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REVIEW

The role of the complement system in HIV infection and preeclampsia

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Abstract

Background The complement system is a key component of the innate immune system that plays a vital role in host defense, maintains homeostasis and acts as a mediator of the adaptive immune response. The complement system could possibly play a role in the pathogenesis of HIV infection and preeclampsia (PE), both of which represent major causes of maternal death in South Africa.

Recent findings The relationship between PE and HIV infection is unclear as PE represents an exaggerated immune response, while HIV infection is associated with a decline in immune activity. Although the complement system works to clear and neutralize HIV, it could also enhance the infectivity of HIV by various other mechanisms. It has been suggested that the dysregulation of the complement system is associated with the development of PE.

Conclusion There is currently a paucity of information on the combined effect of the complement system in HIV-associated PE. This review highlights the role of the complement system in the duality of HIV infection and PE and provides new insights into this relationship whilst also elucidating potential therapeutic targets.

Keywords Complement · Preeclampsia · HIV · Inflammation

Introduction

The human immunodeficiency virus (HIV) is a retrovirus which invades the immune system and is associated with the impairment of cellular immunity and an increased susceptibility to opportunistic infections [1, 2]. HIV infection remains one of the leading health concerns in the world. In 2017, the recent tally of people living with HIV globally was 36.9 million (31.1–43.9 million) [3]. South Africa (SA) represents the country with the highest HIV epidemic in the world, with 7.52 million people living with HIV infection in 2018 [4, 5]. Furthermore, women constitute more than half of all people living with HIV infection [4], in SA approximately one-fifth of women in the reproductive age of life (15–49 years) are HIV positive [5].

In SA, non-pregnancy-related infections (mainly HIV) accounts for 25% of maternal deaths while hypertensive disorders of pregnancy (mainly preeclampsia) constitutes 14.8% of maternal deaths [6]. Preeclampsia is a pregnancy-specific multi-systemic disorder complicating 3–8% of all pregnancies globally and is a major cause of maternal mortality and morbidity especially in low- and middle-income countries [7, 8]. Preeclampsia is diagnosed by new onset hypertension (blood pressure ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic) accompanied by one or more of the following conditions at or after 20 weeks' gestation: (i) proteinuria, (ii) maternal organ dysfunction including acute kidney injury, liver involvement, neurological complications, hematological complications, and (iii) uteroplacental dysfunction [9]. Maternal complications of preeclampsia (PE) include acute renal failure, liver failure, eclampsia (seizures), pulmonary edema and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome [10]. In addition, fetal complications include placental abruption, intrauterine growth restriction, prematurity, and an increased risk of perinatal death [10].

The pathogenesis of PE is thought to occur in two stages. The first stage being abnormal placentation and the second stage is the clinical expression of the disease [11]. Currently,

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no definitive cure exists and the only effective treatment is delivery of the fetus and placenta [12]. Therefore, therapeutic strategies are focused on prolonging pregnancy by lowering high blood pressure and preventing the maternal and fetal complications associated with PE [13]. In normal pregnancy, significant adaptations of the innate and adaptive immune system occur to ensure survival of the fetal allograft while protecting the mother and fetus from pathogens [14]. A common hypothesis to explain abnormal placentation in PE is an altered maternal immune response or inadequate development of maternal tolerance to the fetus [15]. Conditions of acquired immunodeficiency such as HIV infection could prevent the development of PE as immune hyperactivity could be neutralized [16].

The mechanisms by which HIV invades and bypasses the body's immune response, specifically the innate immune system is not clear [17]. The complement system is an integral part of the innate immune system. In pregnancy, it optimizes placentation and defends both the mother and fetus against invading pathogens [18]. However, excessive complement activity could contribute to the pathogenesis of PE, emphasizing the importance of maintaining a delicate balance between complement activation and regulation for a successful pregnancy [8]. The role of the complement system in HIV infection is multifaceted. It can aid in the protection of the host against HIV infection, on the other hand it can also enhance HIV infectivity [19]. Taken together the combined effects of excessive complement activation in PE, and its dual role in HIV infection further complicates both disorders. In light of the high geographic prevalence of both conditions in SA, this review examines the role of the complement system in the dyad of HIV infection and PE mediating a better conceptual framework of combined pathologies with new insights into potential therapeutic targets.

The complement system

The complement system is comprised of various plasma proteins and cell membrane proteins [20, 21]. These components work together to ultimately result in the opsonization of target surfaces, lysis of pathogens and cells, and the induction of pro-inflammatory responses [21]. The complement system needs to be tightly regulated to prevent an attack against our own cells; therefore, complement activation is controlled by serum and cell surface regulatory proteins [18]. Whilst the complement system is vital in host defense, it also orchestrates the clearance of apoptotic cells, injured tissue debris and immune complexes contributing significantly to maintaining homeostasis [22]. In addition, it also acts as a mediator of the adaptive immune response [23].

