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Original Article

Relationship between FcγRIIB gene polymorphisms, periodontitis and adverse pregnancy outcomes in pregnant women

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Abstract: Background: FcγRIIb acts as a negative feedback regulator by inhibiting B-cell antigen receptor-elicited activation signals through tyrosine phosphorylation of immunoreceptor tyrosine-based inhibitory motif (ITIM). FcγRIIb gene polymorphisms might be related to the lower level of IgG antibody response to periodontal bacteria and lead to the development of periodontitis. Our previous studies showed that there was significant association between FcγRIIb gene polymorphisms in pregnant women and adverse pregnancy outcomes, such as preeclampsia or preterm birth with low birth weight. Periodontitis as a risk factor for adverse pregnancy outcomes has been widely and generally reported, and many studies found inflammation might lead to the development of adverse pregnancy outcomes. Review: We assume the development of adverse pregnancy outcomes may be attributed in part to inflammation such as periodontitis enhanced by FcγRIIb gene polymorphisms. Although significant associations between clinical periodontal parameters and adverse pregnancy outcomes have not been found, subgingival levels of periodontal bacteria were associated with adverse pregnancy outcomes in our study. Therefore, we will summary and discuss previous studies about associations between FcγRIIb gene polymorphisms, periodontitis and adverse pregnancy outcomes, as well as the biological mechanism between them in this review.

Keywords: FcγRIIb gene polymorphisms, periodontitis, adverse pregnancy outcomes, inflammation

Introduction

Adverse pregnancy outcome represents a significant problem for modern obstetrics because of their increasing frequency and resulting socioeconomic impact. Many studies have implicated inflammation caused by maternal periodontal infection in adverse pregnancy outcomes development, [1-4] however, the mechanism of underlying this relationship is unclear. The role of genetic polymorphisms in systemic diseases development has been generally and widely accepted. In previous studies, we have identified significant association between FcγRIIb gene polymorphisms and periodontitis, between FcγRIIb gene polymorphisms and adverse pregnancy outcomes [5-9]. Therefore, we hypothesized the development of adverse pregnancy outcomes might be associated with FcγRIIb gene polymorphisms-associated inflammation caused by periodontal infection. Although we did not find direct significant associations between the prevalence of periodontitis and adverse pregnancy outcomes in pregnant women, a significant association between subgingival periodontal bacteria and adverse pregnancy outcomes was identified [10]. In this review, we will summarize and discuss previous studies about the association among FcγRIIb gene polymorphisms, periodontitis and adverse pregnancy outcomes, and analyze the possible biological mechanism

FcγRIIb

FcγRII is encoded by three homologous genes on chromosome 1q23: FcγRIIa, b and c [11]. FcγRIIa and FcγRIIc elicit activatory signals via

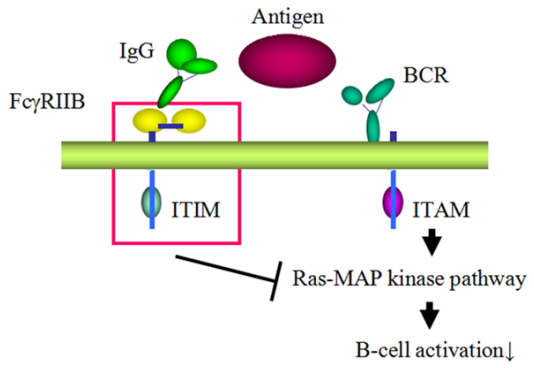

Figure 1. Signaling pathway for inhibitory FcγRIIB. FcγRIIB acts as a negative feedback regulator by inhibiting B-cell antigen receptor (BCR)-elicited activation signals through tyrosine phosphorylation of immunoreceptor tyrosine-based inhibition motif (ITIM).

