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Maternal fetal cross-talk through, cell-free fetal DNA, telomere shortening, microchimerism, and inflammation

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Abstract

There exists a strong correlation between unscheduled inflammation at the maternal-fetal interface and the continuum of pregnancy complications. In normal pregnancy, immunological tolerance is established to protect the semi-allogeneic fetus. There has been extensive research on how the immunity, endovascular trophoblast migration, and hormonal nexus are orchestrated during pregnancy at the maternal-fetal interface to program a normal pregnancy outcome. What else contributes to the plasticity of uterine immune tolerance, fetal survival, and long-term post-partum health of the mother and the offspring? Old and new concepts have reemerged and emerged that include cell-free fetal DNA (cffDNA), telomere shortening, microchimerism involving bidirectional migration of maternal and fetal cells, and pregnancy as a stress factor. The question is how these pathways converge in a gestational age-dependent manner to contribute to the health of the mother and the offspring later in life and respond to an array of inflammatory challenges. In this Review, we provide pertinent discussion on maternal fetal cross-talk through cffDNA, telomere shortening and microchimerism in the context of inflammatory and anti-inflammatory settings, particularly how these pathways lead to normal and adverse pregnancy outcomes.

Keywords

Immune tolerance; telomere; cell free DNA; microchimerism; adverse pregnancy outcomes

1. CELL-FREE FETAL DNA (CFFDNA) IN PREGNANCY

Cell-free fetal DNA (cffDNA) is a group of small DNA fragments < 313 bp length that are derived from apoptotic and necrotic placental cells and released into maternal circulation.^{1,2} During normal gestation, cffDNA undergoes a progressive rise, which peaks at term and then rapidly drops to undetectable levels postpartum.²⁻⁵ In support of this, increasing apoptosis of trophoblast cells has been observed at the end of pregnancy.⁶⁻⁹ Elevated circulating levels of cffDNA have been reported in adverse pregnancy complications.¹⁰⁻¹⁴

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The questions arise whether cffDNA can be used as a putative biomarker for pregnancy complications and whether cffDNA in normal pregnancy is different from gestation with adverse pregnancy outcomes. Recently, detection of cffDNA in maternal blood has been developed as a non-invasive prenatal diagnostic test to detect chromosomal abnormalities in the fetus.¹⁵ To this end, epidemiological studies with a focus on the SRY/DYS/RhD gene sequences in maternal plasma/serum have shown that cffDNA is significantly elevated in women with adverse pregnancy outcomes including preterm birth,^{16–21} fetal growth restriction,²² gestational diabetes²³ and preeclampsia.^{11, 24–26}

Human cffDNA contains unmethylated CpG motifs similar to bacterial and viral DNA. Thus, cffDNA may interact with Toll-like receptor 9 (TLR9), a pattern recognition receptor involved in innate immunity, leading to the activation of NF- κ B and increased production of proinflammatory cytokines and chemokines.⁵ On the other hand, cffDNA may activate Stimulator of Interferon Genes (STING),¹⁵ a protein that is expressed in haematopoietic cells, endothelial and epithelial cells. Activated STING in turn complexes with TANK-binding kinase, leading to phosphorylation of transcription factors IRF3 and NF- κ B. Through this TLR9-independent pathway, cffDNA induces release of type 1 interferons, IFN- β and IFN- α , and other pro-inflammatory mediators.²⁷ Thus cffDNA can act as a pro-inflammatory trigger with a unique capability to ignite inflammatory cascades. In this regard, our laboratory has provided compelling evidence for such signaling events promoted by interaction of DNA and TLR9.²⁸ Our results demonstrated that intraperitoneal injection of a TLR9 agonist CpG oligodeoxynucleotide (ODN) induced fetal resorption and preterm birth in IL-10 knockout mice, but not wild-type mice depending on gestational age of administration. ODN treatment also increased TNF- α release in the maternal circulation and induced an influx of neutrophils and macrophages into the uterus and placenta. Moreover, ODN-induced adverse pregnancy outcomes could be reversed by depleting macrophages or by neutralizing maternal TNF- α , but not by depleting neutrophils. These data suggest that IL-10, TNF- α and macrophages are implicated in regulating DNA-TLR9 promoted pregnancy complications. Importantly, these findings have been confirmed by Sun et al in nonobese diabetic (NOD) mice, a strain featuring low regulatory T cells (Tregs) and IL-10 positive cells.²⁹ Intriguingly, using the same NOD mouse model, Lin et al³⁰ found that CpG-induced fetal resorption and preterm birth were prevented by administration of IL-10 or Tregs, and that CpG injection did not induce any adverse complications in pregnant wild-type mice. These findings provide strong evidence for importance of IL-10-mediated protective regulation in DNA-promoted adverse pregnancy outcomes. Additionally, administration of CpG during gestation caused maternal hypertension and increased vasoconstriction in pregnant rat.³¹