Complement activation

The complement system is activated by three main pathways—the classical pathway (CP), the lectin pathway (LP) and the alternative pathway (AP), all of which lead to a common terminal pathway [22]. The CP is activated by the binding of recognition molecule C1q to IgM or IgG immune complexes bound to the surface of a microbe or other structure [24, 25]. This binding leads to a conformational change which results in the sequential activation of C1r and C1s. C1s then cleaves C4 and C2 to form the C4bC2a complex which is a C3 convertase [22, 26]. The LP becomes activated when recognition molecules, i.e., mannose-binding lectin (MBL) and ficolins bind to mannose and other sugar molecules found on the surface of a variety of microorganisms [22, 27]. This binding activates the LP serine proteases MASP-1 and MASP-2, which cleave C4 and C2 to also form the C3 convertase, C4bC2a [13, 28].

In contrast to the CP and LP, the AP is continuously activated at low levels in healthy individuals acting as a surveillance system [21]. The AP is activated by the spontaneous hydrolysis of a thioester bond within C3 to form $C3(H_20)$, this results in the binding of Factor B and cleavage by Factor D to form the C3 convertase, C3bBb. The convertase is stabilized by the plasma protein properdin [13, 29]. In addition, properdin could initiate AP activation through the interaction with surface AP C3 convertase or microbial antigens [22].

Hence, all three pathways produce C3 convertase which catalyzes the cleavage of C3 to C3a and C3b. The C3b molecule acts as an opsonin and binds to pathogens, immune complexes and apoptotic cells promoting phagocytosis [22, 24]. Furthermore, C3b can combine with C3 convertase to form the C5 convertase which cleaves C5 into C5a and C5b. C3a and C5a are both anaphylatoxins which are powerful pro-inflammatory molecules that attract and activate leukocytes by binding to their respective receptors, namely C3a receptor (C3aR) and C5a receptor (C5aR). In addition, C3a and C5a can also regulate vasodilation and increase vascular permeability [13, 22]. C5b interacts with C6, C7, C8 and C9 to form the membrane attack complex (MAC) or C5b-9, which forms a membrane pore, promoting membrane rupture and resultant cell lysis (Fig. 1) [24, 30].

Complement regulation

Complement regulators govern complement activation by inhibiting activation or initiating the degradation of complement components [24]. They include several soluble

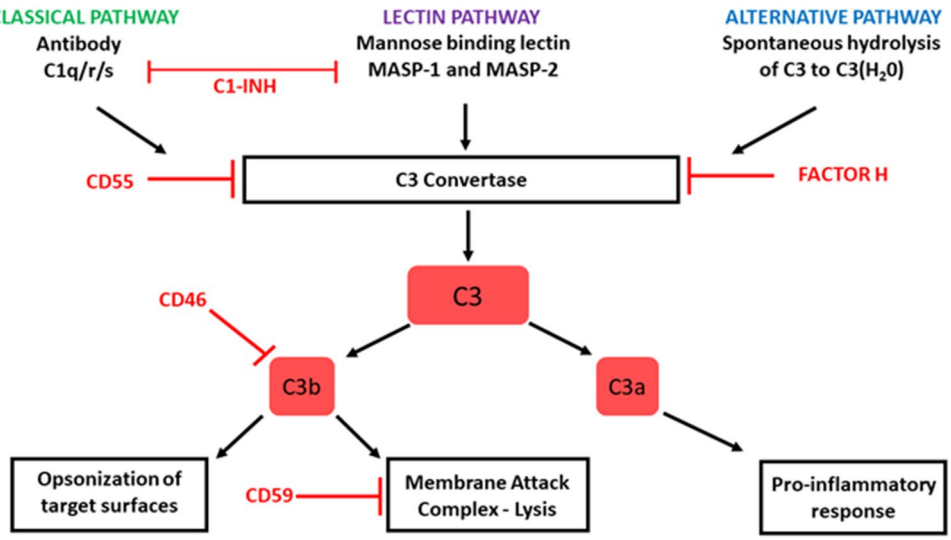

Fig. 1 Schematic diagram illustrating complement activation and regulation. Activation of the complement cascade occurs via three pathways namely, the classical, lectin and alternative pathway. The classical pathway is initiated via antibody and C1q binding, the mannose-binding lectin pathway is activated when MBL binds mannose on pathogen surfaces and the alternative pathway is activated by the spontaneous hydrolysis of C3 to form C3(H_20). All three pathways result in the production of C3 convertase that cleaves C3 into C3a and C3b. Activation of the complement cascade results in inflammation, opsonization and the generation of the membrane attack complex which eventuates in cell lysis

