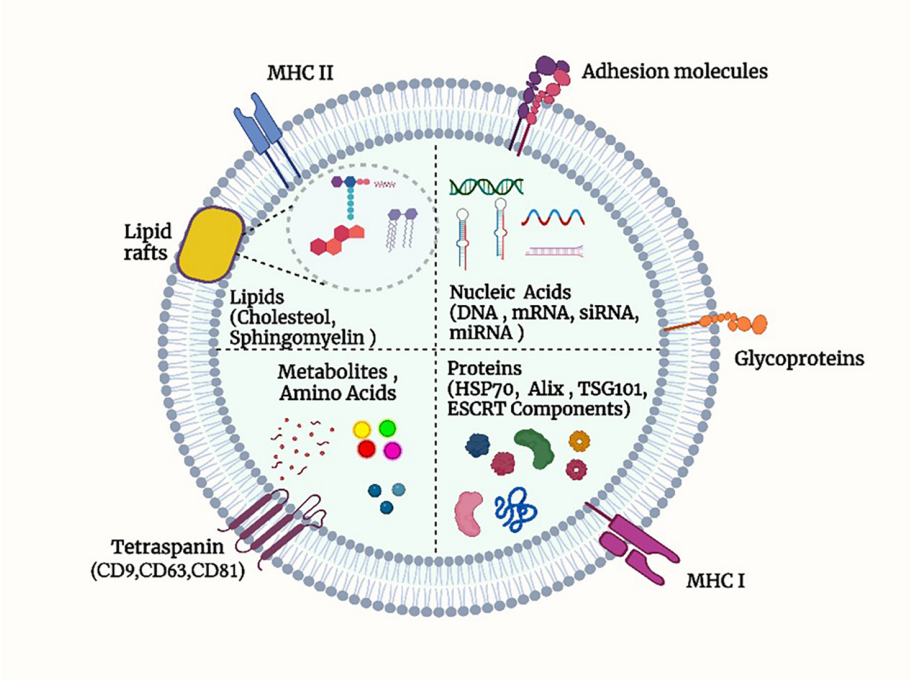

FIGURE 2 A schematic diagram of an exosome.

Complement component C5

This protein consists of alpha and beta polypeptide chains connected by a disulfide bridge. Furthermore, stimulation of the complement system via complement pathways may result in enhanced synthesis of C3 and C5 convertases, which cleave C5 into C5a and C5b.[31] C5a is an essential factor in chemotaxis. C5b is the first component of the complement MAC. Complement component 5 plays a significant function in inflammatory and cell-killing activities.[17]

Membrane attack complex (MAC) and complement component C9

C9 is a membrane protein that serves as a sentinel host defense against pathogenic attacks. It plays a role in the etiology of some liver diseases, damage, and healing. Component 9 of MAC is involved in pore formation.[32] The MAC is generated through the sequential assembly of the soluble complement proteins C5b, C6, C7, C8, and C9. Experimental methods for assembling membrane attack complexes include heterologous sera4, zymosan-activated sera, sequential addition of recombinant C5b6, C7, C8, and C9, and high-titre panel reactive antibodies that primarily react with non-self-class I and class II major histocompatibility complex molecules on endothelial cells.[33] The MAC causes various physiological changes, including apoptosis and pro-inflammatory cytokines. Pro-inflammatory cytokines (TNF-α, IL-2) can cause excessive inflammation, leading to enhanced complement activation.[34]

EXOSOMES

Exosomes are nanoscale extracellular vesicles (EVs) released by nearly all cell types. They range in size from approximately 40 to 160 nm (average ~100 nm). Exosomes are generated in endosomal compartments called multivesicular bodies (MVBs). Exosomes carry a range of cargo molecules, such as lipids, proteins, DNAs, mRNAs, and microRNAs (as seen in Figure 2). The majority of the cargo is involved in exosome formation and transport.[35]