Scharfe et al²⁶ assessed the effects of fragmented fetal genomic DNA, which is larger in size than cffDNA, on pregnancy. They found that fetal DNA stimulation led to increased production of IL-6 in peripheral blood mononuclear cells (PBMCs) isolated from pregnant women. Their observation further showed that injection of fetal DNA, not genomic DNA (containing few unmethylated CpG sequence motifs) during gestational days 10–14 induced high rates of fetal resorptions in wild-type mice. However, this effect was not observed in TLR9 deficient mice, suggesting a fetal DNA-induced inflammatory response through activation of TLR9 pathway. In contrast to CpG ODN-induced effects in pregnant IL-10

deficient mice,^{28,29} fetal DNA injection only induced a localized inflammatory response in the uterine tissues of wild-type mice, and failed to produce preterm birth.⁵ Recently, Conka et al³² reported that administration of various types of human fetal DNA or mouse adult DNA during late gestational days 14–18 did not elicit preeclampsia-like features in wild-type mice. This discrepancy may be attributed to the fact that wild-type mice contain anti-inflammatory IL-10, which inhibits TLR9-mediated signaling pathway, and cffDNA extracted from healthy cells is an ineffective agonist for TLR9.⁵ In addition, fetal DNA may exert more severe negative effects on maternal immune tolerance during early gestations versus late gestation days.

Collectively, association of cffDNA with adverse pregnancy complications has emerged as a new area of extensive investigation. Numerous questions, however, remain to be addressed. For example, is cffDNA a causative factor for the pathology of adverse pregnancy outcomes or just a pathological consequent byproduct? Does cffDNA persist to trigger severe systemic inflammation, leading to vulnerability of organs to injury in later life? Due to the heterogeneity in participants, sampling time points and methodologies used to extract and quantify cffDNA, many epidemiological studies have provided conflicting evidence regarding correlation between cffDNA and pregnancy complications.¹⁵ Moreover, mechanistic studies on cffDNA effects in animal models are still lacking. We and others have provided evidence showing that CpG ODN when coupled with IL-10 deficiency induces significant pregnancy complications. This suggests that cffDNA may not be an exclusive factor that contributes to the pathogenesis of pregnancy complications. Thus, *in vivo* investigation of cffDNA-associated pathological effects may be warranted in the context of other immune dysregulations. In addition, studies using cffDNA that is extracted from pathological altered placental tissue or trophoblast cells are also needed to address the role of cffDNA in adverse pregnancy outcomes.

