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REVIEW

Preeclampsia and health risks later in life: an immunological link

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Abstract Pregnancy represents a period of physiological stress, and although this stress is experienced for a very modest portion of life, it is now recognized as a window to women's future health, often by unmasking predispositions to conditions that only become symptomatic later in life. In normal pregnancy, the mother experiences mild metabolic syndrome-like condition through week 20 of gestation. A pronounced phenotype of metabolic syndrome may program pregnancy complications such as preeclampsia. Preeclampsia is a serious complication with a myriad of manifestations for mother and offspring. This pregnancy syndrome is a polygenic disease and has been now linked to higher incidence of cardiovascular disease, diabetes, and several other disorders associated with vulnerable organs. Furthermore, the offspring born to preeclamptic mothers also exhibit an elevated risk of cardiovascular disease, stroke, and mental disorders during adulthood. This suggests that preeclampsia not only exposes the mother and the fetus to complications during pregnancy but also programs chronic diseases in later life. The etiology of preeclampsia is thought to be primarily associated with poor placentation and entails excessive maternal inflammation and endothelial dysfunction. It is well established now that the maternal immune system and the placenta are involved in a highly choreographed cross-talk that underlies adequate spiral artery remodeling required for uteroplacental perfusion and free flow of nutrients to the fetus. Since normal pregnancy is associated with a sequence of events represented by temporal events of inflammation (implantation), anti-inflammation (gestation), and inflammation (parturition), it is quite possible that unscheduled alterations in these regulatory responses may lead to pathologic consequences. Although it is not clear whether immunological alterations occur early in pregnancy, it is proposed that dysregulated systemic and placental immunity contribute to impaired angiogenesis and the onset of preeclampsia. This review will focus on important aspects of the immune system that coordinate with placental dysfunction to program preeclampsia and influence health in later life.

Keywords Preeclampsia · Inflammation · Immune tolerance · NK cells · Regulatory T cells · Microparticles · Aggregated proteins · Damage-associated molecular patterns · Chronic diseases

Introduction

Preeclampsia is a polygenic disorder and a leading cause of maternal and neonatal morbidity and mortality. This devastating pregnancy complication affects 5–8 % of all pregnancies worldwide and is characterized by de novo onset of hypertension and proteinuria in pregnant women [1–10]. The new clinical definition also includes severe hypertension and end-organ dysfunction which may or may not occur in conjunction with proteinuria after 20 weeks of gestation [2]. Despite much improved clinical care and extensive investigation, preeclampsia still remains enigmatic, and no effective treatments are available. Delivery is the only effective

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treatment of controlling maternal symptoms associated with preeclampsia [1–10]. The incidence of preeclampsia may rise globally depending on the local environmental inflammatory cues and stress. Severity of preeclampsia pathology is also a leading cause of preterm birth. Thus, if an altered immune system contributes to the systemic and local symptoms of preeclampsia [11–22], it is tempting to speculate that the same or diverse underlying immune changes may predispose to different phenotypes of the syndrome. Dysregulation of immunity in preeclampsia is thought to start with inadequate immune tolerance to paternal alloantigens present on trophoblasts. Thus, the issue of altered immune responses in preeclampsia has to be addressed in the context of both primiparity and paternity [9, 23]. A primiparity pregnancy with preeclampsia is preceded by poor placentation, local ischemia, oxidative stress, and inflammatory milieu. What are the chances that this profile will be repeated in second pregnancy and beyond? Based on the observations in humans and animals, it is proposed that a first pregnancy can provide immune education to paternal antigens and may reduce the occurrence of preeclampsia during subsequent cycles of pregnancy. However, this immune education may be lost if there is exposure to distinct paternal antigens or if there is an extended period gap between first and second pregnancy. So, the question is whether the poor maternal response to paternal antigens or inadequate environmental cues lead to poor placentation in whichever pregnancy cycle it occurs? The pathophysiological link between these two possibilities remains enigmatic. Nevertheless, recent data suggest that the defective immune intolerance to the conceptus may be involved through primary and secondary immune responses. Although a considerable number of reviews have already focused on different aspects of immune responses including the role of macrophages in preeclampsia [11–22], this review will provide contemporary discussion on NK cells and regulatory T cells (Tregs) and their participation in the pathology of this pregnancy complication. A focus on NK cells and Tregs can be rationalized because NK cells predominantly populate the pregnant uterus and guide trophoblast invasion whereas Tregs are recruited to the endometrium in response to hormones to establish immune tolerance. Both these pathways of trophoblast invasion and immune tolerance play a central role in normal pregnancy but are compromised in preeclampsia. Below, we first discuss the unique properties of uterine NK cells and Tregs and their functions in normal pregnancy and preeclampsia. We will further discuss experimental and clinical evidence for their imprinted functions postpartum and later in life. Changes or alterations in these two cell types are thought to contribute to a number of immediate or longer-term problems including infertility, spontaneous miscarriage, intrauterine growth restriction, or preterm birth, in addition to preeclampsia [24–27].