Exosomes have a variety of roles in the formation during development and differentiation, including immunological response, antigen presentation, programmed cell death, angiogenesis, inflammation, coagulation, and morphogen transporters.[6] These roles vary based on the cell or tissue of origin. Since exosomes contain proteins, lipids, and nucleic acids specific to individual cells, they represent a particular type of intercellular messenger. Moreover, exosomes produced by parental cells can attach themselves to target cells, modifying their phenotypic characteristics and behavior and facilitating the horizontal transfer of genetic material through interactions with surface adhesion proteins.[36] Exosomes are found in almost all body fluids and are cell-specific and broadly disseminated. As such, they may be used as biomarkers. Exosomes have thus been shown to be effective delivery systems for delivering biological treatments to target cells over a variety of biological targets.[37]

Role of exosomes in the immune system

The immune system frequently encounters exosomes in both health and disease, where they either develop or

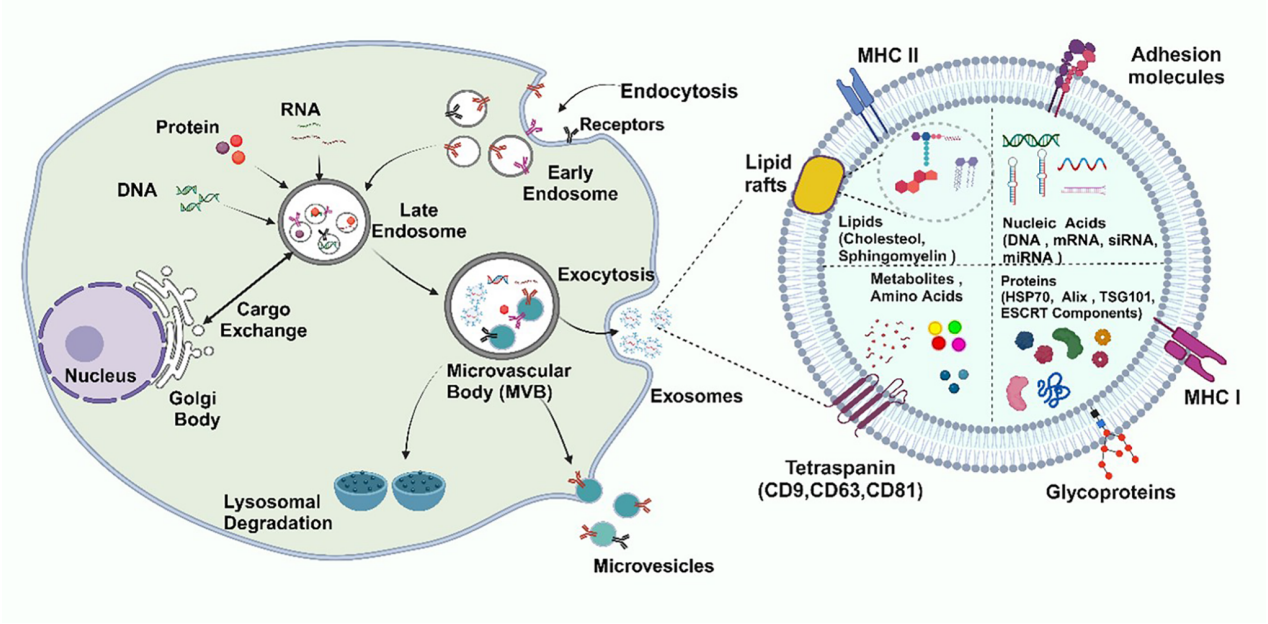

FIGURE 3 Schematic diagram of the immunomodulatory function of exosomes.

expose mechanisms to evade recognition or modulate the immune system to induce immune tolerance. The immune system interacts with exosomes based on their origin, which can include antigens derived from diseased cells (such as tumors or virus-infected cells), immune-modulating molecules enclosed in the vesicular container, or the result of a hyperinflammatory response (e.g., PE).[38]

The presence of exosomes containing the FasL ligand indicated their appearance during the early stages of embryonic development.[39] This molecule plays a multitude of roles in immune modulation, including B-cell regulation, the development of autoimmunity, the establishment of immune privilege in specific organs like the brain, ovary, testis, pregnant uterus, placenta, and eye, and T cells' self-tolerance toward fetal tissue during gestation.[40] Exosomes can support both innate and adaptive immunity through additional pathways, and the complement system is one example.

