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Review

# Regulation of the complement system and immunological tolerance in pregnancy

Laura Teirilä[a,1], Jenni Heikkinen-Eloranta[b,1], Juha Kotimaa[a], Seppo Meri[a], A. Inkeri Lokki[a,*]

[a] Department of Bacteriology and Immunology, University of Helsinki and Helsinki University Hospital, Translational immunology research program, Research programs' Unit, University of Helsinki, FIN-00014 Helsinki, Finland
[b] Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, FIN-00029 Helsinki, Finland

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ABSTRACT

Preeclampsia is a serious vascular complication of the human pregnancy, whose etiology is still poorly understood. In preeclampsia, exacerbated apoptosis and fragmentation of the placental tissue occurs due to developmental qualities of the placental trophoblast cells and/or mechanical and oxidative distress to the syncytiotrophoblast, which lines the placental villi. Dysregulation of the complement system is recognized as one of the mechanisms of the disease pathology. Complement has the ability to promote inflammation and facilitate phagocytosis of placenta-derived particles and apoptotic cells by macrophages. In preeclampsia, an overload of placental cell damage or dysregulated complement system may lead to insufficient clearance of apoptotic particles and placenta-derived debris. Excess placental damage may lead to sequestration of microparticles, such as placental vesicles, to capillaries in the glomeruli of the kidney and other vulnerable tissues. This phenomenon could contribute to the manifestations of typical diagnostic symptoms of preeclampsia: proteinuria and new-onset hypertension. In this review we propose that the complement system may serve as a regulator of the complex tolerance and clearance processes that are fundamental in healthy pregnancy. It is therefore recommended that further research be conducted to elucidate the interactions between components of the complement system and immune responses in the context of complicated and healthy pregnancy.

## 1. Introduction

Preeclampsia is a life-threatening vascular complication of the human pregnancy characterized by new-onset hypertension and proteinuria or subjective symptoms during the second half of the pregnancy [1,2]. Preeclampsia affects 3–5% of pregnancies worldwide, but the mechanisms underlying the disease remain elusive and no curative treatment is available [3]. However, immunological mechanisms are strongly indicated in the disease process [4]. Preeclampsia is initiated in the early pregnancy, when the invading placental trophoblast cells fail to complete the remodulation process of the maternal spiral uterine arteries resulting in an aberrant high-volume, high-pressure circulatory conditions in the intervillous space of the placental tissue [5–7]. Mechanical shear and turbulent blood flow cause injury to the syncytiotrophoblast layer, the single fused cell barrier between the placental tissue and maternal blood flow [8]. Concurrently, ischemic injury due to pulsatile reperfusion may result in placental dysfunction and impaired placental capacity [9–11]. As a result, the placental syncytiotrophoblast disintegrates exposing the villi to components within the maternal blood and resulting in an increased load of released placental debris [12,13]. The placental microparticles enter the maternal circulation and challenge both her innate and adaptive immune systems [14,15]. As a consequence, the placental debris could activate the complement and coagulation systems, cause microthrombi, endothelial damage, and breakdown of the systemic maternal-fetal tolerance [16–18].

The complement system is an integral part of innate immunity consisting of more than forty factors that interact in a progressive cascade to instigate terminal pathway activation. Complement activation may become initiated via any of three distinct pathways, the classical, lectin, or the alternative pathway (Fig. 1). A step-wise enzymatic cleavage of the activating components will generate opsonizing molecules to label targets for phagocytosis and anaphylatoxins that are potent chemoattractants. The classical pathway (CP) is activated when

* Corresponding author at: Department of Bacteriology and Immunology, PO Box 21 (Haartmaninkatu 3), 00014, University of Helsinki, Finland.
*E-mail addresses:* laura.teirila@helsinki.fi (L. Teirilä), jenni.k.heikkinen@helsinki.fi (J. Heikkinen-Eloranta), juha.kotimaa@helsinki.fi (J. Kotimaa), seppo.meri@helsinki.fi (S. Meri), inkeri.lokki@helsinki.fi (A.I. Lokki).
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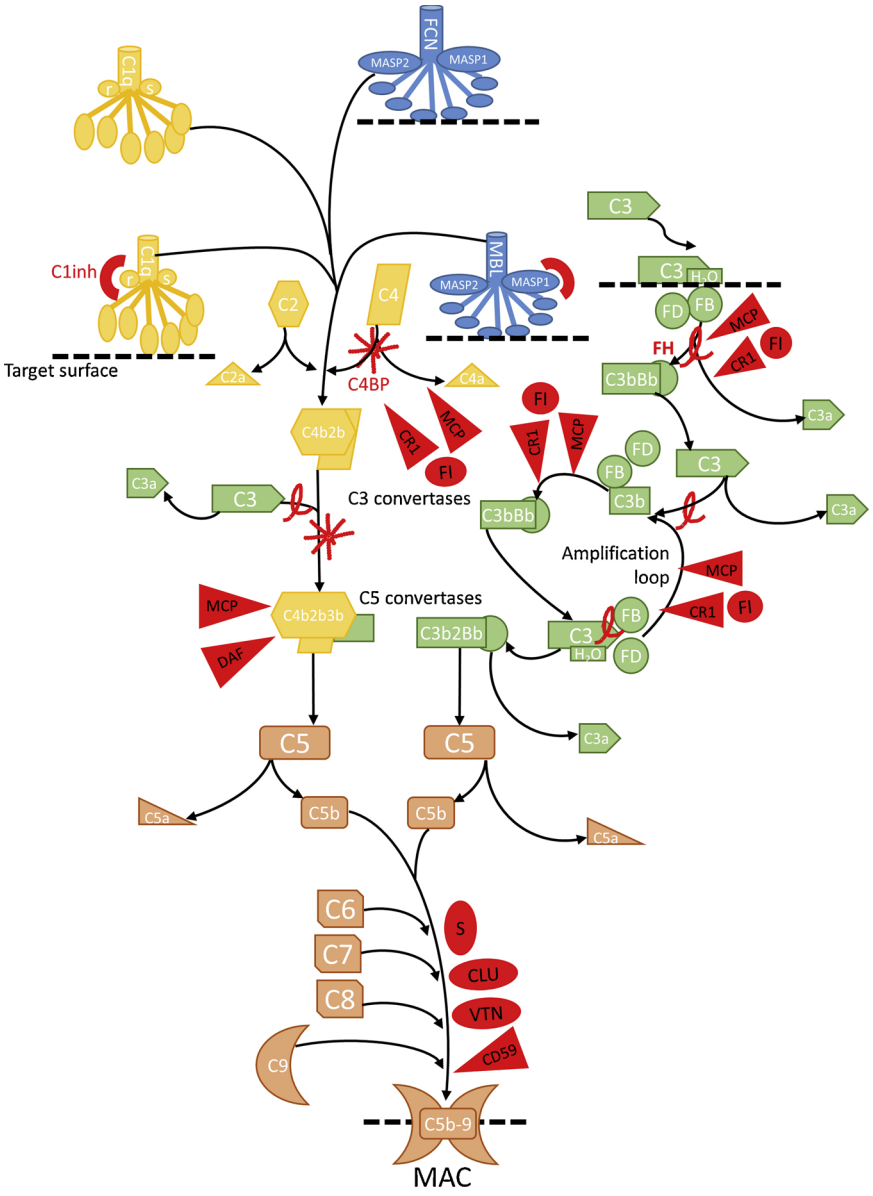