Decidual and peripheral blood NK cells in normal pregnancy

Decidual NK (dNK) cells are large, granular, and $CD56^{bright}CD16^{-}$, which are distinct from a majority of peripheral blood NK cells that are $CD56^{dim}$ $CD16^{+}$ [24]. Several possible origins of dNK have been proposed. For example, dNK cells have been reported to originate from $CD56^{dim}$ $CD16^{+}$ peripheral blood cells or alternatively differentiated from hematopoietic progenitor cells that reside in the endometrium [28, 29]. A recent study by Keskin et al. has demonstrated that peripheral blood NK cells can be converted to dNK cells by in vitro incubation with TGFβ1 [30]. In vitro generated dNK cells exhibit regulatory phenotype and produce angiogenic factors. dNK cells express the full repertoire of the NK-activating receptors including NKp46, NKp30, NKG2D, and NKp44, as well as inhibitory receptors including CD94/NKG2A, KIR2DL4, KIR2DL1, KIR2DL2/L3, and ILT-2, which might function to inhibit the cytotoxic potential of dNK cells [24, 29]. dNK cells are the dominant immune cell type, constituting 70 % of all mononuclear cells at the maternal-fetal interface in the first trimester [31]. They dramatically increase and accumulate as a dense infiltrate around the trophoblast cells at the time of implantation and progressively decline from mid-gestation and almost disappear at term [24, 32]. Although dNK cells are in close contact with invading trophoblast cells, they do not exert natural cytotoxicity, but rather play a supportive role in promoting trophoblast invasion and spiral artery remodeling in an early normal pregnancy by secretion of chemokines such as IL-8 and interferon-inducible protein-10 and a variety of angiogenic factors such as vascular endothelial growth factor C (VEGFC), placental growth factor (PLGF), and angiopoietin 2 [33–37]. These regulatory capabilities of dNK cells are orchestrated by interactions between activating receptors and/or dNK-inhibitory receptors and their specific ligands (HLA-C and HLA-G) expressed on invading trophoblasts [34]. Accordingly, interactions of NK cell-specific receptors and their specific ligands dictate the production of cytokine and angiogenic factors by dNK cells in early pregnancy, which in turn mediate vascular growth and spiral artery transformation. This notion is strongly supported by the finding by Kalkunte et al. that NK cell-derived angiogenic factors are responsible for maintaining their non-cytotoxic phenotype [34, 36].

Do dNK and peripheral blood NK cells exhibit altered phenotype and function in preeclampsia?

It is plausible that low oxygen tension and under-expressed angiogenic factors are secondary to immunological alterations observed in preeclampsia. Several observations in the literature

suggest that defective invasion by trophoblasts and poor spiral artery remodeling can be ascribed to an aberrant maternal immune response against the antigens expressed on the trophoblast. It has been proposed by Sargent et al. that poor invasion by trophoblasts is a result of diminished stimulation of decidual NK cells which participate in the production of immunoregulatory cytokines and angiogenic factors [38]. The maternal syndrome of preeclampsia is later characterized by a systemic inflammatory response involving leukocytes and endothelium. This inflammatory stimulus appears to originate in the placenta and may be caused by the release of trophoblast microparticles, altered protein structures, and nucleic acids. Another important inflammatory could be mitochondrial damage-associated molecular patterns (DAMPS) [39]. Maternal decidual NK cells can be found around the infiltrating trophoblasts, and it has been proposed that they modulate trophoblast invasion in a dose-dependent manner [40]. dNK cells are a source of decidual IFN-γ at early stages of human pregnancy and likely participate in regulating the extravillous trophoblast invasion [33]. Indeed, it has been observed that the inhibition of cytotrophoblast migration is contact-independent and occurs through IFN-γ-induced modulators [40]. Although NK cell- or stroma-produced IFN-γ has been shown to contribute to spiral artery remodeling in rodent models, this cytokine has also been shown to inhibit trophoblast invasion. Interestingly, higher levels of IFN-γ have been observed in preeclampsia [41].