Exosomes have been proposed as a potential alternative mechanism for controlling inflammation, even though the majority of regulatory interactions involving immune cells are mediated by direct cell–cell interaction or by cytokines and chemokines released in response to different stimuli.[41] Exosomes released by DCs, NK cells, and macrophages have been shown to have a paracrine role that makes them pro-inflammatory mediators (Figure 3). They either work directly with the target cells to create their impact or in tandem with cytokines and chemokines to produce synergistic effects on immune systems.[42] Moreover, exosomes are secreted by all immune cell types involved in inflammation and have a variety of roles in inflammatory processes. EVs contain the enzymes needed to produce eicosanoids and other bioactive lipid mediators generated from arachidonic acid that may have chemotactic effects.[43]

Exosomes in the complement system

All vesicular structures, including exosomes in circulation, are prone to activating the complement system, resulting in destruction. This process has been reported for artificial liposomes created for therapeutic purposes that, despite not being directly antigenic, are capable of activating the complement system in an antibody-independent manner by electrostatic interactions with complement proteins.[44] Host cells are naturally protected against the activation of the autologous complement system by expressing membrane-bound molecules that inhibit it, such as CD59, which prevents the formation of the MAC, and CD46 and CD55, which work together to prevent the formation and deposition of C3b and C5b. APC-derived exosomes, generated in antigen-processing intracellular compartments, are coupled with antigenic peptides and should be particularly prone to antibody binding and complement-mediated destruction.

Recent research indicates that complement proteins delivered by exosomes regulate inflammation and processes. Exosomes can activate the conventional complement system by electrostatically attaching to proteins, IgG, and C-reactive protein. When exosomes containing complements interact with target cells, complement cascades are activated on their surfaces.[45] C3a-carrying exosomes stimulate and trigger inflammatory reactions by activating C3aR on the surface of the internal

environment. However, exosomes may prevent complement overactivation via dysregulation of C3 and C5. The fusion of these exosomes with the target cell protects against attack from pathogens and other foreign substances. It is generated during complement activation, which can also trigger the ExMV shedding process, guaranteeing cell viability by allowing it to be eliminated from the plasma membrane.[46,47]

PREECLAMPSIA (PE)

PE is a pregnancy-related multisystem illness whose cause is unknown. PE is often known as a placental disease since it is caused by insufficient placental function.[48] It is one of the most common pregnancy-related medical problems, second only to gestational diabetes mellitus.[49,50] It is defined as the onset of hypertension during pregnancy, which is characterized by a persistent high systolic/diastolic blood pressure of ≥140/90 mm Hg and the absence or presence of proteinuria of ≥300 mg/24 h after 20 weeks of gestation in women with previously normal blood pressure.[1] PE is one of the primary causes of maternal mortality and morbidity, neonatal and fetal death, and preterm birth. PE is the second highest cause of direct maternal death, accounting for approximately 46 000 maternal deaths and approximately 500 000 fetal and newborn deaths occurring annually. The disease's impact is particularly severe in low- and middle-income countries (LMICs). Sub-Saharan Africa (56%) and Southern Asia are responsible for 85% globally.[51]

PE is linked to maternal organ malfunction, including acute renal insufficiency, hepatic, neurological, or hematological problems, uteroplacental dysfunction, fetal growth restriction/intrauterine growth restriction, and intrauterine mortality.[52] Preeclampsia affects both the mother and the fetus. PE in the mother causes renal failure, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelets), liver failure, and cerebral edema with seizures, which is a severe variety of PE. Fetal problems include stillbirth, iatrogenic prematurity, fetal growth restriction/intrauterine growth restriction, oligohydramnios, and a higher risk of perinatal death.[48,53]

PE classification

PE can be divided into two categories based on gestational age: early and late-onset. Clinical signs and symptoms of early-onset PE (EOPE) appear before 33 gestational weeks, whereas late-onset PE (LOPE) appears after 34 weeks of gestation. Maternal and fetal morbidity and mortality rates are higher in EOPE than in LOPE. LOPE has a larger illness load (≥80%), but EOPE is linked to aberrant placentation and increased maternal and fetal morbidity and mortality rates.[54,55]