and membrane-bound molecules [18]. Plasma regulators include: C1-INH (C1 inhibitor), Factor H, and C4BP. C1-INH inactivates C1r and C1s of the CP and MASP-1 and MASP-2 of the LP upon binding, thereby preventing activation of these pathways [22]. Factor H degrades the AP C3 convertase (C3bBb), while C4BP binds to C4b and inhibits the formation of the C3 convertase (C4bC2a) in both the CP and LP [13, 26]. In pregnancy, excessive complement activation is controlled by the presence of three regulatory proteins found on the plasmalemma of trophoblast cells. These proteins include: CD55 (decay-accelerating factor), CD46 (membrane cofactor protein) and CD59. CD55 inhibits formation and initiates degradation of C3 convertase [18]. CD46 mediates the cleavage of C3b and C4b into their inactive forms, while CD59 prevents C9 insertion and formation of the MAC (Fig. 1) [22].

The complement system in normal pregnancy

The fetus is considered a semi-allograft as half of its genes are derived from the father. Hence, significant immune adaptation is required to prevent rejection of the fetus whilst simultaneously providing protection against pathogens [31]. To accomplish this, there is a shift of the maternal response from a T-helper 1 (Th1) type to T-helper 2 (Th2) type immune response favoring an immuno-tolerant microenvironment [15, 30]. The immunological state of pregnancy can be characterized as the enhancement of the innate immune system with concurrent suppression of the adaptive immune system [30]. To compensate for the decrease in adaptive immunity, complement activation is evident in normal pregnancy to aid in the protection against pathogens at the fetal–maternal interface [18, 24, 32–34]. Trophoblast cells secrete complement components C3, C4 and C1q [35]. Furthermore, C1q is synthesized by decidual endothelial cells suggesting a link between endovascular trophoblasts and spiral artery endothelial cells [36]. Interestingly, the decidua is the only tissue where endothelial cells produce C1q under physiological conditions [35]. C1q plays an important role in trophoblast migration and spiral artery remodeling [37]. Singh et al. reported that C1q deficient mice exhibit the characteristic features of PE such as hypertension and proteinuria, highlighting the importance of C1q in normal pregnancy [37].

A study by Albieri et al. showed that activated C3 contributed to normal phagocytic activity of mouse trophoblast cells suggesting C3 may have a role in trophoblast invasion [26, 33]. Whereas, the lack of functioning C3 in mice results in fewer pregnancies and higher resorption rates after implantation [38, 39]. Moreover, the risk of developing PE is increased in women who have systemic autoimmune diseases characterized by complement-mediated injury such as antiphospholipid antibody syndrome (APS) and systemic lupus erythematosus (SLE) [40]. In these women, autoantibodies which target the placenta can induce complement activation [40]. The importance of the complement

system in normal pregnancy has been established, however, various human and animal studies suggest that inadequate control/activation of the maternal complement system could be implicated in the pathogenesis of PE [28, 38, 39].

The role of the complement system in the pathogenesis of preeclampsia

Pathogenesis of preeclampsia

In normal pregnancy, maternal spiral arteries undergo a physiological conversion that mediate an adequate blood supply to the fetus [10]. The proposed mechanism of the pathogenesis of PE involves abnormal placentation, whereby deficient trophoblast invasion and a lack of remodeling of the spiral arteries result in a reduced luminal diameter of blood vessels. This leads to an inadequate blood supply which fails to meet the oxygen and nutrient demands of the fetus [10]. This in turn causes the placenta to become ischemic and release placental factors such as anti-angiogenic factors like soluble fms-like (sFlt-1), soluble endoglin (sEng) and other inflammatory mediators into the maternal circulation [41]. Consequentially, one gets a maternal generalized endothelial damage and systemic vascular dysfunction and the resultant clinical manifestations of PE (Fig. 2) [42].

The complement system in the pathogenesis of preeclampsia

A study by Gelber et al. using the mildly hypertensive BPH/5 mouse model showed that complement activation at