2. TELOMERE MIMICRY IN PREGNANCY

Telomeres are the domains of repetitive DNA sequences (e.g. TTAGGG in mammals) at the distal ends of linear chromosomes, which protect the end of the chromosome from breaks or from end-to-end fusion, and thereby maintain genomic structural integrity and cell survival.⁵ Generally, telomeres are progressively shortened with each cell division, and thus, telomere length is considered to be a determinant of biological clock for natural ageing.^{4,5,33} Normally, telomeres are synthesized by the reverse transcriptase enzyme known as telomerase. Regulation of telomere length can be affected by environmental factors such as oxidative stress. Oxidative stress has been shown to cause telomere shortening by breaking double strand DNA structure and inhibiting repair of telomere breaks via reducing telomerase activity and expression.^{34–36} Telomere shortening in turn makes telomeres more susceptible to oxidative stress and further damage.³⁷ A critical telomere shortening can cause cells to undergo an irreversible proliferative arrest named cellular senescence^{38–40} and apoptosis through p53-dependent and -independent events.^{41–43} Additionally, telomere loss and the resulting senescence have also been shown to trigger sustained activation of transcription factor NF- κ B and overexpression of inflammatory cytokines such as TNF- α , IL-6 and IFN- γ in circulating macrophages, leading to chronic inflammation.^{4,44}

A gradual progression of natural physiological senescence has been found in maternal decidual cells, trophoblasts and fetoplacental membranes of normal pregnancy, which may contribute to the mechanisms of parturition at term. Consistent with these findings, placental and fetal membrane cells have been found to have weak or no telomerase activity, especially during late gestation.^{5,44} Mechanistic data demonstrated that this natural progressive loss of telomere DNA is associated with upregulation of cellular senescence signals, including p38, p53, p21, IL-1b, IL-6, IL-8 and SA- β -gal in the maternal decidual and fetal membranes at term.^{46–48} However, various mitochondrial and endoplasmic reticulum stress inducers such as hypoxia and oxidative stress can cause premature or accelerated senescence and aging in the placenta, leading to pregnancy complications including fetal growth restriction, preeclampsia and preterm birth.^{36,49,50} Indeed, increased telomere shortening, aggregation and dysfunction, reduced telomerase activity, and enhanced expression of senescence markers (e.g. p53, p16, p21) and DNA oxidation have been observed in the placenta from women with preeclampsia and preterm birth associated with premature rupture of the membranes.^{36,47,51} Shorter telomeres in blood leukocytes have been found in women with unexplained recurrent pregnancy loss.⁵² Several studies have revealed a significant decrease in telomere length in the placenta from severe IUGR.^{51,53,54} This reduction of telomere length is associated with increased oxidative stress and cellular senescence signals (e.g. p21, p16 and EF-1 alpha) as well as reduced telomerase activity in the placenta with IUGR deliveries.^{36,51,53} Interestingly, Jones et al⁵⁵ recently demonstrated that telomere length was significantly shorter in the placenta from black women compared to that from white women, suggesting accelerated cellular aging across placental tissues in black mothers. This may provide a plausible mechanism for the increased risk of preterm delivery in African American women.^{56–58}

Adverse uterine environment can lead to altered fetal programming that may contribute to increased health risks in offspring. In this regard, a prior study indicates an association between maternal stress during pregnancy and telomere shortening in the offspring.⁵⁹ Menon et al reported shorter telomere length observed in children born to mothers who smoke during pregnancy.⁶⁰ Moreover, maternal nutritional and sleeping disorders during pregnancy are also linked to fetal telomere shortening.⁶¹

Recently, Phillippe et al. proposed an interesting “cffDNA/telomere” hypothesis to provide a mechanistic explanation for normal parturition and the spontaneous preterm birth.⁵ This hypothesis described that telomere shortening induces apoptosis in placental tissues and subsequently leads to release of cffDNA. As a result, TLR9-promoted inflammatory cascades are activated and reinforced by reduced IL-10 expression in the placenta during late gestation. The activated innate immune response enhances the expression and function of uterine activation proteins, matrix metalloproteinases and uterotonins, leading to cervical ripening, rupture of the membranes and the onset of phasic myometrial contractions.⁵ In support of this hypothesis, there have been many studies showing these signaling events involved in regulating spontaneous parturition at term.⁵ However, dysregulation of these signaling events may result in spontaneous preterm parturition. In this regard, elevated cffDNA levels^{17,17,19} and suppressed IL-10 production^{40,63–65} have been linked to pregnancies complicated with preterm delivery in pre-clinical models. Additionally, a prior study showed significant lower levels of IL-10 in African American women compared to

white women.⁶⁶ This observation is correlated with the fact that African American women have higher levels of telomere shortening, shorter gestations and higher rates of preterm birth.^{5,55,67}