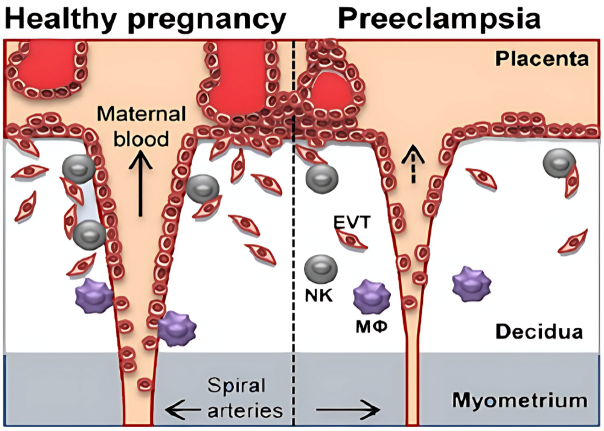

FIGURE 4 Schematic overview of the pathogenesis of preeclampsia.

PE pathogenesis

The pathogenesis of PE is not entirely understood; nevertheless, there is deficient migration of extravillous trophoblast (EVT) cells, as well as the non-physiological conversion of the myometrial spiral arteries.[56] This constricts blood artery diameter, resulting in insufficient blood supply to meet the fetus's oxygen and nourishment requirements (as seen in Figure 4). Furthermore, this induces hypoxia in the placenta, leading to the release of anti-angiogenic chemicals such as soluble endoglin, soluble fms-like (sFlt-1), and inflammatory mediators into the maternal systemic circulation.[57]

Additionally, PE is characterized by dysregulation of different complement components in both the maternal circulation and the placenta. These include C1q, C4, C5a, and C5b-9 (MAC).[14] More precisely, dysregulation of the AP activation fragment Bb occurs in PE, with the highest levels appearing early in pregnancy, emphasizing the complement system's critical role in PE formation.[58] Moreover, complement component C3 is crucial for activating the complement system. It must be activated before either CP or AP may be initiated. C3 activation products include C3a, C3b, and iC3b, which play critical roles in phagocytosis, respiratory burst, and inflammation, all contributing to PE.[59]

Exosomes in PE

The disruption of placentation is considered a fundamental mechanism driving PE pathogenesis, and studying the role of trophoblasts as components of the placenta is deemed significant to understanding this disorder.[60] Trophoblasts are divided into syncytiotrophoblasts (STBs), cytotrophoblasts (CBTs), and EVTs. STB microvilli produced from the placenta may act as pathophysiological indicators of PE, inhibiting EC proliferation and disrupting development.

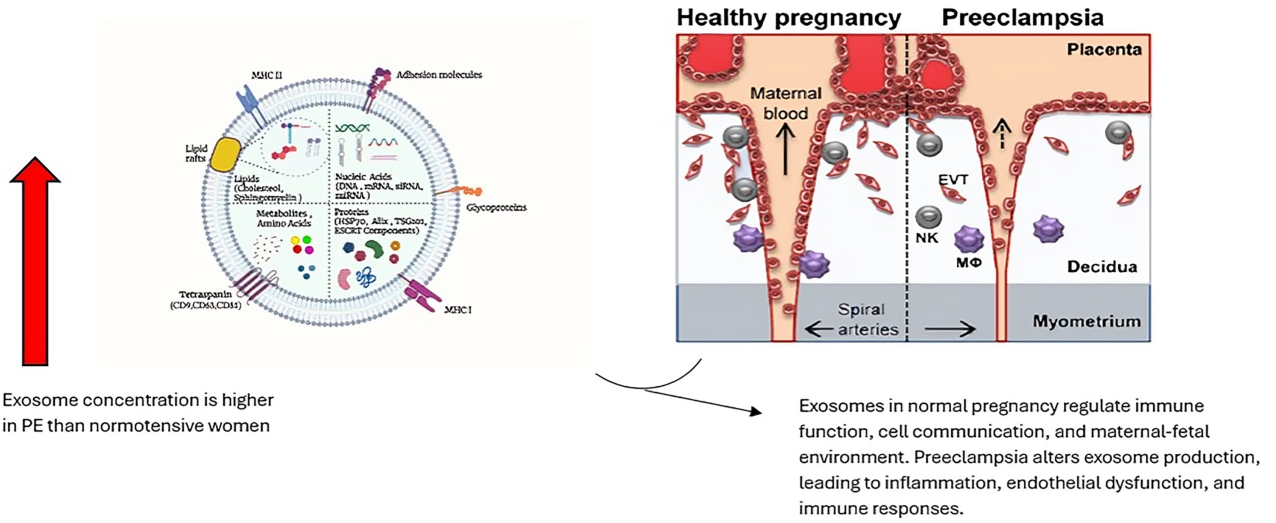

FIGURE 5 The role of exosomes in preeclampsia.