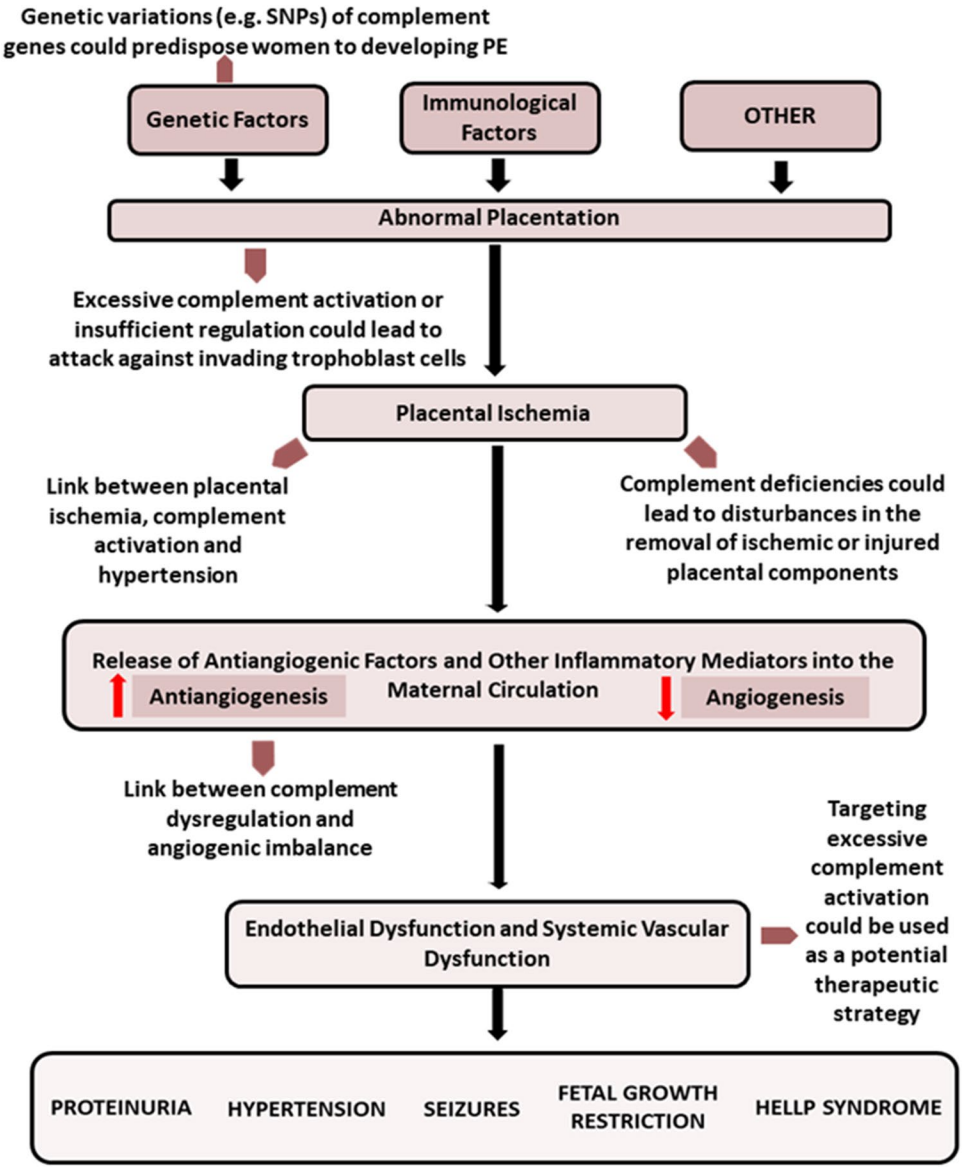

Fig. 2 Schematic diagram showing the role of the complement system in the pathophysiology of preeclampsia. The exact cause of abnormal placentation in PE remains unknown, however, it is hypothesized that genetic and immunological factors could play a role. Following abnormal placentation, the ischemic placenta contributes to complement activation. There is a potential link between complement dysregulation and angiogenic imbalance in PE. The resulting endothelial dysfunction leads to the clinical manifestations of PE

the maternal/fetal interface induces the recruitment of neutrophils that prompts an increase in local TNF-α together with a decline in vascular endothelial growth factor (VEGF) that eventuates in abnormal placentation and fetal death [43]. By blocking the complement pathway with inhibitors at the maternal/fetal interface, features of abnormal placentation were reversed [43]. A link between complement activation and hypertension in pregnancy was found by Lillegard et al. who showed that inhibiting complement activation reduced the progression of high blood pressure following placental ischemia in a rat model [44]. In addition, problems could also develop when there is an inadequate removal of ischemic or injured placental components by the complement system [39].

Increased C5a deposition in macrophages and C5aR expression in placental trophoblasts of PE women have been observed. C5a was found to inhibit the migration and tube formation of trophoblasts, while C5aR knockdown rescued migration and tube formation [45]. Notably, serum C5a was upregulated and correlated positively with maternal blood pressure [45]. The complement system could be involved in the later stages of PE by possibly generating inflammation or tissue damage [39]. This is supported by a case where eculizumab, a targeted inhibitor of complement protein C5, lead to the successful treatment of a patient with severe preeclampsia/HELLP syndrome. The treatment resulted in marked clinical improvement and pregnancy was prolonged [46]. Therefore, components of the complement system could provide a promising therapeutic drug target in PE.