**Fig. 1.** Complement system can be activated via the alternative pathway (green), classical pathway (yellow) or the lectin pathway (blue). They all lead to activation of C3 and of the terminal pathway (orange) by formation of C3/C5 convertases. The most important complement inhibitors are shown in bright red. Factor H (FH) and C4b binding protein (C4BP) are the most important soluble regulators of the early pathways of complement activation. FH is particularly important in the inactivation of C3b, while C4BP is primarily active in the classical pathway of complement activation. The triangular regulators are surface bound inhibitors. C5a and C3a are potent anaphylatoxins with the capacity to recruite and activate immune cells to the site of complement activation. MAC – membrane attack complex, CLU – clusterin, VTN – vitronectin.

the C1 complex binds to the target cell leading to activation of C4, C2 and formation of the C3/C5 convertase, which will activate C3 and initiate activation of the terminal pathway (TP) [19]. C1q deposits directly on apoptotic cells, exposed cellular structures after damage, and some microorganisms. It is also targeted via pattern recognition molecules such as IgGs, IgM, and pentraxins (CRP and PTX-3) [20].

The lectin pathway (LP) of complement activation is analogous to the CP. It is activated by mannose-binding lectin (MBL) or one of the ficolins (ficolins 1, 2 and 3) binding to microbes that have certain oligomeric sugars, such as mannose or N-acetylglucosamine or acetyl groups (ficolins) on their surfaces. With the MBL-associated serine protease enzymes, MASP1, MASP2, and MASP3, the lectins form complement activating complexes. Activation of C4 and C2 leads to their deposition and formation of the C3 convertase, C4b2a.

The alternative pathway (AP) is one of the most evolutionarily ancient method of self-nonself discrimination [21]. In AP activation, C3b is covalently bound on cell surfaces and thereafter either inactivated by soluble or surface-bound complement regulators. Failing inhibition, AP activation becomes accelerated in the so-called amplification loop, where C3bBb convertases will activate an expanding number of native C3 molecules. The generated layer of C3b molecules opsonizes the target and promotes its phagocytosis. AP activation will also lead to activation of C5 and membrane attack complex (MAC) formation as a result of TP activation. The surfaces missing protective regulatory components leading to AP activation include fungi, viruses and certain bacteria [19]. Nonviable endogenous cells, like apoptotic, ischemic, or aged cells, can also become targets for AP attack, if they lose their ability to protect against complement activation.

Complement regulating proteins are integral in protecting healthy cells from destruction. Many of the complement inhibitors are composed of small, approximately 60 amino-acid long units called complement control protein (CCP) domains. These regulators are encoded in a distinct gene cluster on chromosome 1, called regulators of complement activation (RCA) [22]. Nevertheless, an optimal degree of continuous small grade complement activation is maintained for sensing and clearing away injured and dying cells and allowing robust activation on invading microorganisms.

Complement activation can be regulated at the level of initiation, amplification, and generation of effectors such as opsonins, MAC, and proinflammatory anaphylatoxins. Complement regulators can function in solution or on cell surfaces. Soluble inhibitors include C1 inhibitor (C1INH), C4b binding protein (C4BP), factor H, clusterin, and

vitronectin. C1INH controls the C1r, C1s, and the MASP serine esterase enzymes in CP and LP (Fig. 1). The main soluble regulator of AP is C3 inhibitor factor H (FH). FH consists of 20 CCP domains with different binding specificities for C3b in solution and, importantly, on cell surfaces through sialic acid/polyanion binding domains that stabilize the FH-C3b interaction [22]. FH has a crucial function in acting as a co-factor for factor I (FI) in inactivating C3b and in inhibiting the AP C3 convertase, C3bBb. C4BP has analogous functions in promoting inactivation of C4b and controlling the CP C3 convertase, C4b2a. Clusterin and vitronectin act as soluble inhibitors of the TP by scavenging intermediate soluble terminal complement complexes. The membrane-bound regulators CD35, CD46 and CD55 regulate CP and AP of complement activation, while CD59 prevents membrane attack against our own cells.