According to reports, STBs release exosomes into the maternal circulation. Exosome levels were discovered to be higher in preeclamptic mothers, which resulted in endothelial dysfunction, underlining the maternal problems that cause vascular constriction in PE (seen in Figure 5).[61] STB-derived EVs might be the link between placental failure and subsequent PE-related clinical maternal disorders. Although exosome levels in maternal blood were much higher in women with EOPE than in those with LOPE, the etiology of EOPE is thought to be more strongly related to the two-stage theory (i.e., to inadequate placentation) than to that of LOPE.[62] Thus, exosomes significantly connected with trophoblasts may occur in the blood of pregnant women with early-onset PE, and exosome quantities and patterns may reflect the PE phenotype.

Complement activation of exosomes in PE

Furthermore, the study conducted by Ermini et al. (2017) reported that PE-derived exosomes were implicated in vascular dysfunction due to their high sFlt-1 and sEng content. These proteins inhibit EC proliferation, migration, and differentiation, causing endothelial dysfunction. Secreted proteomes are involved in intercellular signaling, innate immunity, and the development of extracellular matrix scaffolds around cells.[63] Interactions between fetal components and maternal cells, especially the effects of exosomes produced by different cell types on one another, may be important in maintaining pregnancy and placentation. Exosomes produced by innate cells, released by the complement system, aid in antigen presentation to T lymphocytes and the establishment of tolerance.[64]

In PE, the placental trophoblast cells release exosomes that may lack sufficient complement regulatory proteins, such as CD46, CD55, and CD59, leading to dysregulated complement activation.[4] Moreover, exosomes from preeclamptic placentas can interact with endothelial cells, leading to complement component deposition (C1q, C2, C3, C4, C5 and MAC) on the endothelial surface, resulting in endothelial activation and injury. This contributes to the hallmark features of PE (as seen in Figure 6), such as hypertension and excessive inflammation.[65]

Exosomes produced from trophoblasts into the maternal circulation have also been identified to play a critical role in the maintenance of the Th1/Th2 balance, which leads to immune response activation via the complement system, resulting in an imbalance that may be responsible for PE pathogenesis.[66] Additionally, exosomes can carry proteins that directly bind to the surface and activate complement proteins, such as C3 and C5. This binding from the exosomes allows C3 and C5a to be cleaved into pro-inflammatory anaphylatoxins (C3a, C5a), causing damage to endothelial cells. Furthermore, the release of C3a and C5a promotes local and systemic inflammation, including the recruitment and activation of neutrophils and macrophages, which further contribute to the vascular dysfunction and endothelial injury seen in PE.[67,68]

Potential therapeutic approaches for PE using exosome-complement pathways

As mentioned in this review, exosomes can activate the complement system by interacting with C3 and C5. These interactions cause complement proteins to be cleaved into active fragments, including C3a and C5a, both of which are potent inflammatory mediators. The complement system, once activated, causes inflammation and vascular damage, resulting in essential PE characteristics such as