The association of genetic variants of complement genes in preeclampsia

An imbalance of complement activation and regulation could arise from genetic variation; therefore, an appraisal of genetic variation of the complement system would offer a better understanding of the pathophysiology of PE [47]. Lokki et al. found three single nucleotide polymorphisms (SNPs)—rs2287845, rs366510 and rs2287848 within the C3 gene that were associated with severe PE. These authors identified 16 SNP haplotypes with extreme linkage disequilibrium in the middle of the gene and based on the allele combination, conferred a protective or predisposing effect to developing severe PE. The location of the genetic variants was in key domains of C3 possibly influencing the function of C3 [39].

A recent study by Mohlin et al. revealed no significant association between polymorphisms of the C3 gene and idiopathic recurrent spontaneous pregnancy loss. Nonetheless, several variations in the C3 gene were identified and some were found to modify the secretion and/or function of the protein [48]. A research group in China noted that polymorphisms of the complement C6 and MASP-1 genes were associated with the pathogenesis of PE and specifically the risk of early-onset PE and severe PE development [47]. Mutations in complement regulatory proteins (CD46, Factor I, and Factor H) were identified by Salmon et al. in women with SLE and/or antiphospholipid antibodies who had PE. Furthermore, the association of variants of CD46 and complement factor I was confirmed in a cohort of PE patients without autoimmune diseases [49]. Contrary to this, a more recent study by Lokki et al. reported that there was no association between the same CD46 variant (rs35366573) and other CD46 SNPs and PE in Finnish women [50]. The diversity of ethnic groups may contribute to conflicting results reported [47].

The complement system and angiogenic imbalance

Angiogenesis, the formation of new blood vessels from pre-existing ones is vital for a successful pregnancy [51]. Several studies have reported a significant increase in the incidence of PE in women with increased levels of sFlt-1 and sEng in the maternal circulation [52], and a potential link between complement dysregulation and angiogenic imbalance has been observed [40, 52]. A recent study revealed that the in vitro activation of the complement system at sub-lethal levels on syncytialized human trophoblast cells induced the up-regulation and secretion of sFlt-1. Data also suggested that C3a significantly increased sFlt-1 mRNA levels but not its secretion from trophoblast cells. The release of the MAC, however, was associated with sFlt-1 secretion [53]. These results are similar to He et al. who demonstrated a correlation between increased levels of the MAC and sFlt-1, correlating complement activation and anti-angiogenic factor enhancement in the plasma of PE women [52]. Increased C3a levels were also found and this correlated inversely with sFlt-1, suggesting sFlt-1 was only upregulated in trophoblast cells and not secreted, thus remaining undetected in maternal plasma [52].

Guseh et al. showed increased plasma sFlt-1, and increased urinary C5b-9 in women with severe PE, rendering urinary C5b-9 beneficial to link complement dysregulation with angiogenic imbalance [54]. Moreover, Sones et al. concluded that angiogenic imbalance precedes complement activation, contributing to abnormal trophoblast invasion and placentation [55]. C3 expression was found to be significantly upregulated at embryonic day (E) 7.5 around decidual vasculature implantation sites and at E10.5 in the placentae of pregnant blood pressure high (BPH)/5 mice whilst angiogenic imbalance was first detected at E5.5 (start of decidualization) with an upregulation of sFlt-1 at E10.5 in the placentae [55].

Evidence of dysregulation of the complement system in preeclampsia

It is possible that both circulating and placental complement components may have test value as biomarkers that predict adverse pregnancy outcome. A dysregulation in various complement components of both the placenta and maternal circulation have been demonstrated in PE [26]. In early pregnancy (between 10 and 20 weeks), Lynch et al. observed a dysregulation of the AP activation fragment Bb in women who develop PE and reported the highest levels of Bb in early pregnancy, implicating a vital role for the AP in protection of the developing fetus and placenta [56]. Nonetheless in the second half of pregnancy (> 24 weeks), an increase in maternal blood Bb levels in PE were noted but remained unchanged in fetal cord blood compared to normotensive women of African–American ethnicity [57]. In contrast, Hoffman et al. showed increased levels of Bb in both maternal and umbilical venous blood in severe PE compared to normotensive pregnancy [58]. These results implicate racial/ethnic difference, disease type and maternal/fetal blood as confounding factors in the dysregulation of the complement cascade [57].