Properdin is the only positive regulator of complement system, acting partially in opposition to FH by stabilizing the AP C3-convertase C3bBb [23]. By preventing membrane insertion of MAC, the TP inhibitors clusterin and vitronectin form a soluble C5b-9 complex that can be used as a diagnostic marker for complement activation. Cells express membrane proteins that protect from excessive complement activation. CD35 (CR1) inhibits C3 activation and binds C3b- and C4b-coated particles to promote their clearance [24]. CD46 (Membrane Cofactor Protein, MCP) acts as a cofactor for FI thus promoting inactivation of C4b and C3b, whereas CD55 (Decay Accelerating Factor, DAF) promotes the disassembly of C3-convertases. CD59 (protectin, MAC-IP) is the only MAC inhibitor on cell membranes, blocking the generation and insertion of polymeric C9 complexes into cell membranes [25].

Severe disturbances in complement regulation can lead to such catastrophic consequences as the atypical hemolytic uremic syndrome (aHUS) and other forms of thrombotic microangiopathy (TMA) [26]. Central to these is complement attack against endogenous tissue structures, endothelial cells, blood cells and platelets with a consequent vascular damage and organ, notably kidney failure. Pregnancy is a well-known potential trigger for such syndromes [27,28]. The underlying reasons in aHUS are usually mutations in genes of complement components that influence its function on surfaces (factor H, MCP, factor I, C3, factor B, thrombomodulin). Most commonly, mutations are located in the C-terminus of factor H. AHUS-related mutations in C3 and factor B lead to their increased activity. Also, autoantibodies against factor H predispose to aHUS.

In this review we explore the multiple interactions, roles, and effects of complement system in the context of pregnancy and pathogenesis of pregnancy complications with focus on preeclampsia.

## 2. Aberrant complement regulation in preeclamptic pregnancy

Complement belongs to the first line of defense in the circulation and tissues. Extravillous trophoblast cells invading into maternal tissues will potentially face complement activating antibodies within the maternal tissue. Therefore, they must be sufficiently protected from the maternal complement system [29,30]. A second site in the need of protection from complement activation is on the syncytiotrophoblast, which is the placental surface that is constantly exposed to maternal blood. Complement activation will result in the release of proinflammatory and chemotactic anaphylatoxins with the potential to cause inflammation, vascular leakage and thrombosis. Insufficiently regulated complement activation may also result in tissue damage characterized by inflammatory lesions and increased apoptosis on the placental villi [31–33]. Generation of the membrane attack complex will lead to calcium influx into target cells, which in itself may cause a metabolic storm, when sublytic C5b-9 induces apoptotic pathways and further stresses the cells with unpredictable consequences. One of the consequences is the release of vesicles in an attempt to remove the accumulating MACs [34].

Complement has been studied in preeclampsia extensively [30,35,36]. The larger body of evidence points towards an overactivation of the maternal complement system in the disease [37]. Hypertensive disorders of pregnancy with impaired placental perfusion have been proposed to result from excessive activation of the complement system causing inflammation or, alternatively, from deficiencies in the system that compromise the proper development and perfusion of the utero-placental unit [38]. Complement activation may occur spontaneously, if control mechanisms are not sufficiently operational [12]. An incompatibility between the maternal immune system and placental cells may also include an imbalance of complement activation and regulation. This can contribute to the pathogenesis of preeclampsia [11]. In discordant cases, complement attack may compromise placental cells, if their protection fails. Alternatively, antibodies or exposed tissue structures may act as the trigger.

C3 is the central component of complement system that has also been the subject of several genetic studies in pregnancy complications. Early work in mouse models demonstrated that the presence of C3 as well as its appropriate regulation are prerequisites for a successful pregnancy [39]. Current literature supports the hypothesis that recurrent miscarriages and preeclampsia may at least partially share common immunological etiology [4,40]. Functional variants of the *C3* gene have been described in idiopathic recurrent miscarriage patients [41]. Furthermore, we found that the haplotype of *C3* in a region that codes for the binding domains of the protein associates to preeclampsia risk in a sequence-specific manner [42]. C3 has also been found to be upregulated both in the acute inflammation of the spiral arteries in preeclamptic patients and in a hypertensive pregnant rat model [43]. Mutations in complement regulators have also been described in systemic lupus erythematosus (SLE) patients with complicated preeclampsia [44].

Factor H is the most potent regulator of the AP, with the capacity to promote inactivation of complement C3b into the opsonin iC3b. Opsonization by iC3b allows for phagocytosis of the target in the absence of full complement activation. Following exposure to active complement, the placental villi are circumferentially protected from complement attack by factor H deposition [45]. Factor H has also been observed intracellularly in placental trophoblasts. Recently, in an unpublished study, we have observed a functionally defective maternal factor H due to possibly de-novo genetic variants in seven cases of severe/complicated preeclampsia. Factor H is known to have a non-canonical immunomodulatory role independent of complement regulation. Factor H promotes the differentiation of inflammatory monocyte-derived dendritic cells (DCs), whereby they are directed towards a tolerogenic interleukin (IL)-10 and TGF- β dominated phenotype [46]. The possible tolerogenic role of factor H outside of complement regulation has not been studied thus far in pregnancy. In contrast to factor H, C4BP, the soluble regulator of the classical pathway C3 convertase, is mostly deposited on apoptotic structures such as placental knots [45]. Hereditary angioedema (HAE) is a disease caused by the lack or insufficient function of C1-inhibitor. The effect of pregnancy on the prevalence of HAE attacks is unpredictable and variable [47]. Interestingly, while plasma levels of C1-inhibitor are physiologically low during pregnancy, the levels are significantly lower in preeclampsia in comparison to normal pregnancy, with lowest values recorded in severe preeclampsia [48].

