Complement in structure and immune homeostasis in placenta

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Abstract

Aberrant complement activation can induce "thrombo-inflammation" attacks to host tissue. Beside kidney and blood vessel, the placenta is also susceptible to these attacks. Complement dysregulation is recently classified as one of the new mechanisms leading to pregnancy disorders. Studies have indicated that dampening complement activation can ameliorate pregnancy outcomes. During pregnancy, the mother's immune system is finely domesticated to accept the semi-allogeneic fetal antigens. As an important part of the innate immune system, some interesting changes have also taken place in complement system during pregnancy. The complement proteins are highly expressed in placenta, and their split products are increased. They are tuned in maintain placental immunity and structural homeostasis. An abundance of evidence shew that complement protein deficiency lead to autoimmunity disease and pathological pregnancy marked by excessive inflammation. Although complement suppressing strategies have been proven effective in treating some pathological pregnancy in individual case studies. we should take the dual role of the complement into consideration that fully and completely inhibit of complement may not be a wise choice.

Introduction

The complement system is a huge family comprised of more than 50 proteins. They play an important role in removing non-self or modified-self danger signals. The complement system is canonically regarded as the first chemical barriers to defend against microorganism infection. Complement effectors can induce inflammation and adaptive immune activation [1]. And it intertwines with other crucial pathways like Toll-like receptor (TLR) signaling pathway[2] and the coagulation pathway [3]. Clearly, they must be carefully controlled. If it fails, complement can target on host tissue and cause damage to it. Aberrant complement activation leads to "thrombo-inflammation" attacks to placenta and destroy the structure and function of it, thus leading to many pregnancy disorders. Studies have indicated that dampening complement activation can ameliorate pregnancy outcomes [4-5].

Although aberrant complement activation is related to many pathological pregnancy events, now large amount of immunological and histological evidences show that complement proteins and its split products are also significantly increased in physisological pregnancy. Placenta (like stromal cells, trophoblasts, endothelial cell, immune cells) synthesize complement proteins in a context-driven (hormone and immune micro-environment) manner and complement activation fragments increased locally and systematically[6]. These changes of complement system may adapt to meet the need of our body during pregnancy.

Complement system

Aberrant complement activation in pathological pregnancy

A number of pregnancy complications including recurrent abortion[7], premature delivery [8], fetal intrauterine growth restriction (IUGR) [9], hypertensive disorders, preeclampsia (PE) [10], HELLP syndrome[11] are

associated with aberrant complement activation. And women with inherited or acquired complement system dysfunction is a risk factor of suffering from these pregnancy disorders. Some complement activation products are potential serum and urine biomarkers to predict adverse pregnancy outcomes [12].

Preeclamptic (PE) is a severe and worldwide pregnancy associated disease[13], leading to multi-organ dysfunction and sometimes is life-threatening. C5a and membrane attack complex (MAC, sC5b-9) are two strong pro-inflammatory products in complement activation cascade, they significantly elevated in severe PE patients. C5a acts as chemotactic factors to recruit leukocytes [14] and induce proteases, free oxygen radicals and pro-inflammatory cytokines[15-17]. C5a/C5aR interaction can induce trophoblasts to an anti-angiogenic phenotype. And it inhibits the tube formation and migration [18]. MAC can not only mediate lysis and apoptosis of trophoblasts but also induce NOD-like receptor family, pyrin domain containing 3 (NLRP3) activation and then secretion of pro-inflammatory cytokines [19] . An in vivo experiment reinforced this conclusion that C6 knock down can significantly reduce inflammatory processes [20]. (Figure 1) Data shew that urinary sC5b-9 level was finely correlated with decreased placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) and increased Soluble fms-like tyrosine kinase-1 (sFlt-1, sVEGFR-1) [21], which forms an anti-angiogenic status and impairs placenta blood vessel formation. Now, C5-C5a axis is a promising target for drug development in complement related pregnancy disorder. It can not only inhibit C5a but also the subsequent generation of MAC.