Additionally, in early pregnancy, complement activation (elevated C3a levels) is enhanced in amniotic fluid in early-onset PE. This advocates that immune dysregulation could precede the clinical signs and symptoms of PE development [59]. In 2010, Derzsy et al. noted significantly higher C-reactive protein, C4d, C3a, and SC5b-9 levels with significantly low C3 levels in PE compared to healthy pregnant women. Notably, the excessive complement activation primes the depletion of C3 in plasma, as C3 synthesis is outpaced by C3 activation [28]. Notably, excessive complement activation or deficient complement regulation could lead to attack against invading trophoblast cells (Fig. 2) [23]. In 2013, Denny et al. found increased concentrations of C5a in maternal plasma and umbilical cord blood in PE compared to gestational hypertension and normotensive pregnancy. This suggests that C5a can diffuse between maternal and fetal circulation and thus contribute to PE development [60]. The exaggerated urinary excretion of C3a, C5a and C5b-9 in severe PE compared to healthy controls has also been reported [61]. Interestingly, the level of excretion of C5b-9 was able to differentiate between severe PE and chronic hypertension [61].

The complement system and HIV infection

Activation of the complement system in HIV infection

The complement system can be activated in the early stages of HIV-1 infection directly without antigen/antibody interaction [17]. HIV-1 surface protein gp41 binds to C1q and activates the complement CP. While the HIV-1 envelope protein gp120 can bind to MBL and possibly neutralize the virus [19, 62]. In addition, once MBL is bound to the HIV virus, it triggers the activation of the complement LP, increases phagocytic uptake and inhibits viral entry to susceptible cells [62, 63]. In support of this, genetic studies have shown that MBL deficiencies are associated with an increased susceptibility to HIV-1 infection and disease progression [64–66]. Following seroconversion, the CP is further activated by HIV-1 specific antibodies (Fig. 3) [67]. Despite a strong and sustained antibody response, it is believed that only a fraction of the antibodies produced have neutralizing activity, thus it is insufficient to prevent the initiation of HIV-1 infection [68].

Complement-mediated enhancement of HIV infection

Although the complement system is activated by HIV-1 infection, HIV-1 in circulation is able to evade complement-mediated lysis and remain infective by various mechanisms [19]. HIV-1 can incorporate host cell complement regulatory proteins like CD59 and CD55 on its viral envelope [19]. The virus acquires these regulatory proteins from the host cell in the budding process. In addition, the complement regulator factor H binds to HIV-1 providing extra protection from complement attack [19, 63]. A study by Hu et al. showed that the inhibition of human CD59 activity enhances complement-mediated virolysis of HIV-1 [69]. Deposition of complement fragments such as C3 and C5a on the surface of the HIV-1 virions facilitates the interaction between HIV-1 and cells expressing complement receptors including macrophages, dendritic cells and non-immune cells including erythrocytes. This results in the enhanced trans-infection of CD4+ T cells (Fig. 3) [17, 63].

Dendritic cells (DCs) are one of the first cell types to come into contact with HIV-1; however, they also enhance viral spread to newly activated CD4 T cells in submucosa and lymph nodes [70]. Tjomsland et al. revealed that complement opsonization of HIV-1 particles promotes MHC class-1 presentation of HIV-derived antigens by DCs [71].