Although controversial, inhibitory interaction between HLA-C and dNK cells is another pathway that can also lead to poor regulatory activation of dNK cells. There exist differential combinations of interactions between maternal polymorphic KIR and dimorphic trophoblast HLA-C. A study by Hiby and colleagues has demonstrated that interactions between certain KIR alleles on dNK cells and certain HLA-C allleles on extravillious trophoblasts induce strong inhibition of dNK cells, which increases the likelihood of poor production of angiogenic factors and subsequent onset of preeclampsia [42]. Interactions between HLA-C2 on trophoblasts and KIR AA on dNK cells have been proposed to result in poor activation of NK cells and pregnancy complications. However, the patterns of expression of these alleles in the Japanese and North Indian Hindu populations suggest against this hypothesis [43]. Saito et al. have suggested that in Japanese women with a high frequency of KIR-AA, mating with Caucasian men with a higher frequency of HLA-C2 does not result in preeclampsia [43]. Thus, it still remains a question whether HLA-C2-KIR-AA interaction is solely responsible for the onset of pregnancy complications, including preeclampsia. Moreover, preponderance of these alleles in women and their offspring will have long-term consequences for systemic immune responses involving HLA-C and KIRs. A fundamental question in reproductive immunology, one that also raises practical considerations in the context of impact on local immune tolerance and successful pregnancy outcome, is whether uterine NK cells change their pregnancy-friendly and immune tolerant phenotype to an adverse phenotype in the setting of excessive inflammation, infection, and stress. Interestingly, our published and unpublished observations strongly suggest that dNK cells have the potential to turn into foes to pregnancy in response to inflammatory triggers. In experimental models, LPS and poly IC treatment of pregnant mice can induce alterations in the phenotype and functional characteristics of dNK cells by stimulating production of inflammatory cytokines such as TNF-α and IFN-γ [44–46]. In humans, it is possible that defective regulatory activation of dNK cells combined with local inflammation or intrauterine infection may program poor placentation and associated pathologies. Thus, inhibition of dNK cell regulatory activation should be considered in the context of accompanying inflammation.

Uterine and peripheral blood regulatory T cells (Tregs) in normal pregnancy

Recent investigations have focused on $CD4^+$ Tregs and Th17 T cells at the maternal-fetal interface and in circulation involving normal pregnancies and pregnancy complications. This is a deviation from an early focus on Th1 vs Th2 paradigm. Uterine regulatory T cells (Tregs) are a specialized subset of T lymphocytes that are essential for mediating immune tolerance to foreign antigens and for preventing pathologic immune responses [47–51]. Tregs are characterized by the surface expression of CD4, CD25, cytotoxic T lymphocyte antigen-4 (CTLA-4), and the transcription factor forkhead box protein 3 (FoxP3) [47–51]. The pioneering work by Robertson and colleagues [52] reveals that exposure of the uterus to male seminal fluid which contains cytokines and chemokines prepares the local microenvironment to attract and expand Tregs that react with paternal alloantigens. Female dendritic cells recognize fetal antigens and cross-present seminal fluid antigens which induce transformation of effector $CD4^+$ T cells into induced Tregs. These newly induced Tregs cells are eventually recruited to the endometrium. In humans and mice, uterine and peripheral blood Tregs increase very early in pregnancy, peak during the second trimester, and then begin to decrease to pre-pregnancy levels [52]. Depletion of Tregs in mice using different approaches prior to or just after mating dramatically impairs implantation, suggesting a critical role of Tregs in implantation and pregnancy success [53]. However, depletion of Tregs after gestational day 6 in mice does not affect pregnancy outcome, implying that Tregs may not be required for maintenance of pregnancy [54]. Our unpublished data suggest that uterine Tregs with inflammatory characteristics can be amplified by triggers such as LPS or poly IC in pregnant mice which then contribute to pregnancy demise or preeclampsia-like features

depending on the gestational age of administration. This suggests that Tregs can be friends or foes of pregnancy based on the uterine microenvironment [24].