The amounts of circulating complement activation products are elevated in early-onset severe preeclampsia and late-onset severe preeclampsia [49]. Urine, but not plasma levels of soluble MAC (sC5b-9) are elevated in preeclampsia [50]. This is likely a reflection of complement-mediated damage of the kidney, which may result in the diagnostic sign of proteinuria. In preeclampsia, proteinuria has been attributed to CP activation and linked to angiogenic dysregulation [51]. On the other hand, the mere proteinuria may result in the generation of soluble terminal complexes in the proximal and distal tubuli of kidneys. Studies in support of overactivation of the AP often report an excess of factor B and its activation products Ba and Bb in the patient sera [52,53]. However, the role of factor B is not clear [37]. A relative excess

of C4d deposition on the placenta is observed in preeclamptic pregnancies in comparison to placentas from healthy pregnancies, where C4d is mostly absent [54]. C4d is also observed in the endothelium of kidney glomerular capillaries in preeclampsia [55]. The C4 protein pool comprises two homologous *C4* gene products. C4A preferentially binds to proteins and C4B to carbohydrates. We have previously shown that maternal heterozygous deficiencies of the *C4A* and *C4B* genes correlate with severity of preeclampsia [45]. Specifically, in this small cohort, *C4A* deficiencies were observed in 43% of early-onset preeclamptic mothers in comparison to none observed in non-preeclamptic controls. While homozygous *C4A* deficiencies are associated with autoimmune diseases including SLE, homozygous *C4B* deficiencies are linked to intolerance to sulphonamides and doxycycline as well to predisposition to various infections by encapsulated bacteria and to post-infectious symptoms [56].

Already in early immunohistochemistry studies C1q, C3 and C9 were seen in the preeclamptic placenta [57]. The syncytiotrophoblast of early-onset preeclamptic placenta displays the highest amount of deposited C1q [45]. On the other hand, extravillous trophoblast cells of placental origin express C1q, and first trimester cytotrophoblasts express components C3 and C4, of the complement system in an IFN-γ driven process [58,59]. These findings, although interesting, remain isolated observations. The role of the fetal complement system in preeclampsia has not been studied thus far.

The TP of complement activation has a role in preeclampsia. In one patient case, eculizumab, a monoclonal antibody inhibiting C5, was used successfully for the treatment of severe preeclampsia and the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. Its use resulted in improved laboratory values, as well as in the alleviation of preeclampsia symptoms [60,61].

## 3. Complement in apoptosis and inflammation in preeclampsia

In the early stages of pregnancy, a certain amount of inflammation is needed in order for the placentation process to succeed and lead to a healthy pregnancy [62,63]. This is also reflected in complement activation, where soluble anaphylatoxins C3a and C5a are observed in increased amounts during the healthy pregnancy [64]. In preeclampsia, however, the inflammatory response is inflated. Apoptotic structures and other injured tissue derived from the placenta and disrupted systemic maternal endothelium increase the requirement for waste management and debris removal by phagocytosis [65,66]. Facilitating phagocytosis is among the key roles of the complement system. In the presence of the regulators (factor H, C4BP, MCP) the key activation product C3b is inactivated by factor I into the opsonin iC3b, which is the main ligand for complement receptors 3 and 4 (CR3 and CR4, respectively). Complement receptors CR3 and CR4 are integrin-type receptors with signaling functions. They have an important role in the clearance of apoptotic structures and other unwanted materials through phagocytosis. Most apoptotic cells are cleared independently of complement in the early stages of the apoptotic process. However, when the number of apoptotic bodies increases, effective recognition of these structures by complement has a crucial role in maintaining sufficient clearance by phagocytosis [67]. We have recently discovered several preeclampsia-related genetic variants within the genes coding for CR3 (*ITGAM*) and CR4 (*ITGAX*) with functional effects on the receptors' interaction with iC3b. Excess burden or abnormal function of the complement system may limit its capacity to perform the necessary waste disposal function. Consequently, placental material cannot be properly cleared, and accumulation may occur in maternal tissues, such as in the lungs or blood vessels of kidneys causing inflammation and vascular damage. Indeed, there is a growing body of evidence that failure of the complement-facilitated phagocytosis of placental debris and microthrombosis may contribute to the disease pathogenesis (Fig. 2) [68–71]. Occlusion in the vascular capillaries could be due to accumulation of microvesicles released from placenta or to a