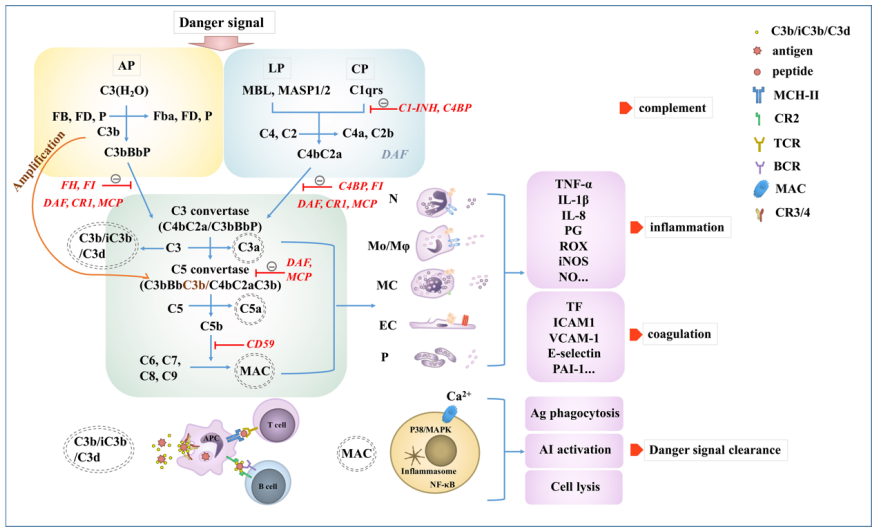

Figure 1: complement activation, regulation, and its biological effects when facing danger signal. In the presence of danger signals like DAMP and PAMP, complement is activated through three major pathways: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP) to produce effector molecules, including opsonins (C3b, C4b, etc.), anaphylatoxins (C3a, C5a) and Membrane Attack Complex (MAC). C3a, C5a promote the recruitment of neutrophils, mast cells degranulation. And they bind to the specific receptors on macrophages and monocytes to promote inflammasome activation, proteases and reactive oxygen species releasing. MAC mediate P38/MAPK and NFκB signaling pathway and induce inflammasome activation and inflammatory cytokines production. Complement can also mediate a hypercoagulable state. C5a /C5aR1 interaction on endothelial cells and monocytes induces the tissue factor and adhesion molecules expression and promotes the coagulation pathway. C3a /C3aR interaction on platelets and primes its activation. MAC inserts into platelet membrane to promote platelet prothrombotic microvesicles releasing. Overall, complement activation can induce an "thrombo-inflammation" response and form a two-hit stress to host. Opsonins C3b/iC3b/C3d can bind to CR3/4 to promote antigen phagocytosis and presentation to T cells. CR2 bind to C3d modified antigen peptides to promote B cell activation and specific antibody production. MAC insert into cell surface to lyse the damaged or infected cells. These

effectors organized to promote the timely removal of danger signals. Neutrophil (N); Macrophages (Mφ); Monocytes (Mo); Lymphocytes (L); Dendritic cells (DC); Endothelial cells (EC); Mast cell (MC); Platelet (P); Antigen (Ag); Adaptive immune (AI).

Physiological complement activities in placenta structure and immune homeostasis

Cell apoptosis in placentation

A total reconstruction on maternal-fetal interface takes place during placenta development. Trophoblast invade into the decidual, accompanied by the replacement of maternal decidual and the generation of the new tissue, a so called "remodeling" procedure. It has been found that the proliferation and apoptosis of trophoblast are stay in balance in the process of placentation. Apoptosis is a normal physiological phenomenon throughout gestation period. Whole data indicated that apoptosis is important in placenta development, remodelling and function[22].

In physical condition, dying cells can be recognized by a series of molecules, which lead to their phagocytosis by immune cells or even its neighboring cells. The removal of apoptotic cells is so rapid that few cells are seen in tissues even in thymus where up to 95% of its cells undergo apoptosis procedure. Timely clearance of dying cell is a crucial for tissue homeostasis, since these cells are a main source of self-antigens which can stimulate adaptive immunity activation and mount a pathologic response to host tissue under inflammatory conditions. Therefore, the carefully and precisely regulated clearance of apoptosis cell involves in maintaining an anti-inflammatory and self-tolerance state.