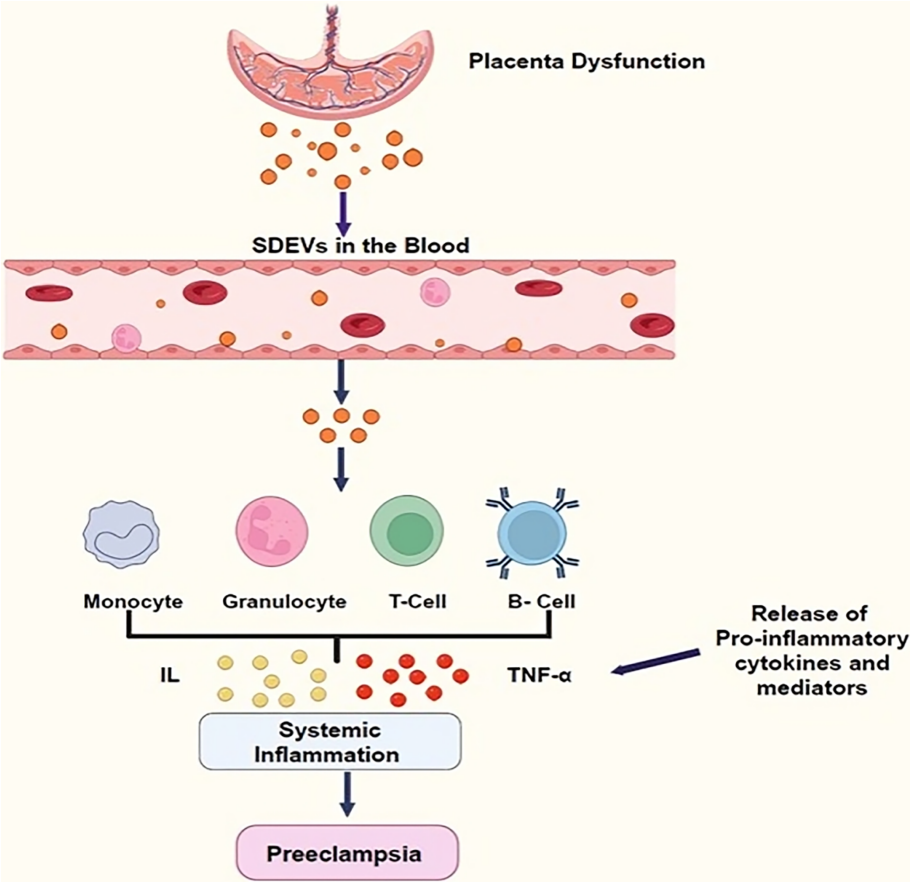

FIGURE 6 Exosomal circulation in preeclampsia.

hypertension and systemic endothelial dysfunction.[64–66] Therefore, it is plausible that possible treatment approaches should include selectively suppressing complement components C3 and C5, which may prevent excessive complement activation in PE.[69] Given that C3 and C5 activation induces inflammatory anaphylatoxins (C3a, C5a) and contributes to endothelial dysfunction, C3/C5 inhibitors may attenuate the inflammatory response.[70] For example, eculizumab, a C5 inhibitor used in atypical hemolytic uremic syndrome, could be repurposed to treat PE by reducing complement-induced vascular damage.[71] Moreover, targeting the inhibition of other complement components such as the MAC, C1q, C2, and C4 may also prove to be a potential avenue for treatment. However, further research needs to be conducted on this treatment approach.

Another possible interesting treatment approach is to target the exosome biogenesis pathway. Modifying exosome biogenesis pathways in trophoblast cells may limit the release of damaging exosomes containing sFlt-1 and sEng, both of which affect endothelial function in PE. Targeting these exosome formation pathways with small molecule inhibitors of the endosomal sorting complex needed for transport (ESCRT) system may limit exosome release.[72,73] This may be achieved using nanotechnology to deliver small molecule inhibitors to trophoblast cells, which may provide a more controlled strategy to decrease damaging exosome release.[68] Nanoparticles loaded with ESCRT inhibitors could be tailored to preferentially target placental tissue and prevent the shedding of harmful exosomes, thereby alleviating endothelial dysfunction and systemic inflammation in PE.[74]

CONCLUSION

Exosomes play a critical role in mediating immune interactions between the mother and fetus during pregnancy through communication with the complement system. In PE, dysregulation of the complement system activation facilitates the release and contents of placental exosomes, contributing to placental dysfunction and leading to systemic inflammation and endothelial damage. As such, exosomes need to be studied further to target their pathways involved in exosome-mediated complement activation, which may provide new strategies for managing PE and improving pregnancy outcomes.

AUTHOR CONTRIBUTIONS

M. David: Conceptualization; visualization; writing – original draft; writing – review and editing. **N. Maharaj:** Conceptualization; investigation; supervision; writing – review and editing. **A. Krishnan:** Software; visualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

There is no data available for this study, as this is a review article.

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