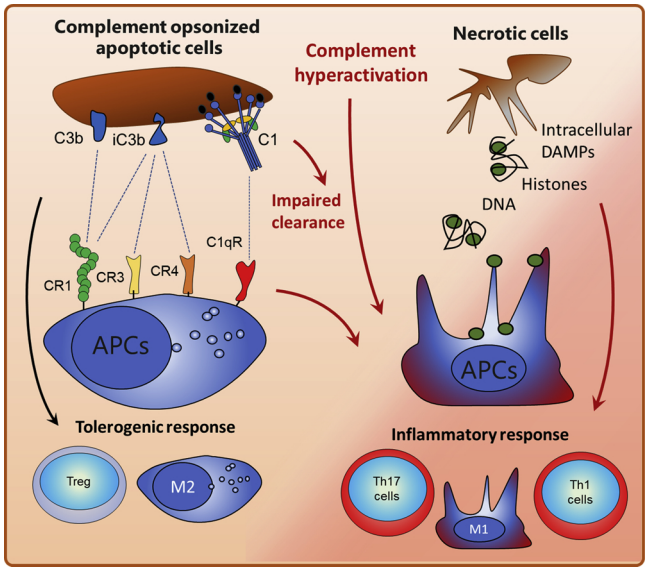


**Fig. 2.** Using complement receptors CR1, CR3, and CR4, antigen presenting cells phagocytize placental particles that have been opsonized by complement components such as C3b, recognized by CR1 or iC3b recognized by all three. C1q is recognized by C1q receptors C1qR and C1qBP also expressed on antigen presenting cells such as macrophages. In the normal system (black arrow) a tolerogenic M2 response is induced. Due to mutations in complement receptors or complement components, a dysfunctional complement activation (red arrows) may result in impaired clearance. Inadequate clearance may also arise due to complement hyperactivation and increased load of damage associated molecular patterns (DAMPs) that is associated with preeclampsia. Inflammatory M1 response can lead to further disruption of endothelial function disruption and systemic consequences, including hypertension and proteinuria, which are the diagnostic criteria in preeclampsia.

disturbance in the regulation of the coagulation system [72]. Furthermore, antibodies, tissue degradation products or insufficient regulation of complement activity may lead to complement overactivation with all its inflammatory vascular consequences.

CR3 has been shown to have a dual role in regulating immune system responses. Traditionally, it has been regarded as a pro-inflammatory receptor promoting innate immune-mediated inflammation. For example, it promotes the phagocytic uptake of particles and phagocytosis-related cytotoxic functions especially in neutrophils [73,74]. In monocytes, the engagement of CR3 or CR4 can lead to the production of pro-inflammatory cytokines (IL-8, MIP1α, MIP1β, IL-1β) [75,76]. In addition, CR3 interacts and supports the function of other essential immune receptors such as CD14, Toll-like receptors (TLRs), and FcRs [73]. In addition, the proinflammatory response (degranulation, release of cytokines, and oxidizing compounds) related to phagocytosis of serum-opsonized particles and phagocytosis-induced apoptosis, was impaired in CR3-deficient mouse neutrophils [77]. This observation emphasizes the inflammatory role of CR3 in these cells. In addition to proinflammatory roles, CR3 also has a clear anti-inflammatory role in immunity, reviewed in [78]. CR3 (and the related receptor CR4) are important for clearance of apoptotic cells, which is associated with a reduced secretion of pro-inflammatory cytokines such as IL-1, IL-6 and IL-12 [79]. The recognition of iC3b-opsonized apoptotic cells leads to inhibition of pro-inflammatory NFκB signaling in macrophages and dendritic cells [80]. Signaling through CR3 can also suppress TLR responses [81–83]. Other outcomes of CR3 signaling include a decreased ability of dendritic cells to produce inflammatory cytokines and dendritic cell -mediated suppression on activation of T-cells, which both negatively regulate activation of the adaptive immunity [84–87].

Leukocyte-endothelial cell interaction is increased in preeclampsia. This mechanism likely contributes to the increased infiltrate of

neutrophils and mononuclear perivascular cells into the preeclamptic placenta. The CR3 ligand, fibrinogen, which is related to tissue repair has been shown also to affect signaling via the integrins, and enhance the inflammatory response of the responding leukocytes [88].

In addition to phagocytic leukocytes, the subset of innate lymphoid cells, natural killer (NK) –cells express CR3, which has been regarded as a maturation marker on both mouse and human NK cells [89,90]. C3 fragments (C3a, iC3b) have shown to have a negative regulatory effect on NK-cell activities (decreased production of IFN-γ, reduced ability for direct and antibody-dependent tumor cell killing) [91,92]. In the first trimester of pregnancy, the main decidual immune cells are uterine NK cells with a $CR3^{-}$ ($CD11b^{-}$) phenotype [93]. Besides their regulatory role in placental development, the uterine NK cells have been shown to promote the development of tolerogenic DCs and monocytes and suppress T helper type 17 (Th17)-mediated local inflammation [93,94]. To conclude, CR3 appears to be a receptor, which regulates the nature of the triggered immune response. The appropriate response depends considerably on the type of the responding immune cell.

The structurally very similar CR4 appears to have overlapping functions with CR3, and its specific role has been unclear for a long time. Specific functions for CR4, i.e. tasks, which are more preferred by CR4 than CR3, have just recently been elucidated. They suggest a division of labor between these two integrins [95]. These include a more relevant role for CR4 than for CR3 in the regulation of macrophage inflammatory functions [74].

In contrast to apoptosis, necrotic cell death may lead to an uncontrolled release of intracellular constituents into the extracellular space. They can trigger the release of pro-inflammatory chemokines and cytokines from immune cells that recognize the endogenous alarm signals. Consequently, the immune system is further alarmed to recruit a sufficient number of phagocytic cells to sites of injury to prevent the spreading of infection or injury.