The trophoblasts invade and replace the maternal decidua tissue, generating a large number of sub-cellular debris and apoptotic cells. They accumulate in placenta and even deported into maternal circulation in large quantities. They need to be cleared rapidly to prevent the release of intracellular cytotoxic substances to the extracellular microenvironment[23]. An unbalance of cell apoptosis result in sever inflammation, placenta vascular damage[23], altered trophoblast function. When these cell wastes shedding into the maternal blood-circulation, systematic vascular damage and dysfunction happens. (Figure 2) These changes were found in pathological pregnancy like intrauterine growth retardation and pre-eclampsia[22].

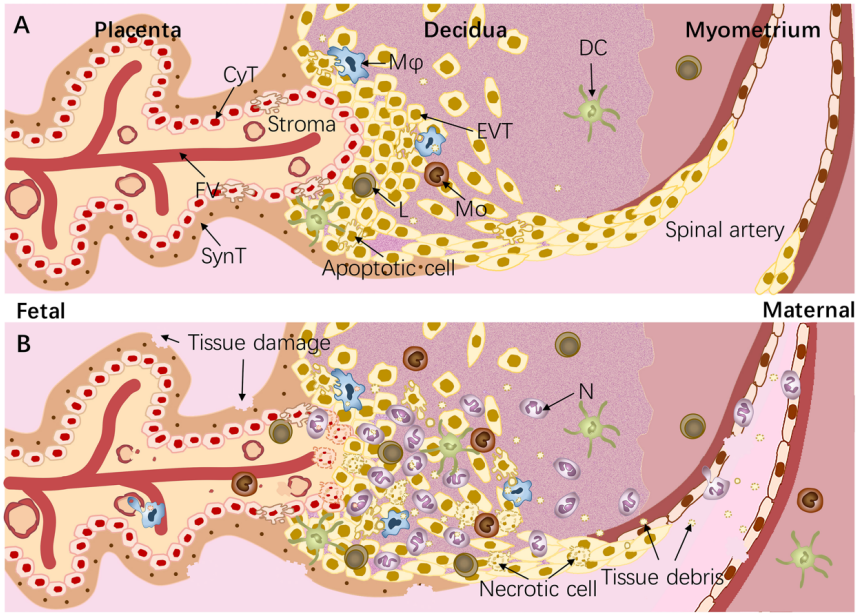

Figure 2: Both complement deficiency and complement over-activation can lead placenta damage. (A) Trophoblast cells invading the maternal decidua is accompanied by a large number of apoptotic

cell and tissue debris in normal placenta. These apoptotic cells are quickly cleared by phagocytes without inducing immune activation. **(B) In one situation** , complement over-activation promotes neutrophil recruitment, mediates the release of inflammatory cytokines, and activates the adaptive immune system to jointly induce placental damage. Trophoblast cell invasion ability decline, and their apoptosis and necrosis are accelerated, a large amount of tissue debris enter the circulating blood, and spiral artery remodeling is obstructed. At the same time, complement-mediated hypercoagulation leads to local microthrombosis and the following fetal ischemia and hypoxia, forming a "second hit" to pregnancy. **In another situation** , complement deficiency leads to the accumulation of apoptotic and necrotic cells in the placenta. These apoptotic and necrotic cells activate the inflammatory signaling pathways to provoke inflammatory responses, like neutrophil recruitment and adaptive immune activation, and induce placental malformation and dysfunction. The pathological manifestations of the placenta are similar to the previous ones (complement over-activation(B)). Extravillous trophoblast (EVT); Cytotrophoblast (CyT); Syncytial trophoblast (SynT); Fetal blood vessels (FV); Neutrophil (N); Macrophages (Mφ); Monocytes (Mo); lymphocytes (L); Dendritic cells (DC).

2. Complement in clearance of apoptotic cell

The complement system is an important part of the innate immune system and play crucial role in apoptotic cell clearance. "Eate me" signals were expressed on apoptotic and necrotic cells surface, they attract the initiators of complement system such as C1q, mannose binding lectin (MBL), ficolins and trigger complement activation. C1q, MBL, and opsonins (C3b/C4b) are all participate in phagocytosis and clearance of apoptotic cells and necrotic debris. It is critical for development, regeneration, tissue remodeling, and homeostasis procedures[24].