Are Tregs dysregulated in preeclampsia?

Since the intrauterine milieu in preeclampsia entails oxidative stress, inflammation, or hormonal dysregulation (our unpublished observation), it is tempting to speculate that Tregs are either poorly recruited to the pregnant endometrium or converted into cells with an inflammatory phenotype [24]. Although not completely understood yet, several studies have shown that patients with preeclampsia display decreased Treg expansion in peripheral blood and the decidua, suggesting an association between the failure of pregnancy compatible Treg transformation and the pathogenesis of preeclampsia [55–58]. In a transgenic model of preeclampsia, physiologic restoration of Tregs has been shown to improve intrauterine growth restriction without affecting hypertension and production of anti-angiogenic factors such as Flt-1 [59]. Although these results are very exciting, it is possible that overwhelming transgenic gene expression overrides the control of hypertension and other factors. In this regard, if Tregs are not hormonally propagated to be recruited to the endometrium, they may not counter all the pathologic features of preeclampsia. We have recently shown that in a human serum-based mouse model of preeclampsia, uterine Tregs are intrinsically reduced, and treatment with recombinant hCG can restore normal pregnancy level of Tregs and ameliorate the maternal phenotype of preeclampsia (manuscript in preparation). This suggests that dysregulated Tregs do play a role in the pathogenesis of preeclampsia. As discussed above in the case of dNK cells in LPS or poly IC-treated pregnant mice, Tregs also have the ability to become hostile to pregnancy in response to these inflammatory triggers. Interestingly, Tregs from LPS or poly IC-treated pregnant mice do not acquire Th17 phenotype. This altered phenotype of uterine Tregs may be regulated by induced NF-kB transcriptional machinery [24]. The questions that still remain poorly addressed are whether Tregs undergo epigenetic changes such as acquiring an exhausted phenotype as a result of expression of negative stimulatory co-receptor programmed death receptor-1 (PD-1) or whether Tregs are poorly differentiated for recruitment to the endometrium. Is their poor recruitment or inflammatory uterine phenotype associated with immune dysregulation, placental ischemia, oxidative stress, and/or protein mimicry?

Preeclampsia and consequences beyond: an immunological link

Here, we will focus on two main health issues that may have their etiological origin in dysregulated immune responses that occur during preeclampsia pregnancy and may persist and cause long-term health risks. First, in a parity-independent scenario, a short interval between first pregnancy and second pregnancy challenged with new alloantigens (new partner) is associated with heightened risk of preeclampsia [60, 61]. Second, although pregnancy represents a modest portion of the life course, it is now recognized as a window to women's future health, often by unmasking predispositions to conditions that only become symptomatic decades later. Indeed, meta-analysis of large longitudinal databases has revealed how a history of preeclampsia might predispose women to a wide range of chronic long-term sequelae later in life, including chronic hypertension, ischemic heart disease, cerebrovascular disease, thromboembolism, hypothyroidism, stroke, diabetes mellitus, and premature death and end-stage renal disorder [62–66]. We recently proposed that preeclampsia may be a risk factor for the onset of Alzheimer's disease [67], suggesting that preeclampsia causing factors or pathways remain active or can be triggered in response to environmental challenges such as inflammation and its associated hyperlipidemia and dyslipidemia or vice versa as suggested by Staff et al. [68]. On the other hand, no association of preeclampsia with future risk of cancer was found [63]. Can these post-preeclampsia pathologies be related to chronic systemic inflammation that is augmented during preeclampsia pregnancies?