Obesity carries an increased risk for preeclampsia possibly due to metabolic and/or immunological causes [96]. Adipose tissue may harbor sterile inflammation, and it can be a source of complement activation e.g. by actively producing the essential AP factor D (adipsin) [97]. It has been shown that the chronic inflammation spanning from the pregravidity phase of an obese mother bears consequences for the pregnancy by an increase in the heterogeneous macrophage population. This includes upregulation of CR3 in the placental macrophages [98], which is also reflected in the activation of peripheral blood mononuclear cells of the mother. A subset of macrophages identified by high expression levels of CR4 is associated with increased lipid metabolism, lipid antigen presentation and inflammation, while the macrophages low in CR4 have a role in growth, remodeling and, maternal immunoregulation. The strongly CR4-expressing macrophages may regulate the decidual NK cell cytokine responses [99].

## 4. Complement receptors in preeclampsia and autoimmunity

The inability to handle apoptotic and necrotic waste is crucial in the development of autoimmune disease, where the tolerance breaks down. Insufficient CP activation and C1q deficiency have been shown to be strongly involved in SLE, an immunoinflammatory disease considered to result from an insufficient clearance of waste [100]. Some autoimmune diseases, like SLE, tend to become worse during pregnancy, possibly because of a greater challenge to the clearance system posed by material derived from the placenta [101]. Interestingly, SLE shares common features with the pregnancy complication preeclampsia, SLE carries a 2- to 4- fold increased risk for preeclampsia during pregnancy [96,102]. A polymorphism of *ITGAM*, which encodes the alpha subunit of CR3, is associated with susceptibility to SLE [103,104]. The rs1143679 *ITGAM* variant (encoding the R77H protein variant of CR3) is considered as a major risk factor for the development of SLE. R77H mutation leads to the reduction in CR3 functions in neutrophils, B cells, and macrophages [105–107]. The R77H-substituted integrin receptor was shown to adhere weakly to the complement factor iC3b and displayed reduced iC3b-dependent phagocytosis. In addition, the R77H-CD11b variant was linked to increased levels in IL-6 production [108] and increased type I interferon production in the context of SLE [109]. The evaluation of further risk variants in CR3 confirmed the reduced ligand binding and reduced complement-mediated phagocytic capacity of neutrophils carrying the mutant proteins [110]. This is in accordance with the present knowledge, whereby the impaired clearance of dying cells due to phagocytic defects has been implied in the pathogenesis of SLE [111]. However, as CR3 plays many anti-inflammatory roles in immune responses, it is clear that also immunological processes other than clearance of apoptotic cells may be affected by the *ITGAM* variants that are associated with SLE. The interaction between CR3 and iC3b-opsonized apoptotic cells also leads to downregulation of the expression of MHC class II antigens and costimulatory molecules in the phagocytic cells [80]. This may serve to diminish the immune response following phagocytosis of apoptotic cells.

SLE is an autoimmune disease, where pathogenic Th17-responses have also been implicated [112,113]. A common complication of lupus nephritis includes immune cell infiltration into the kidney. This may result in tissue damage and onset of proteinuria [114]. Also in preeclampsia, the Th17 cells have been shown to be the predominant T cell population, while the number and function of Tregs is decreased [115]. Th17 cells are a distinct type of helper T cells, which are important in protection against extracellular bacterial and fungal infections. In addition, they have been implicated in the pathogenesis of several autoimmune diseases [116]. Since Th17 cells require cytokines (IL-1β, IL-6, and IL-23) to differentiate and proliferate, the decreased secretion of pro-inflammatory cytokines (cytokine skewing) from CR3-activated and tolerogenic DCs may play a primary role in the suppression of pathogenic Th17 responses [117]. In line with this, it was shown that mice carrying CR3-deficient antigen presenting cells exhibited loss of peripheral tolerance and increased Th17 cell numbers [118]. Furthermore, it was shown that CR3 regulates the Treg/Th17 balance in murine rheumatoid arthritis via interleukin-6 [119], while preeclampsia has elsewhere been shown to predispose to rheumatoid arthritis [120]. It was recently proposed that preeclampsia and rheumatoid arthritis share the lack of transgenerational maternal-fetal microchimerism, i.e. material passed on from previous pregnancies of the mother and grandmother, suggesting a shared mechanism of lacking possibly HLA-mediated tolerogenic process in the two diseases [121]. CR3 is also associated to negative regulation of B-cell receptor signaling to maintain autoreactive B cell tolerance [105]. Furthermore, B-cells lacking the complement receptor 2 (CR2, CD21) have been found to be enriched in patients with autoimmune conditions such as SLE [122,123]. The role of CR2 as a receptor for C3d/C3dg and nuclear components and as an activator of B-cells makes it as a potential candidate for influencing the pathogenesis of autoimmune diseases [124,125]. By being the receptor for Epstein-Barr virus, CR2 may also promote polyclonal auto-antibody responses [126].

Human complement receptor 1 (CR1, CD35) is widely expressed, including erythrocytes, myeloid cells such as neutrophils and monocytes, B-cells and also few T-cell populations [127]. CR1 expression is observed in certain type of epithelial cells in the eye, skin and kidney. In the latter, CR1 on glomerular epithelial cells has been shown to bind immune complexes and protect the kidney glomeruli by regulating the activity of complement. This suggests a role for CR1 in protecting the kidney from complement-mediated damage [128]. CR1 mediates the transport and promotes the phagocytosis of particles opsonized with several complement-related proteins: C1q, C3b, C4b, MBL, and ficolin-2. CR1 facilitates the clearance of pathogens and immune complexes from the circulation [129–131]. The complement activity of CR1 includes acceleration of the decay of CP and AP C3 and C5 convertases and co-factor activity for factor I -mediated cleavage of C3b/C4b to iC3b/iC4b [132–135]. Reduced levels of CR1 and proteolytic cleavage of CR1 are observed in patients with SLE [136]. Interestingly, reduced

cell surface levels of CR1 correlate also with the severity of pre-eclampsia symptoms [137]. A genetic variant resulting in a reduced expression of CR1 was found to be associated with preeclampsia, being even more common in the severe phenotype of HELLP syndrome [137]. Because of both the clearance and complement regulating activities, CR1 function is among the most interesting candidates of preeclampsia susceptibility.