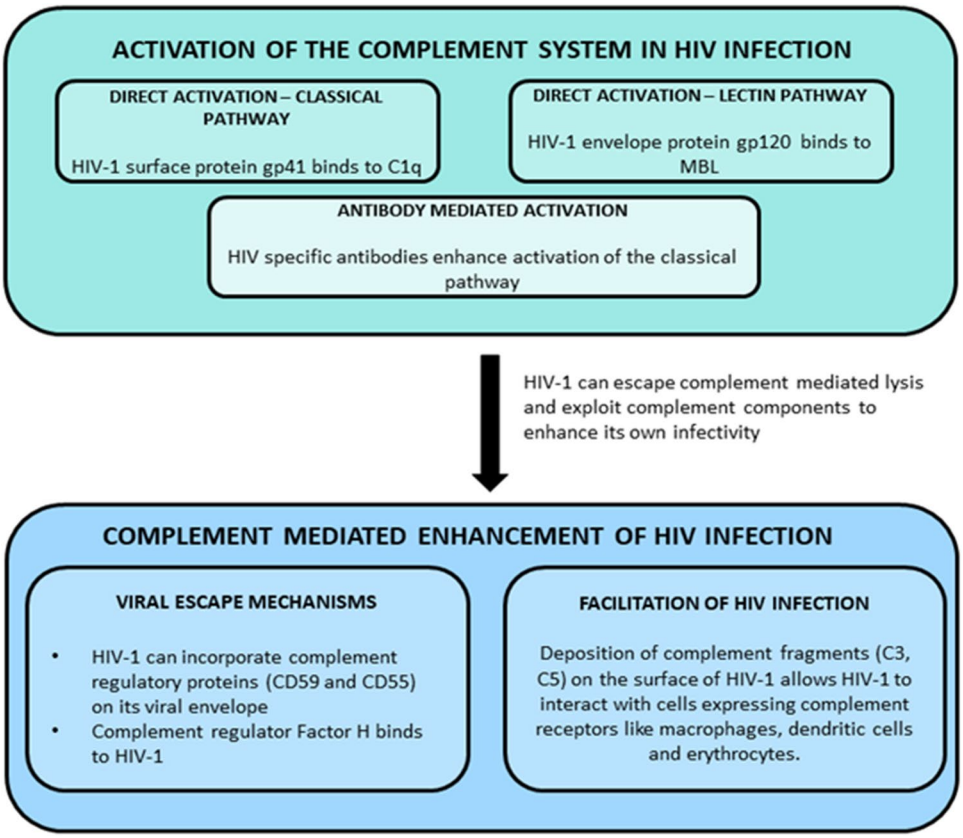

Fig. 3 Schematic diagram showing the role of the complement system in HIV infection. The complement system can be directly activated by the HIV-1 virus via gp41 and gp120 binding. HIV-specific antibodies can further contribute to complement activation. However, HIV-1 can also escape complement-mediated lysis by incorporating CD59 and CD55 on its viral envelope. Additionally, complement deposition on the surface of HIV-1 facilitates the interaction between the virus and cells expressing complement receptors

In contrast, complement opsonization of HIV-1 enhances infection of DCs through the complement receptor 3 (CR3) [72]. A study by Ellegard et al. showed that free HIV-1 induces inflammatory cytokines such as IL-1β, IL-6 and TNF-α. However, after complement opsonized HIV-1 and complement and Ab-opsonized HIV-1 exposure, there is a decrease in the inflammatory response, or it is absent [72]. Mishra et al. found a significantly lower surface expression of CR3 and CD46 on DCs in antiretroviral-naïve and treated HIV-1-infected individuals compared to controls (seronegative donors) and significantly higher complement activation in treatment-naïve HIV-1-infected individuals than controls [73]. These results suggest alterations in the expression of CR3 and CD46 on DCs and complement activity could influence HIV-1 disease progression [73].

The complement system in HIV infection and preeclampsia

In light of the high prevalence of HIV infection and PE in Sub-Saharan Africa, it is important that we understand the combined effect of the complement system in the duality of HIV infection and PE. An upregulation of various complement components in PE [28] suggests increased activation of the complement system and may lead to increased opsonization of HIV virions in HIV-infected women, resulting in enhanced infectivity [17]. In PE, there is an increased production of inflammatory cytokines by pro-inflammatory T cells, with a concomitant decrease in regulatory and anti-inflammatory cytokines. As a result, this imbalance leads to chronic immune activation [74, 75]. Similarly, HIV infection creates a chronic inflammatory state, attenuated by the use of highly active antiretroviral therapy (HAART), albeit not completely resolved [76]. Excessive or poorly controlled complement activation could shift the balance from health to inflammatory pathologies [77], creating a cycle between tissue damage, complement activation and inflammatory cells which aggravate clinical complications [77].

Complement components C3a and C5a are upregulated in PE [28, 60] and have the ability to induce inflammation, recruit DCs and macrophages for HIV-1 infection [63]. When C5a is present, an increase of pro-inflammatory cytokines TNF-α and IL-6 have been reported, both of which are liable for promoting HIV-1 infection and regulation [78, 79]. The inhibition of C5aR reverses the enhancement of HIV infection induced by C5a [78]. Therefore, the chronic inflammatory state noted in HIV infection and PE could be further exacerbated by excessive complement activation. A study by Rossheim et al. showed a 54% increase in complement activation (measured by C3a levels) in adults with well-controlled

HIV infection (on antiretroviral therapy) compared with healthy controls [76]. Huson et al. reported increased C3 and C1q-C4 levels in asymptomatic patients with HIV infection compared to healthy controls. However, MBL deficiency did not influence complement activation, suggesting HIV infection activates the complement system primarily via the CP [80].

To the best of our knowledge, Khan et al. were the first to investigate regulatory complement (Creg) proteins CD35 and CD55 in HIV-associated PE. They showed an increase in CD35 and CD55 in PE compared to normotensive pregnant women irrespective of HIV status [81]. Lokki et al. observed C4 deficiencies in placentas of PE women compared to normal pregnancy; however, they did not detect any differences in the expression patterns of membrane regulators (CD46, CD55 and CD59) in PE women compared to normal pregnancies [23]. Therefore, CD55 upregulation suggests a protective mechanism against excessive complement activation in PE, further complicated by HIV infection [81]. In addition, the upregulation of CD55 could lead to enhanced HIV-1 infection [19].