Role of paternal antigens in preeclampsia and beyond

As mentioned above, inadequate fetal allorecognition has been associated with poor placentation, placental oxidative stress, and release of pro-inflammatory cytokines. Epidemiological studies have shown that prior and prolonged exposure to paternal seminal fluid decreases the likelihood of preeclampsia, and inadequate maternal exposure to paternal antigens prior to pregnancy increases risk of preeclampsia [61, 69]. This suggests that paternal antigen exposure may facilitate maternal immune tolerance to paternal HLA [69]. Although primiparity predisposes to preeclampsia, the maternal immune system develops a memory phenotype with respect to these antigens which can be recalled during a second pregnancy conceived within a short period without compromising the memory immune responses [13, 23, 60]. In support to these findings, animal experiments have demonstrated that exposure to seminal fluid promotes maternal immune tolerance to paternal alloantigens through expansion of the Tregs pool [13]. A prior study by Rowe et al. [23] has shown that pregnancy selectively induces the expansion of fetal-specific Tregs, and after delivery, these Tregs persist at elevated levels, sustain tolerance to pre-existing fetal antigen, and rapidly re-accumulate during second pregnancy [23].

These data may explain why a first pregnancy confers tolerance to a second pregnancy and why rates of preeclampsia and other complications associated with inadequate fetal tolerance are reduced in secondary compared with primary pregnancy [23]. However, the above-mentioned studies do not address the issue of recurrence of preeclampsia in response to overwhelming inflammation and the causative factors generated during first pregnancy. Below, we discuss some of the causative factors whose persistence may program recurrence of preeclampsia and diseases later in life.

Mechanisms of health risk consequences after preeclampsia

Numerous studies have shown that women with preeclampsia display excessive chronic inflammatory response locally in the placenta and systemically in many other organs [11–16]. What may be the underlying factors for sustained pathologic inflammation? It has been suggested that the exaggerated systemic inflammatory response in preeclampsia is a result of oxidative stress, increased release of microparticles, autoantibodies, misfolded and aggregated proteins, and nuclear and mitochondrial damage-associated molecular patterns (DAMPS) which impart both local and systemic adverse effects leading to poor trophoblast invasion and vascular growth, endothelial dysfunction, and excessive inflammation [2, 11–16, 39]. The discussion on the concept of oxidative stress has been extensively covered in other reviews. Below, we will review recent advances in the research on microparticles, misfolded proteins, and DAMPS and their association with systemic inflammation in preeclampsia. At the end of description of these factors, we will provide discussion on how these factors can program diseases in later life.

Microparticles

Microparticles are a group of small membrane vesicles (0.05–1μm) with heterogeneous origins released from the cell surface by blebbing of plasma membrane during cell activation and apoptosis [70–77]. All eukaryotic cells have the ability to release microparticles including platelets, endothelia, leukocytes, and syncytiotrophoblasts [70–77]. Microparticles of different sizes including exosomes can be detected in circulation and carry chemokines, cytokines, enzymes, mRNA and microRNA, trophic factors, and signaling proteins. It has been implied that they play a pivotal role in thrombosis, angiogenesis, inflammation, and cell-cell communication by activating unknown receptors or by transferring their cargo including mRNAs and microRNA to target cells under physiological conditions [70–77]. Redman and Sargent first proposed that placenta-derived microparticles could play a role in the pathogenesis of preeclampsia [75].

In normal pregnancy, microparticles are commonly present in the plasma. Accumulating evidence has shown that microparticles derived from syncytiotrophoblasts induce production of inflammatory cytokines and activation of peripheral blood leukocytes when co-cultured with PBMCs and endothelial cells [71, 72, 74–76]. Accordingly, microparticles have been proposed as an immunoregulator for programming mild inflammation in normal pregnancy. However, microparticles may change their phenotype and become foes to pregnancy in the context of adverse maternal placental microenvironment. Indeed, numerous studies have demonstrated that women with preeclampsia exhibit increased levels of microparticles derived from T lymphocytes, B lymphocytes, and granulocytes as compared to normotensive pregnant women and this may contribute to development of endothelial dysfunction and maternal systemic inflammatory response in preeclampsia [70–77]. Syncytiotrophoblast-derived microparticles (STBMs) isolated from preeclamptic women have been shown to induce higher levels of superoxide radicals produced by neutrophils than STBMs from normotensive pregnant women. Guller et al. [77] have suggested that STBMs express factors which harbor the potential to alter the fibrinolytic and angiogenic balance at the maternal-fetal interface and play an important role in the preeclampsia pathology. Moreover, a recent study by Lee et al. [70] demonstrated that microparticles from hypoxic trophoblasts induced higher concentrations of IL-6 and TNF-α secreted by the peripheral blood mononuclear cells (PBMCs) than microparticles from normal trophoblasts. Taken together, microparticles may entail diverse functional phenotypes as a result of their cargo composition when shed from different cell origins under different conditions. Dysregulated microparticles may be associated with vascular dysfunction and exaggerated systemic inflammatory response in the context of different RNA moieties, misfolded proteins, and inflammatory triggers [70–75]. The mechanisms underlying phenotype re-programming of microparticles and how they contribute to the pathogenesis of preeclampsia remain to be further explored, particularly in the context of their peak appearance in the plasma. Microparticles are detected at their peak concentration in third trimester, suggesting that they probably contribute to programming of systemic preeclampsia syndrome.