## 5. Inflammation and angiogenic regulation in pathological pregnancy

The interplay between vascular and endothelial disruption and inflammatory responses is complex [11]. CR1 variants are known to influence susceptibility also to placental malaria [138]. The persistence of preeclampsia in the human population has been hypothesized to be driven by selection pressure against placental malaria susceptibility through immunological and vascular interactions. African-American and certain Latin American populations have at least double the incidence of preeclampsia, when compared to populations of European origin [139,140]. In areas of Africa, where *Plasmodium falciparum* is endemic, first pregnancies share a particular risk not only for pre-eclampsia but also for placental malaria [141]. In a malaria endemic region of Papua New Guinea in a cohort of pregnancies with high parasitemia, a heterozygous genotype causing lower than regular expression of CR1 was associated with higher hemoglobin levels at birth [142]. Also, an association to a low birthweight of infants was suggested [142].

Soluble fms-like tyrosine kinase 1 (sFlt1 a.k.a. soluble vascular endothelial growth factor receptor 1 sVEGFR1) is a soluble antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). Flt1 is expressed on inflammatory cells and endothelial cells [143]. Interestingly, it has been shown that in placental malaria, the fetal tissue will express an excess of sFlt1 apparently in an attempt to regulate the maternal inflammatory response and thereby to reduce the rate of spontaneous abortions [144].

In preeclampsia, an excess production of sFlt1 from placenta is observed [145]. Consequently, maternal serum concentration of sFlt1 increases. Indeed, sFlt1 is one of the best biomarkers for preeclampsia. During pregnancy, Flt1 is thought to limit vascular remodelling and neovasculogenesis and to restrict placental growth [146]. Consequently, positive selection of a genetic variant with capacity to resist placental malaria may have influenced *FLT1* allele frequencies within the general population sufficiently enough to introduce a novel risk to preeclampsia [147].

sFlt1 has also been implicated to have an anti-inflammatory function [148]. Further evidence of the immunological interactions of VEGFR1 come from a an antibody-independent mouse model of spontaneous miscarriage and intrauterine growth restriction (IUGR), where an increase in complement activation resulted in increased levels of circulating VEGRF1 [149]. It was also confirmed that monocytes can be stimulated to express an excess of VEGFR1, when exposed to the anaphylatoxic complement activation products C3a and C5a in vitro [149]. Furthermore, complement activation, i.e. C3a causes upregulation of Flt1 by the syncytiotrophoblast. Release of the overexpressed sFlt1 required activation of the TP [150] and complement activation is correlated with sFlt1 expression [151]. Also macrophage polarization to proinflammatory M1 and tolerogenic M2 is possibly driven by the VEGF-signaling pathway, which is dysregulated in preeclampsia [152]. Genetic association of the *FLT1* gene, which encodes Flt1, with both fetal and maternal susceptibility to preeclampsia was recently confirmed [153,154]. It seems possible that in preeclampsia, the excess of sFlt1 and inflammatory stimuli are linked to each other, but the exact causality and dynamics of the complex interactions are still unclear.

## 6. Complement-mediated clearance of free fetal DNA

The maternal-fetal interface undergoes a major reconstruction during the placental development. It follows that there also has to be a considerable amount of apoptosis and cell necrosis going on. Furthermore, a significant number of particles will be shed into the maternal circulation from the placental syncytiotrophoblast from the very early stages of pregnancy onwards [155].

The preeclamptic pregnancy results in an increased load of apoptotic cells and sub-cellular debris into the maternal circulation [156]. An increased load of free-floating DNA is observed in the maternal plasma of preeclamptic women prior to the onset of the disease [157]. Extracellular fetal DNA has a proinflammatory effect, which has been linked to an adverse pregnancy outcome [158]. The C4BP is a soluble regulator of the CP that binds to chromatin and facilitates clearance of the fetal free-floating DNA from the maternal circulation in an anti-inflammatory fashion [159]. Mutations in the gene coding for C4BP have been linked with recurrent pregnancy loss [41]. Furthermore, deposition of C4d and C4BP in the sub-endothelial layer of the glomerular capillary walls in a preeclamptic patient suggests a role for complement activation in the endothelial dysfunction that is characteristic to the disease [55].

CR3 and CR4 have been observed to recognize certain danger-associated signals, like HMGB1 and extracellular DNA in a process that likely has clinical consequences in promoting chronic inflammation [160,161]. CR2 on B-cells and follicular DCs also binds free-floating DNA leading to a possible humoral immune response against the free-floating fetal DNA [124]. However, the proportion of fetal to maternal DNA in the maternal plasma is very low. Therefore the pathological role of increased fetal DNA load as observed in preeclampsia is unclear.