2.1 MBL and C1q

MBL and C1q are two soluble pattern recognition molecules in complement classical pathway (CP) and lectin pathway (LP). Report found that C1q widely distributed in decidual stroma and the vessel wall of the spiral arteries [25.] C1q is synthesized by extravillous trophoblasts, decidua endothelial cells and macrophages in placenta[26]. In addition to local expression of C1q, excessive complement activation leads to increased local recruitment of C1q from the blood circulation into the placenta, especially in areas of fibrinoid necrosis in maternal decidua [27].

MBL and C1q recognize and bind to a variety of damage-associated molecular patterns (DAMPs) like phosphatidylserine, mitochondrial membranes, histones, DNA, Annexins 2 (A2) and A5 on apoptotic cell[28]. C1q comprise of N-terminal domain (also called collagen-like domain) and a C-terminal globular domain (gC1q)[29]. Immobilized C1q can enhance FcγR-mediated phagocytosis of either immobilized or soluble immune-complex (IC), antibody or complement-opsonized targets [30,31]. C1q can trigger an immediate response to enhance their phagocytosis. Moreover, gene expression profiles found that multiple pro-phagocytic genes were upregulated in C1q treated bone marrow derived macrophages (BMDM) in mice. C1q binds to apoptotic cell [32] by the globular head region [33]. Accumulated evidence confirmed that C1q can enhance phagocytosis of apoptotic cells both in vitro and vivo (reviewed in (Galvan et al., 2012) [34]). C1q and MBL have similar collagen-like domains. Experiments also found that MBL can facilitate apoptotic cells clearance. The expression of MBL is increased on the apoptotic cell[35]. Low MBL levels can result in impaired apoptotic cell clearance[36]. Aside from direct recognition and removal of apoptotic cells by acting as an opsonin, C1q and MBL also play an indirect role in apoptotic cell clearance by C3 cleavage fragments. The active C1 complex cleaves the following components C4 and C2, resulting in the assembly of the C3 convertase (C4b2a) and C3b/iC3b production disposition on targets, which are strong opsonins for phagocytosis. Increased apoptotic cells were detected in lymph nodes and other tissues in C1q-/-mouse[37-38].

In addition to promoting apoptotic phagocytosis, C1q/MBL is also involved in inducing immune tolerance thus help silent removal of dying cell. When binding to apoptotic cells, C1q maintain dendritic cells (DCs) in immune tolerance state through interact with gC1qR[39] and suppresses Th17 and Th1 cell proliferation[40,41]. C1q-/- mice were detected to produce elevated levels of IL-12p40 compared to wild type mice[42]. At the

same time, immobilized C1q can increase the production of IL-10 known as anti-inflammatory mediators [43,44]. C1q/gC1qR interaction on DCs or macrophages can negatively regulate IL-12p70 production through activating the phosphoinositide 3-kinase (PI3K) pathway [45]. C1q also inhibits immune complex induced IFN-α production in pDCs [46]. These evidence reinforced that C1q and its receptor complex could regulate DC induced inflammation[47].

C1q attracted on apoptotic cells bind to C1qRs on macrophage to suppress IL-10, IL-27, IL-33, and IL-37 secretion and inhibit inflammasome activation. At the same time, it can also increase the level of negative regulators [40]. Another experiment indicated that C1q mediated apoptotic cells clearance procedure can increase the expression of Programmed death-ligand 1 (PDL-1) and PDL-2 and decrease the expression of CD40 on macrophages or DCs surface [41]. It induces elevated regulatory cell (Treg) differentiation and anti-inflammatory cytokines production, such as TGF-β, IL-10, IL-37, IL-27 and Prostaglandin E2 (PGE2), and lead to immune tolerance. In addition, C1q opsonization the phagocytosis of apoptotic cells and promote the expression of PDL-2 and suppress the expression of CD86 on DCs surface. It largely slow down the antigen presenting procedure and immunogenic efficiency, and ubsequently, it inhibits Th1 and Th17 proliferation (Figure 3). In all, C1q is critical for the silent clearance of apoptotic cells in and non-immunogenic state[41].