DAMPS

Recent observations clearly suggest that shed nuclear and mitochondrial products can facilitate effector immune responses [78–84]. It is proposed that cell death and injury can lead to release of nuclear and mitochondrial DNA (mtDNA) which can act as a damage-associated molecular pattern and interact with Toll-like receptor 9 (TLR9) [39]. Impaired mitochondrial function has been observed in the human placenta from pregnant women with metabolic syndrome

conditions [78]. Importantly, hypoxia has been shown to generate DAMPS, and since ischemia/hypoxia is key event in preeclampsia, it is plausible that DAMPS are critical contributors to the preeclampsia pathology. The preeclampsia placenta, particularly associated with intrauterine growth restriction, exhibits high content of mtDNA DAMPS [70–79]. Recent evidence clearly suggests that circulating mtDNA DAMPS cause inflammatory responses via activation of TLR9 signaling pathway [80, 81]. Taking a cue from these studies, it can be proposed that poor placentation and trophoblast cell death result in production of mitochondrial milieu containing mtDNA DAMPS which can utilize TLR9 to mount a potent systemic inflammatory response, vascular deficiency, and preeclampsia-like features associated with IUGR [39, 82]. In normal pregnancy, fetal DNA is detectable in maternal plasma from 7 weeks of gestation with higher concentration in late pregnancy [83]. Many in vitro experimental studies confirmed fetal DNA as a strong inflammatory agent, which can initiate inflammation through TLR9 activation, release of IL-6, and activation of NF-kB by B cells and mononuclear cells [82, 84]. Injection of human fetal but not adult DNA into pregnant mice resulted in fetal resorption with elevated levels of TNF-α and IL-6 and infiltration of inflammatory cells in the placenta [82]. Notably, higher levels of fetal DNA were observed in women with preeclampsia as compared to controls, and this increased level can be even detected 3 weeks before the appearance of symptoms of preeclampsia [79, 82–84]. Moreover, trophoblast DNA is hypomethylated at CpG motifs in the preeclampsia placenta and acts in the same way as bacterial and viral DNA, particularly in the placenta from early onset disease. Hypomethylated trophoblast DNA has been shown to activate immune responses through interaction with TLR9 [82]. The question is whether shed nuclear and mitochondrial DNA DAMPS persist to trigger severe systemic inflammation, leading to vulnerability of organs to injury.

Misfolded and aggregated protein in preeclampsia

We and others have provided compelling evidence showing that preeclampsia is a disease of protein misfolding and aggregation [67, 85, 86]. These aggregated proteins can be detected in maternal serum and urine as well as in the placenta [67, 85, 86]. The mechanism of protein misfolding and aggregation has been studied extensively in neurodegenerative diseases such as Alzheimer's disease (AD) [67, 87, 88]. We have identified that proteins such as transthyretin (TTR) and amyloid precursor protein (APP) product Aβ undergo aggregation in preeclampsia [67, 85]. TTR is a 55 kDa homotetrameric protein that transports thyroxine and retinol to deliver thyroid hormones and vitamin A to many organ sites. Aβ cleaved from APP is the major component of amyloid plaque formation in AD [87, 88].