Immature DCs induce the differentiation of naïve CD4+ T cells into regulatory T (Treg) cells to maintain immune tolerance, while mature DCs induce the differentiation of naïve CD4+ T cells into activated Th1 cells mediating inflammatory responses [82, 83]. Despite the number of DCs in the decidua being non-significantly different between PE and normal pregnancies, the ability of DCs to induce Treg cells is significantly impaired in PE [84]. Zhang et al. report that the proportion of Th1 cells and mature dendritic cells was significantly higher in PE women compared with healthy pregnant women. This suggests the maturation of decidual DCs lead to an increase in Th1-type cells and a constant inflammatory state in PE [82]. In contrast, a study by Ellegard et al. showed complement opsonized HIV-1-modulated DC responses and their cross-talk with natural killer (NK) cells to inhibit killing and encourage the increase of factors associated with immune suppression (PD-1, TIM-3, LAG-3) and susceptibility to infection (TCM, CD38, CXCR3, CCR4) on CD4 T cells [70]. Therefore, it is plausible to assume HIV infection in conjunction with the complement system may also attenuate the heightened inflammatory state in PE. An association has been demonstrated between higher plasma C3 levels and metabolic syndrome in an older cohort of HIV-infected individuals treated with combination antiretroviral therapy compared to HIV-negative controls [85]. The relationship between metabolic syndrome and the incidence of PE has been studied and it was observed that the risk of PE was increased among women with metabolic syndrome [86].

The role of antiretroviral treatment in HIV infection and preeclampsia

The current treatment of HIV infection is HAART. In pregnancy, HAART is used to reduce maternal viral replication and mother to child transmission of HIV by lowering the plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns [87]. It is plausible to assume that immunosuppressive conditions such as HIV infection could inhibit immune hyper-reactivity thus reducing the incidence of PE development [88, 89]. Antiretroviral therapy, however, re-instates the immune response. Nonetheless, the correlation of HIV infection, HAART, and the risk of PE development are conflicting as reports of an increased, decreased and a neutralization of PE development have been put forward [90–95].

Wimalasundera et al. report that HIV-infected women who received no antiretroviral therapy have a significantly lower rate of PE development compared to HIV-infected women on triple antiretroviral therapy [90]. Similarly, a cohort study by Suy et al. concluded that HIV-infected women on HAART prior to pregnancy are associated with a higher risk of developing PE and with high fetal mortality [91]. A retrospective study by Sansone corroborated these results in that HIV-infected women on HAART had a significantly higher risk of PE compared to the non-HAART group and HIV-negative women [92]. These findings suggest women not treated against HIV infection are unlikely to induce an exaggerated inflammatory response during pregnancy due their immunocompromised state and are, therefore, protected against the development of PE. However, when HAART is administered, it re-establishes the mother's immune response to fetal antigens, and thus exacerbates the risk of PE development [90].

In contrast, a prospective observational cohort study by Landi et al. suggests that HIV-infected pregnant women have a significantly lower rate of gestational hypertension and PE, and this effect exists independently from the treatment received [93]. A report by Kalumba et al. demonstrated that the rate of HIV/AIDS was significantly lower in women with PE in comparison to normotensive healthy pregnant women [94]. Whereas in a matched cohort study by Boyajian et al. no difference in the risk of developing PE was demonstrated between HIV-infected pregnant women on HAART versus uninfected pregnant women [95]. In 2016, Adams et al. conducted a systematic review which showed to date that evidence was inconclusive to confirm that women receiving antiretroviral treatment have an increased risk of developing PE compared to women who are HIV non-infected [96].

Conclusion

The relationship between HIV infection and PE is complex and uncertain. Although the complement system is vital in host defense, it plays a role in both HIV infection and PE. In HIV infection, the complement system is activated by HIV-1 directly or in the presence of antigen/antibody interactions. However, HIV-1 can also incorporate complement regulatory proteins like CD59 and CD55 from host cells onto its viral envelope aiding in viral escape. On the other hand, complement deposition on HIV-1 virions can enhance HIV-1 infectivity by facilitating the interaction with cells expressing complement receptors such as monocytes/macrophages and DCs. Various complement components are elevated in PE which could further enhance HIV infectivity, whereas complement opsonized HIV-1 can modulate DC response and their cross-talk with NK cells to promote the upregulation of factors associated with immune suppression possibly attenuating the constant inflammatory state of PE. Thus, it may be assumed that neutralization of the immune response is expected in HIV-associated PE. However, this notion is further complicated by the interplay of complement activation in both HIV infection and PE development. Nonetheless, urgent research is required to unravel the mystique of complement activation and regulation in HIV-associated PE. Also, identification of complement components could serve as biomarkers ultimately leading to better management modalities with targeted drug therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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