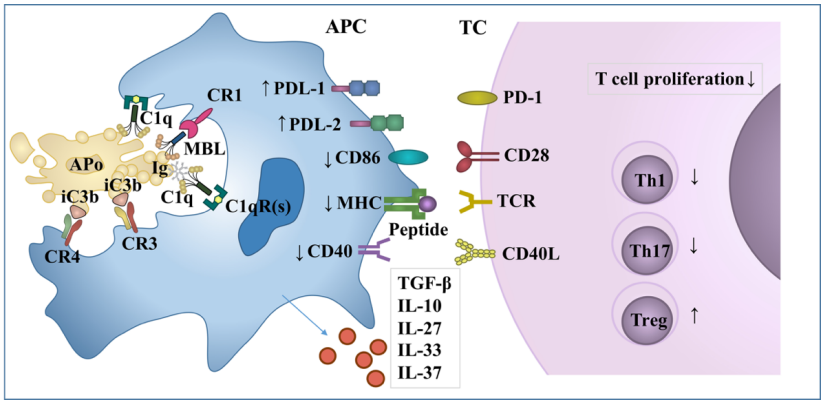

Figure 3: Complement involved in clearing apoptotic cells and inducing immune tolerance under static state. In the static state, antigen presenting cells (APC) can orderly phagocytose apoptotic cells free from inflammation and adaptive immune activation. Complement activation products C3b/iC3b/C3d and pattern recognition molecules C1q, MBL can bind to DAMP on the surface of apoptotic cells, these molecules bind to specific receptors C1qR, CR1, CR3, CR4 on the surface of APC to mediate phagocytosis and degradation of apoptotic cells. Studies have found that this process can induce APC to form a tolerance phenotype, secrete inflammation inhibitors, down-regulate the expression of costimulatory molecules (MHC, CD86, and CD40), and up-regulate the expression of inhibitory molecules (PDL-1 and PDL-2). Thereby reducing the efficiency of antigen presentation, inhibiting the activation of downstream T cells activation, proliferation and differentiation. Eventually, the complement system eliminates apoptotic cells in time and induces immune balance and tolerance.

C1q gene defect is a strong risk factor for SLE[48]. It may be related to C1q mediated "waste disposal" disorder as well as subsequent disrupted immune tolerance. Increased apoptotic cells, free floating DNA fragments and sub-cellular debris were detected in tissues in SLE patients, which act as self-antigen to provoke immune activation. Interestingly, preeclampsiahave many similar pathological features to SLE, and the risk of SLE patients suffering from PE increased by 2-4 times [49]. PE women have an increased accumulation of apoptotic cells and its debris in placenta and maternal circulation[50]. Large amount of plasma free-floating DNA in the maternal circulation were detected in pregnant women before the onset of PE [51]. Indeed, evidence shew that failure in complement-facilitated phagocytosis of debris may contribute to SLE as well as pathologic pregnancy [52,53]. C1q gene defect is a strong risk factor for SLE [54,55], and

C1q deficiency can also lead to pathological pregnancy like PE, and anti-C1q antibodies is associated with recurrent pregnancy loss (RPL)[56-58]. The level of C1q in the placenta of PE patients are significantly higher than those of normal pregnant women. Excessive complement activation leads to increased local recruitment of C1q in the placenta, especially in areas of fibrinoid necrosis in maternal decidua[27]. And excessive placental C1q level may be an indicator of adverse pregnancy outcomes. While too low C1q levels may impair the elimination of apoptotic cells and also subsequent immune homeostasis in placenta which threaten pregnancy. C1q deficiency can lead to pathological pregnancy like PE, and anti-C1q antibodies is associated with recurrent pregnancy loss (RPL) [56-58]. These evidences indicate that C1q play an important part in the maintenance of pregnancy.