3. DOES INFLAMMATION, INFECTION OR STRESS DISRUPT MICHROCHIMERISM DURING PREGNANCY?

Microchimerism in pregnancy is defined as a vertical transfer of maternal cells to the fetus at detectable levels. Reciprocally, fetal cells can also be found in mothers, making the microchimerism exchange between the mother and the fetus a physiologically relevant process.^{68,69} This bidirectional migration of cells occurs at a very low level, albeit 1 in 10³ fetal cells in maternal peripheral mononuclear cells (PBMCs) at the beginning of second trimester of human pregnancy,⁷⁰ and is highly conserved across placental pregnancies in mammals. The process may start very early in gestation as observed in both humans and mice.^{71–73} Accumulation of microchimeric cells reach peak during the late stages of pregnancy and these cells can persist for decades after delivery.⁶⁸ It has been suggested that maternal microchimeric cells are involved in the maturation of fetal immune system.^{72,73} A global consequence of these physiologically retained microchimeric cells within mothers and their offspring is thought to be long-term programming of genetic and immune tolerance for future reproductive outcomes. Keeping the foreign nature of the antigenic cargo of these cells, it can be predicted that these cells entail beneficial as well as detrimental consequences. For example, maternal microchimeric cells have been shown to result in preferential augmentation of regulatory T cells (Tregs) from fetal CD4⁺ T cells.⁷³ There have been numerous reports suggesting that circulating Tregs begin to increase in numbers very early in pregnancy and reach peak mid-gestation.⁷⁴ This parallels the increase in uterine Tregs. Their absence or functional dysregulation has been associated with failed implantation or pregnancy loss.^{75,76} These observations suggest that bidirectional seeding of maternal or fetal cells helps during pregnancy and beyond.

What are the consequences of microchimeric cells? Can inflammation, infection, stress or change their functional characteristics and/or reduce their seeding? We propose that pathological events will alter the total number of microchimeric cells and program health risks during pregnancy and later in life by affecting differentiation into pregnancy compatible immune cells such as Tregs. For example, *Listeria monocytogenes* has been shown to induce fetal demise by disrupting maternal Treg-assisted fetal tolerance.⁷⁷ Our unpublished data suggest that Tregs amplify in response to a different set of inflammatory triggers. Surprisingly, these significantly increased Tregs acquire inflammatory phenotype and induce disruption of pregnancy. On the other hand, it is poorly understood whether management of microchimerism associated with differentiation into Tregs and production of cfDNA are controlled by cytokines such as IL-10, a signature product of Tregs. Is telomere shortening a part of microchimerism? It is possible that inflammation or stress-associated drop in microchimeric Tregs or B cells leads to IL-10 deficiency and health risks during pregnancy and later in life. These concepts warrant further studies on microchimerism in pre-clinical models of pregnancy.

4. MATERNAL TOLERANCE TO PATERNAL-FETAL ANTIGENS

As described above, there are many physiological events such as cfDNA, gestational age-dependent shortening of telomere, and maternal and fetal microchimeric cells generated from the mother and the semi-allogeneic fetus during normal pregnancy. How does maternal immune system orchestrate the interplay involving this cascade of events to maintain a successful pregnancy? A successful pregnancy is a unique and well-choreographed balance between pro-inflammatory and anti-inflammatory responses, leading to maternal immune tolerance.^{78–81} Indeed, the maternal immune tolerance plays a pivotal role in the regulation of placentation, trophoblast invasion and angiogenesis, and thus is essential for placental development and normal fetal growth.⁷⁸ Defective fetal allorecognition and impaired immune response have been involved in poor placentation, release of pro-inflammatory cytokines, and hormonal imbalance at the maternal-fetal interface, leading to adverse reproductive outcomes.^{78,80}