## 7. Tolerance in pregnancy

The fetus and placenta together constitute a genetic allograft nourished by the maternal circulation. In a healthy pregnancy, an immunosuppressed balance persists throughout the pregnancy. In addition to being efficiently controlled itself, the complement system may also act directly or indirectly to establish and maintain tolerance during pregnancy. The complement system plays an important part in helping adaptive immune responses. In a murine pregnancy model, an interaction of complement receptor 3 (CR3) with iC3b at the maternal-fetal interface results in the induction of local anti-inflammatory cytokine expression. Furthermore, in late murine pregnancy, iC3b has a role in promoting production of the anti-inflammatory cytokines IL-10 and TGF-β1 [162]. Typically, complement removes endogenous waste products with the help of iC3b, which has been rapidly generated from C3b on host cell structures. Cells containing receptors mediating intake of iC3b coated particles, are typically capable of producing the immunosuppressive cytokines IL-10 and TGF-β1. IL-10 is known to suppress T–cell activation by preventing proinflammatory cytokine production and up-regulation of molecules involved in antigen presentation by DCs and macrophages [163] TGF-β1 has an important role in preventing T-cell activation by self-antigens [164]. In addition, the deposition of C3dg and C3d on antigens is an important means of antigen uptake to antigen presenting cells, such as DCs, follicular DCs, B cells, and macrophages, and further in their delivery to the adaptive lymphatic system [165]. The role of complement in orchestrating adaptive immune responses is relatively well understood. However, in the context of human pregnancy, the extent to which the complement system orchestrates the adaptive immune response and the development of tolerance remains largely unexplored.

There are several well-known mechanisms at the fetomaternal interface guarding the well-being of the fetus (Fig. 2). The placenta is protected by a syncytium layer of fused trophoblast cells. Complement inhibitors have been shown to be strongly expressed by cells in the placenta and in the outer layer of the syncytium [45,166]. While the

placental trophoblast cells do not express the classical major histocompatibility complex (MHC) molecules, the tolerogenic HLA-G, HLA-F, and HLA-E, all with unremarkable polymorphism, are expressed by the extra-villous trophoblast. HLA-G expression on the extra-villous trophoblast protects the placenta from cytotoxic reactions. Low soluble HLA-G plasma levels have been linked to severe preeclampsia [167]. During placentation, the invasive extra-villous trophoblast cells express HLA-C receptors that interact with the KIR-receptors of the uterine natural killer cells to establish an anti-inflammatory, immunotolerant maternal response to the fetus in the healthy pregnancy [168–172]. Uterine NK cells have been shown to be less cytotoxic, when compared with their peripheral blood counterparts [173,174]. They are essential in the placental development and in the encounter with invading extra-villous trophoblast cells. Despite efforts not to express polymorphic HLA molecules on the surface of the placenta, the syncytium contains intracellular HLA-DR molecules [175]. The reason for this is not known.

Regulatory T cells (Tregs) have been shown to be essential in the very early stages of pregnancy [175]. Paternal antigen-specific Tregs are considered to be induced already before pregnancy through exposure to semen, which contains paternal antigens and TGF-β [4]. TGF-β is important in Treg induction. On the maternal side, the decidual macrophages are predominantly of the anti-inflammatory type (M2) [176]. Healthy pregnancy is characterized by an early M2 polarization of the decidua, while M1-dominated pregnancies are associated with spontaneous abortions [177]. C1q is upregulated in macrophages by anti-inflammatory cytokines, suggesting a possible tolerance-inducing role for the complement-macrophage interaction in the maternal-fetal interface [178]. This would be logical for the proposed role of macrophages in removing placental debris with the help of C1q in a noninflammatory fashion. Indeed, a clear decrease in the serum level of C1q in preeclamptic patients has been observed, likely due to depletion of C1q in heavy demand [179]. In preeclampsia, increases in the levels of pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and IL-6 have been recorded [180]. A shift towards the inflammatory Th1-type reactivity, instead of the noninflammatory Th2 reactivity, is a known phenomenon in preeclampsia [181]. Possibly in a compensatory attempt, increased plasma levels of immunosuppressive IL-10 have been reported in the third trimester of preeclamptic pregnancies [180]. Additionally, indoleamine 2,3-dioxygenase (IDO) is present and an important part of the tolerance mechanism in the fetomaternal interface [182]. T cell activation in the IDO environment induces anergic and regulatory T cells. While the exact interaction between IDO and complement system is not known, murine studies have shown that the inhibition of IDO unleashes local complement activation and promotes inflammation with possible clinical consequences [183].

## 8. Conclusions

Pregnancy brings about tremendous changes in the body fluid volume and distribution. Fundamentally, preeclampsia is a disease that reflects an underlying failure in regulating vascular and hemodynamic changes in pregnancy. This may be due to a dysregulation of immunological processes and the subsequent loss of tolerance to the allogenic fetoplacental unit. This process would be analogous to that seen in autoimmunity and SLE [184]. As the woman is exposed to a genetically foreign fetus during pregnancy, there could be an intentional reason for the enormous load of placental shedding that occurs [185]. Apoptotic bodies are ingested by macrophages and DCs, and the environment and receptors included in the process determine whether tolerance or an immunoinflammatory process is initiated. In a healthy pregnancy, clearance of the apoptotic cells of fetal origin may serve to induce a tolerogenic response, while in a preeclamptic pregnancy, the response could be inflammatory. It is therefore conceivable that the pregnant woman's ability to process the released material from placenta contributes to the risk of the pregnancy complications and compromised endothelial integrity with possible consequences for vascular health in later life. The complement system likely acts as a mediator and regulator of the key processes in the pathogenesis of preeclampsia including breach of tolerance, inflammation, and waste management. The emerging noncanonical roles for the complement system have the potential to improve the understanding of the role of complement receptors and regulators as guard keepers in healthy and preeclamptic pregnancy.

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