MBL, the initiator of the LP, is able to bind to specific glucosamine on the pathogen surface. In humans, MBL deficiency can lead to bacterial, fungal and viral infections [59]. The level of MBL in the peripheral blood increased in early pregnancy [60]. Endovascular trophoblasts, decidua stroma cells, endothelial cells, and Hofbauer cells in placenta can express MBL [61]. MBL weakens the combination ability of LPS to DC cells and inhibits the differentiation of immature DC cells into the mature one and reduces their production of IL-12, TNF-α, thus preventing allogeneic T cell proliferation [62]. Moreover, MBL can also suppress TLR3 activation then the following pro-inflammatory cytokine production[63], suggesting a possible anti-inflammatory property of MBL in special conditions. Women with low MBL have excessive TNF-a production [64], which can induce inflammation and lead to further trophoblast cell dysfunction [65]. Genetic variations of the MBL-2 gene are associate with susceptibility to SLE and PE [66,67]. MBL2 gene polymorphisms leading to MBL deficiency are at higher risk of miscarriage in women with rheumatoid arthritis (RA)[68]. It has reported that[61,69,70] low levels of MBL during pregnancy is closely related to placenta male-function, such as placental lesions, inflammation which leading to low gestational age and low birth weight[71], recurrent abortions [69,70,72,73], IUGR, PE, premature delivery and chorioamnionitis[74,75].

2.2 C3b/iC3b and its receptors

C3 are mainly synthesized by the liver. But interestingly, placental locally synthesize complement proteins in high level. The central components C3, C5 and cascade-components responsible for C3 activation, like complement factor B (FB), factor D (FD), C1s, C2[Figure 1] are also found in pre-implantation embryo as well as chorionic tissue[76,77]. The mRNA analysis unexpectedly revealed the presence of C4, C3, C6, C7, C8 and C9 in both freshly extracted trophoblasts and HTR8/SVneo trophoblast cell line, and C4, C3, C6 protein were also detected in its cell supernatant. Cytotrophoblasts analysis even found complement components at tissue level exceeding in macrophages known for synthesizing complement components[78].

Although complement over-activation is related to many pathological pregnancy events, now, large amount of immunological and histological evidences show that complement split products are also significantly increased in serum and placental physisological pregnancy, indicating an vigorous systematic and local activation of complement during pregnancy. Lokki et al. (2014) and Buurma et al. (2012) [79,80]demonstrated that C1q along with C3b/iC3b/C3d are stained in normal placenta and even in pre-implantaion embryo cell surface and zona pellucida (ZP)[81].

C3 is the center complement protein. C3 is cleaved by C3 convertase into C3a and C3b. C3b is further processed into a potent opsonin iC3b [Figure1]. iC3b condense on the surface of the apoptotic cells to enhance its phagocytosis through diverse receptors like CR1, CR3 and CR4. CR1 (CD35) expressed on most nucleated cells as well as erythrocytes, it not only regulates C3 breakdown but also involved in enhancing DAMPs and immune complex phagocytosis procedure[82]. CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are expressed on phagocyte like monocytes and macrophages. They stimulate iC3b-mediated phagocytosis[83,83]. Specific antibody blocking the chains of CR3 can inhibit of up to 40% of apoptotic cell clearance by splenic DCs [85]. iC3b/CR3 is required for long-term tissue homeostasis[86,87], increased apoptotic cells accumulation, pro-inflammatory cytokines secretion and accelerated cell degeneration were detected in the brain of CR3 deficient mice[88]. In addition, these complement receptors also involved in inducing an immune tolerance state to facilitate removal of apoptotic cells without elicit adaptive immune activation and further inflammation.