Inflammation is a key pathologic hallmark of many protein misfolding and aggregation diseases including AD. Aggregated proteins such as TTR and Aβ are cytotoxic and have been confirmed to cause ER stress, oxidative stress, inflammation, anti-angiogenic factor release, inflammation, and apoptosis [67, 87–92]. Aβ aggregates are capable of activating glial cells and astrocytes as well as inducing release of pro-inflammatory cytokines and chemokines such as TNF-α and IL-1β [90–93]. In addition, Aβ has been shown to activate NF-kB signaling cascade in neurons, astrocytes, glial cells, and brain endothelial cells [92].

We previously demonstrated that aggregated proteins from preeclampsia serum induced production of sFlt-1 from human trophoblasts and caused preeclampsia-like features in pregnant mice [85]. The relevant question here is whether protein aggregates continue to be present after preeclampsia delivery or whether they are further augmented by subsequent preeclampsia incidence, environmental exposures, and stress. Protein aggregates have been shown to cause cardiovascular disease [67]. It is thus tempting to speculate that long-term presence of protein aggregates in women with a history of preeclampsia can contribute to the onset of diseases, including cardiovascular disease. We also propose that preeclampsia could be a risk factor for AD-like disease [67]. However, many questions still remain to be elucidated; for instance, how protein aggregates accumulate in the placenta and how these aggregates contribute to the pathogenesis of preeclampsia and health risks later in life.

Could microparticles, DAMPS, and aggregated proteins participate in the origins of health risks later in life?

It has been suggested that pregnancy transiently unmasks a woman's tendency to the metabolic syndrome of insulin resistance and this may become a chronic pathology leading to proatherogenic condition in later life in women who experienced preeclampsia [94, 95]. Short (median 3 years) and longer (15–25 years) follow-up of preeclampsia women has suggested that these women had clinically apparent or subclinical symptoms of metabolic syndrome, including elevated body mass index, elevated blood pressure, triglycerides, and total and low-density lipoprotein cholesterol [96, 97]. Kvehaugen et al. showed evidence of chronic systemic inflammation and persistent endothelial dysfunction 5–8 years postpartum in women with and their offspring after preeclampsia [98]. Thus, the metabolic syndrome and chronic inflammation can be risk factors for diseases such as cardiovascular disease, type 2 diabetes, and even neurodegenerative diseases. The common link between all these diseases is

systemic inflammation. Given the inflammation-inducing potential of protein microparticles, DAMPS and protein aggregates, we propose that they are likely to contribute to systemic diseases in later life of women with preeclampsia. It is possible that dysregulated immune responses will contribute to systemic inflammation. In this regard, syncytiotrophoblast microparticles (STBMs), DAMPS, and aggregated proteins, if present in the postpartum period, may activate monocytes, dendritic cells (DCs), NK cells, and neutrophils promoting inflammatory milieu constitutively or in response to environmental triggers. Importantly, NK cells and Tregs, important components of immune tolerance during pregnancy, may acquire immunological memory to detrimental antigens and could play a role in the long-term sequelae of preeclampsia such as cardiovascular disease. As mentioned earlier, several studies have suggested that total Tregs are reduced during preeclampsia. If Tregs remain dysregulated postpartum, it will allow the elevated presence of inflammatory T cells, resulting in production of inflammatory cytokines and autoantibodies. In this regard, it is noteworthy that administration of aggregated proteins present in preeclampsia serum in pregnant mice induces production of sFlt-1 and reduces uterine Treg population (our unpublished observations). Although we detected aggregated Aβ in the preeclampsia placenta, it is not clear what physiological role Aβ plays in normal pregnancy. An exciting hypothesis has been put forward by Kumar et al. in their recent publication [99]. These authors suggest that Aβ is intrinsically generated and plays a physiological role by inhibiting fungal and bacterial infections in mouse, nematodes, and cell culture models of AD. It is then plausible that native Aβ plays a protective role at the maternal-fetal interface and overwhelming infections or inflammation drives its aggregation and amyloidosis contributing to health risks in later life. Future experiments should focus on determination of inflammatory T cells, presence of microparticles/DAMPs/aggregated proteins, and markers of metabolic syndrome in the postpartum years in women and their offspring after preeclampsia.