The mechanisms underlying maternal immune tolerance to genetically foreign fetal tissues are still poorly understood. Prior studies have revealed that maternal immune tolerance are associated with the increase in immunosuppressive signals, the inactivation of immune cells via chemokine gene silencing, the decrease in complement deposition and the entrapment of professional antigen-presenting cells.⁷³ In this context, IL-10, a potent immunosuppressive cytokine, has been considered as a pivotal modulator of immune tolerance at the maternal–fetal interface.⁸¹ Compared to wild type mice, IL-10 knockout mice during pregnancy are more susceptible to immunogenic insults, such as treatment with low doses of LPS, CpG, and polyinosinic:polycytidylic acid (polyI:C).^{82–84} In humans, IL-10 deficiency has been found to be associated with many complications such as recurrent spontaneous abortion (RSA), preterm birth, and preeclampsia.^{62,65,83,85,86} Uterine NK (uNK) cells are the major lymphocytes present in the decidua during pregnancy and have the ability to secrete IL-10, and their activity can also be regulated by IL-10.^{87–90} Importantly, unlike the primordial immune functions of NK cells, the specialized uNK cells support pregnancy with the ability to regulate trophoblast invasion and vascular remodeling.^{85,91} Decidual NK (dNK) cells have been shown to maintain immune tolerance and successful pregnancy by suppressing inflammatory Th17 cells, a lineage of pro-inflammatory T helper cells.⁹² In normal human pregnancy, only a small population of Th17 cells exists in the decidua during the first trimester. Redundant Th17 cells have been reported to impair immune tolerance in transplantation and pregnancy.^{93,94} An inflammatory microenvironment induced by IL-1 β and IL-6 in the decidua of women with RSA promotes the expansion and recruitment of Th17 cells.⁹² Importantly, the expression levels of IL-10, IL-1 receptor antagonist and IFN- γ were significantly decreased in dNK cells from women with RSA. These findings suggest that IL-10, IFN- γ and IL-1 receptor antagonist in dNK cells may be synergistically implicated in regulating the inhibition of Th17 cells, which contributes to dNK cell-mediated immune tolerance.⁹² Blois et al recently reported that uNK cells are the key source of IL-10 that is required to modulate the phenotype of uterine dendritic (DC) cells and successful pregnancy, and that interaction of uNK cells with DC through IL-10 play a unique role in regulating maternal innate and adaptive immune responses at the fetal-maternal interface during the establishment of a health gestation.⁹⁵ In addition, DC cells as

antigen-presenting cells have the unique ability to regulate T cell-mediated immunity and immunologic tolerance.⁹⁶

Furthermore, expansion of uterine regulatory T cells (Tregs) at the maternal-fetal interface during pregnancy also contributes to maternal tolerance machinery for suppressing paternal alloantigens and preventing pathological immune responses.^{97–102} 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).⁷⁸ Fetal microchimeric cells that carrying unique paternal-fetal antigens progressively increases in the uterine and maternal circulation throughout pregnancy and peak at parturition in humans and other mammalian species.^{103–105} Correlating with this paradigm of fetal cells, uterine and circulating Tregs increase very early in pregnancy and peak during the second trimester.^{74,98,106} This suggests that accumulation of maternal Tregs both locally in the uterus and systemically in maternal circulation may contribute to expanded immune tolerance to accommodate seeded fetal microchimeric cells. In support of this notion, blunted systemic expansion and decidual accumulation of maternal Tregs have been implicated in pregnancy complications such as preeclampsia and spontaneous abortion.¹⁰⁷ Interestingly, depletion of Tregs in mice prior or just after mating remarkably disrupt implantation resulting in gestation failure, which indicates a critical role of Tregs in implantation and immune tolerance regulation during early stages of conception.^{76,108} However, depletion of Tregs after gestational day 6 in mice does not influence pregnancy outcome, suggesting that Tregs may not be required for maintaining pregnancy.¹⁰⁹ Intriguingly, our unpublished data showed that uterine Tregs with inflammatory characteristics can be amplified by injection of triggers such as LPS or poly IC in pregnant mice, which then resulted in 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.⁸⁰