CR1 was defined as a CIP for its multiple actions in regulating complement activation which highly expressed on erythrocytes and some myeloid cells. CR1 can bind to C3b/ C4b trapped immune complexes[89] thus transfer them to the phagocytes (like Kupffer cells, macrophage) in the liver or spleen [90] for their engulfment [91] (Figure 4). Aligning with the growing evidences, CR1 was found play context dependent roles in inducing immune tolerance [92,93]. Low level of CR1 was detected on B cells in rheumatoid arthritis (RA) patients. CR1 is involved in blocking BCR induced B cell proliferation and differentiation into plasmablasts, and then antibody production [94]. iC3b dose dependently reduces the TLR9 stimulated activation markers of B cells through CR1. TLR9 induced cytokine production, antibody production, and B cells proliferation were all impaired through iC3b/CR1 interaction[95]. As mentioned above, CR1 can mediate the elimination of circulating immune complexes and participate in inducing B cell anergy to self-antigens depending on the micro-environment. Because of the immune complex clearance and complement regulating ability, CR1 deficiency are involved in some inflammatory or self-tolerance disorder-related disease like SLE. SLE is characterized by the accumulation of IC and auto-antibodies [96], and it can induce systematic chronic inflammation thus leading to tissue destruction. Increased apoptotic cell, sub-cellular debris and ICs derived from the placentation procedure pose a greater challenge to mother, thus, generally, SLE become worse during pregnancy[97]. Reduced cell level of CR1 was detected in patients with SLE, an independent risk factor leading to pathological pregnancy[98]. At present, it is not clear whether CR1 is directly involved in adaptive immune tolerance in the local placenta. However, it is currently known that CR1 gene defects are related to pregnancy diseases such as PE and premature birth, and it is more common in the severe HELLP syndrome [99], where inflammation is an important feature of all these diseases [99,100].

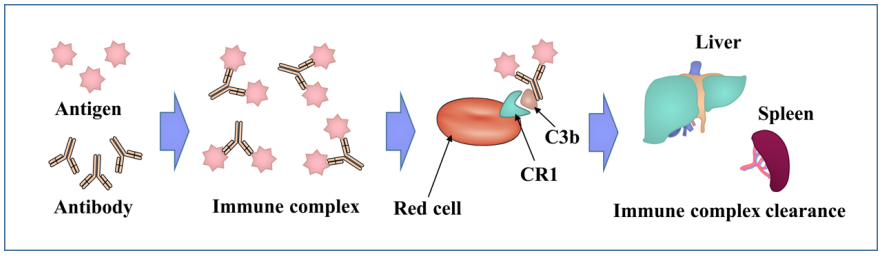

Figure 4: C3b/CR2 interaction on red cell participate in immune complex (IC) clearance. CR2 is expressed on the surface of red blood cells. C3b can bind to IC and attach to the surface of red cells through CR2. With the blood flow, it enters the spleen and liver to be finally degraded. This is the main way for IC clearance. It is important for immune tolerance induction.

CR3 was once considered to be one of the pro-inflammatory receptors in innate immune system. Interestingly, the clear anti-inflammatory and immunoregulatory role of CR3 under certain circumstances has been widely identified [101]. iC3b/CR3 mediated apoptotic cells clearance procedure can induce an anti-inflammatory response. iC3b/CR3 interaction inhibit TLR/nuclear factor-ϰB (NFϰB) pathway to inhibit pro-inflammatory cytokines (such as IL-1, IL-6 and IL-12) secretion by macrophages and dendritic cells [102,102-105]. It can also inhibit monocyte-derived DCs (Mo-DCs) differentiation through stimulating IL-10 and TNF-α production [106], and subsequently inhibits allogeneic CD4+ T cell proliferation through mitogen-activated protein kinase (MAPK) signaling pathway[107]. iC3b/CR3 downregulate the expression of costimulatory molecules (major histocompatibility complex) and MHC class II antigens on the phagocytic cells thus suppress further activation of adaptive T cell response [103]. In addition, C3b/iC3b interact with the CRIg expressed on human DCs and inducing T cell stay in silent [104,105]. CR3 also express in NK cell and serve as a maturation mark on it [108,109]. C3 lysate have been shown to play a negative regulatory role in IFN-γ production and cell killing activity in NK cells [110,111]. CR3/iC3b interact on DCs cell and inhibit IL-6, IL-23 and IL-1β secretion to restrain differentiation and proliferation of Th17 cells[112]. In line with this, mice with CR3 deficiency in antigen presenting cells (APC) have increased Th17 cell level and disrupted peripheral tolerance [113]. (Figure 4)

A polymorphism of rs1143679 ITGAM encodes the variant alpha subunit of CR3 (R77H protein) and it weaken the adherence ability of iC3b then impair iC3b-dependent phagocytosis. R77H gene variant is associated with increased susceptibility to both SLE and PE[114,115]. CR1-CR4 are all receptors for iC3b mediated phagocytosis. It has been also reported that women with any protein deficiency in anyone of CR1-4 has a higher susceptibility to both PE and SLE [52].