Conclusions

Although the etiology of preeclampsia is still poorly understood, dysregulated maternal immune system has been recognized as a crucial contributor to the pathophysiological programming of preeclampsia (Fig. 1). As a leading cause of maternal and fetal morbidity and mortality, preeclampsia not only causes an array of clinical manifestations in women antepartum but also place mothers and their children at an increased risk of developing a variety of diseases postpartum. Pregnancy affected by preeclampsia has profound long-term health care complications. Women with preeclampsia should

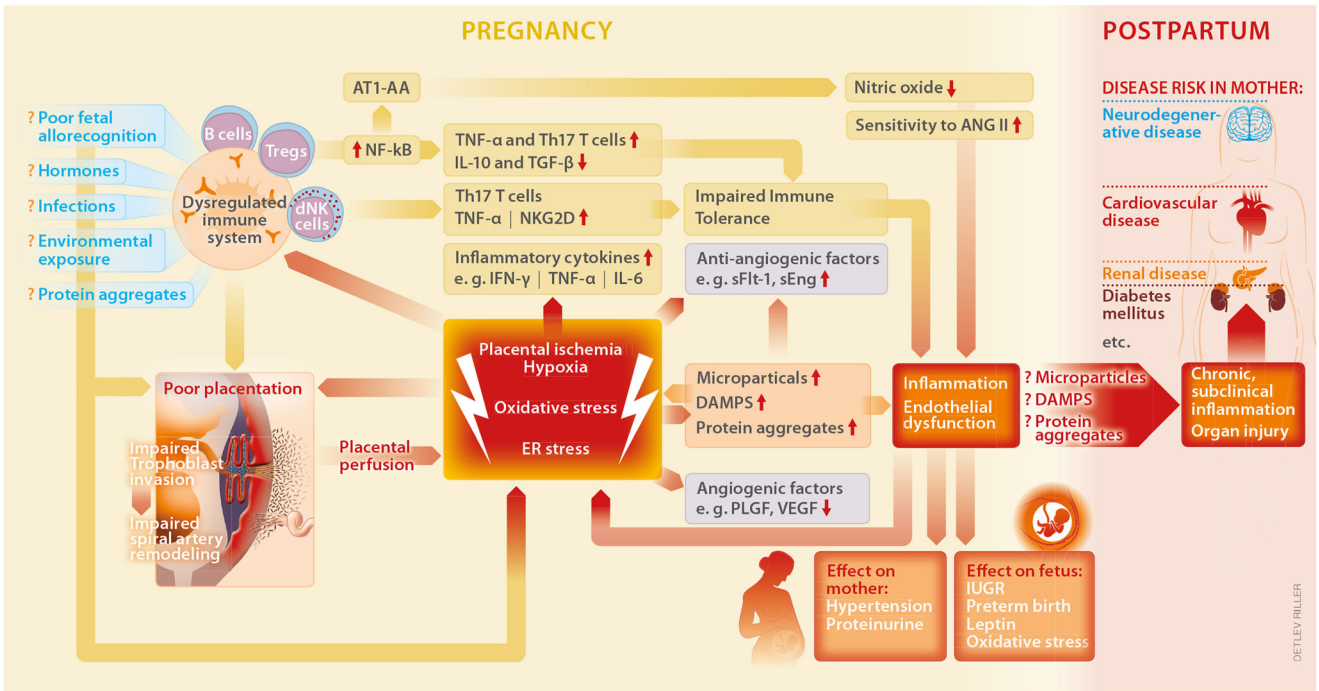

Fig. 1 Schematic diagram showing how maternal immune system contributes to the pathophysiology of preeclampsia and health consequences later in life. Briefly, poor placental perfusion-induced placental ischemia/hypoxia, oxidative stress, and endoplasmic reticulum (ER) stress disrupt tolerant maternal immune system, which in turn impairs the pregnancy-compatible functions of decidual immune cells, including Tregs and dNK cells. This may activate subpopulations of B cells to produce autoantibodies [11]. High levels of inflammatory factors, angiogenesis-related factors, microparticles, DAMPS, and protein aggregates that are involved in the preeclampsia pathogenesis may persist and sensitize organs and cause diseases later in life

be informed of this increased risk of adverse health outcomes in their later life, and postpartum long-term surveillance should be taken for timely interventions.

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