Epidemiological studies have revealed that prior and prolonged exposure to paternal seminal fluid decreases the likelihood of preeclampsia, and inadequate maternal exposure to paternal antigens prior to pregnancy enhances risk of preeclampsia.^{110,111} This implies that exposure to paternal alloantigens may facilitate maternal immune tolerance to paternal HLA.¹¹¹ Mechanistically, seminal fluid exposure has been shown to promote maternal immune tolerance to paternal antigens through expansion of the Tregs pool.¹¹² Moreover, pregnancy selectively induces the expansion of fetal-specific Tregs, and after delivery, these Tregs still persist at high levels, sustain tolerance to pre-existing paternal-fetal antigens carried in microchimeric cells, and rapidly re-accumulate during second pregnancy.¹¹³ These findings may explain why a first pregnancy confers tolerance to a second pregnancy and why incident rates of preeclampsia and other adverse pregnancy outcomes associated with inadequate fetal tolerance are decreased in secondary pregnancy as compared with primary pregnancy.¹¹³ Expanded immune tolerance primed by pregnancy persists not only in mothers but also in the offspring due to retaining of reciprocally transferred maternal and fetal microchimeric cells, which has been in detail reviewed by Kinder et al.⁷³

Despite extensive investigation, many issues regarding the mechanisms for maternal immune tolerance still remain to be addressed. For instance, how do microchimeric cells, shortened telomere and cfDNA interact with immune cells to influence maternal immune tolerance

and how critical roles of these mimics play in triggering maternal immunological response? How does persistent presence of these pathogens in mothers and their offspring impact their immunity in late life? How do different types of maternal immune cells interact with each other and cross-talk with fetal trophoblast cells in immunological tolerance machinery? Whether can the findings obtained from mice be translated to understanding of the mechanisms occurring in human pregnancy? Resolving these issues may provide potential targets for developing therapeutic strategies to treat pregnancy-related complications.

5. CONCLUSION

Pregnancy is a complex but highly choreographed process involving an active cross-talk between maternal and fetal tissues throughout gestation. Survival of the allogeneic embryo in the uterus depends on the maintenance of immune tolerance at the maternal-fetal interface. The pregnant uterus is replete with activated maternal immune cells. How this immune tolerance is acquired and maintained has been a topic of intense investigation. In placental mammals, an array of highly orchestrated response at the maternal-fetal interface support successful pregnancy outcome. This includes active communication between maternal immune cells and trophoblast cells. This intricate process is required for placentation, immune regulation, and redirection of maternal blood to the fetus. However, what has not been fully addressed is how this immune-trophoblast axis is maintained or breaks down during adverse pregnancy outcomes in response to unscheduled inflammation or stress. Intense research efforts have begun to shed light on the roles of cffDNA, telomere mimicry, and microchimerism (Figure 1). These factors are attracting a great deal of attention as a result of advanced maternal age of pregnancy, increasing incidence of pregnancy complications such as preterm parturition, preeclampsia and gestational diabetes, and challenges from sterile and infection-associated inflammation. Understanding and answering questions related to cffDNA, telomere shortening, and microchimerism will not only add to our knowledge regarding the biology of pregnancy, but mechanisms underlying these multiple pregnancy complications will allow the development and availability of much improved therapeutic options and diagnostic tests. The themes discussed in this review are currently the focus of extensive research and may present a major paradigm shift in our thinking related to normal pregnancy and adverse pregnancy outcomes.

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Figure 1. Diagram showing signaling events involving maternal fetal cross-talk through telomere, microchimerism, cell free fetal DNA and inflammation. Mito: mitochondria.