C3 with its split products (C3b, iC3b, C3d) were detected in high level in placenta, it is worth noting that C3 is essential for pregnancy maintenance in mice. C3 ablation can increase fetal re-absorption rate and decrease conception rate in mice. The fetal and placental weights of C3-knockout mice group were lower than the control group[116]. In pregnancy mice model, CR3/iC3b interaction induce an elevated local anti-inflammatory cytokine expression (like IL-10 and TGF-β1) at the maternal-fetal interface [117]. IL-10 and TGF-β1 are typical anti-inflammatory cytokines in suppressing T-cell activation and differentiation [118].

3. Complement activation is well balanced by CIPs during pregnancy

Apoptotic cells lose the expression of "don't eat-me" signals and instead exposing "eat-me" signals such as phosphatidylserine on its cell surface. They are exposed on the cell surface then attracts C1q, MBL, binding strongly to the late apoptotic cells and leading to activation of complement cascade on its cell surface. The "first-half" complement components MBL/C1q and C3b/iC3b recognize and bind to its specific receptors on phagocytes to mediate silent and timely clearance of the apoptotic cell. But if the complement cascade is uncontrolled, it would result in potent anaphylatoxin C5a and MAC formation, the "second-half" products of the complement cascade, with strong cytotoxicity and pro-inflammation potency. However, due to the presence of two potent complement inhibitors C4BP, complement factor H (FH), which are strongly binding to the apoptotic cells surface, the complement cascade is finely attenuated at C3 level, thus cell lysis and the further inflammation is curved.

C4bp and FH level increased in both peripheral blood and placenta in early pregnancy [119]. C4bp is a protein binding to C4b and regulating C3 convertase in CP. C4bp was stained in apoptotic fragments in normal placenta [119], serve as a potent soluble inhibitor of the CP and LP. FH is a potent soluble inhibitor of the complement alternative pathway (AP). FH level in peripheral blood and placenta increased in early pregnancy [119]. Intense FH deposition was detected in the stroma of the placenta[119]. FH acts the similar role as to C4BP, they accelerate the decay of C3 convertase and play as a co-factor with complement factor I (FI) to cleave and inactivate C3b.

Aside from controlling spontaneous activation of the complement AP, FH also plays an important role in silent removal of apoptotic cells[120]. FH can be actively internalized by apoptotic cells, promote intracellular catalyzation of C3 to C3b. Cell-derived C3b additionally translocate to the cell surface and promote its clearance.

The levels of C3a and C4d (involved in AP and LP) in the uterus and peripheral blood were significantly higher in pregnant women than the none-pregnant one [121]. But it does not reach to the level of PE patients. CRP, C4d/C4, C3a/C3, SC5b9 levels in PE patients are significantly higher than healthy pregnant women. Buurma and its colleagues found that C3a increased in a larger extent than sC5b-9 in normal pregnancy but the production of sC5b-9 and C3a is completely synchronized in PE patients [80]. sC5b-9 has strong cytotoxicity and pro-inflammation potency. sC5b-9 is sharply increased in PE women, while finely controlled in normal pregnant women. And sC5b-9 level in blood and urine are potent indicator for severity and prognosis of PE patient[122].

Though complement is also obviously activated in normal pregnancy, it is different from the pathological status. Under physiological condition, complement activation is more moderate and finely regulated in the presence of CIPs, especially the terminal pathway which has strong pro-inflammation potency.

Conclusion

Overall, the complement system needs to stay in a balanced state. Both excessive and insufficient complement activation can lead to pregnancy disorders. Our review will help us to have a more comprehensive

understanding of the relationship between complement system and pregnancy. Moderate complement activities during pregnancy take part in keeping structure and immune homeostasis in placenta. Though, complement suppression strategies have been proven effective in the treatment of some pregnancy disorders [10,11] in some individual case studies. It must be emphasized that we may exert calibrated modulation, rather than complete inhibition of complement system. Our review will provide evidence for the design of complement therapy strategies for complement disorder related pathological pregnancy.

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