an immunoreceptor tyrosine-based activation motif (IAIM). In contrast, FcγRIIb contains an immunoreceptor tyrosine-based inhibition motif (ITIM) on the cytoplasmic tail [12]. FcγRIIb encodes three transcripts (IIb_1, IIb_2 and IIb_3) due to alternative mRNA splicing. $FcγRIIb_1$ is exclusively expressed on B cells and has complete domains from all exons. Upon-co-cross-linking with the B-cell antigen receptor (BCR) by IgG immune complexes (ICs), $FcγRIIb_1$ acts as a negative feedback regulator by inhibiting B-cell antigen receptor-elicited activation signals through tyrosine phosphorylation of immunoreceptor tyrosine-based inhibition motif (ITIM) [13, 14] (**Figure 1**). The paired expression of activating and inhibitory molecules on the same cell is important for a balanced immune response. The FcγRIIb is one of receptors of the immunoglobulin G (IgG) that is the main type of antibody found in blood and extracellular fluid. By binding many kinds of pathogens such as viruses, bacteria, and fungi, IgG protects the body from infection. Previous studies have demonstrated FcγRIIb triggered inflammation using FcγRIIb deficient mice [15]. The studies of FcγRIIb expression regulation showed that the level of FcγRIIb expression might be reduced by complement component 5a, interferon-g, tumor necrosis factor-a and interleukin-1b. It was reported that interleukin-4 could up-regulate FcγRIIb expression on myeloid cells and down-regulated that on activated B cells. Interleukin-5, 10, 13 and transforming growth factor-β up-regulated FcγRIIb expression on innate effector cells [16-19].

FcγRIIb gene polymophisms and related diseases

Studies showed that a lower level of IgG production against periodontal bacteria caused by FcγRIIb gene polymorphisms may lead to periodontitis [7, 20]. IgG is the only isotype that has receptors to facilitate passage through the human placenta, thereby providing protection to the fetus in utero. Along with IgA secreted in the breast milk, residual IgG absorbed through the placenta provides the neonate with humoral immunity before its own immune system develops [21, 22]. Therefore, reduced maternal IgG levels caused by FcγRIIb gene polymorphisms might lead to the development of adverse pregnancy outcomes. These studies suggested that FcγRIIB gene polymorphisms were greatly related to the diseases.

Eleven single-nucleotide polymorphisms (SNPs) in the FcγRIIb gene were previously identified and confirmed to be FcγRIIb-specific. Of these SNPs, three SNPs and one SNP resulted in amino acid substitutions in exon4 (Thr203-Met, Tyr205-Phe and Ser207-Ala) and exon5 (Ile232-Thr), respectively. The other five SNPs were detected in introns 4 and 5, leading to no amino acid substitution [5] (**Table 1**). FcγRIIb-Ile232 polymorphism significantly increased in systemic lupus erythematosus and lupus nephritis patients [23, 24]. Studies also demonstrated that there was an association between FcγRIIb-Ile232 and susceptibility to anti-GBM disease [25]. FcγRIIb promoter variant-386C-120A downregulated the expression of FcγRIIb and greatly related to the chronic inflammatory demyelinating polyneuropathy. Helicobacter pylori infection also downregulated the expression of FcγRIIb and induced idiopathic thrombocytopenic purpura [26]. These studies showed that the FcγRIIb gene polymorphisms were associated with several diseases, especially autoimmune diseases [27, 28].

FcγRIIb gene polymorphisms and periodontitis

Periodontopathic bacteria such as *Porphyromonas gingivalis* are known to affect the local host immunity [29-31]. Indeed, patients with periodontitis displayed significantly higher serum IgG responses to the *P. gingivalis* 40-KDa outer membrane protein (OMP) than those of the healthy group. The serum IgG subclass distribution for patients with periodontitis

Table 1. FcγRIIB gene polymorphisms

Nucleotide	*Amino acid*	*Position*	*Nucleotide*	*Position*
nt 608 (C → T)	Thr 203 → Met	Exon4	nt 645+7 (A → C)	Intron4
nt 609 (G → A)	Thr 203 → Thr	Exon4	nt 645+25 (G → A)	Intron4
nt 612 (G → A)	Leu 204 → Leu	Exon4	nt 646-184 (A → G)	Intron4
nt 614 (A → T)	Tyr 205 → Phe	Exon4	nt 646-86 (C → T)	Intron4
nt 619 (T → G)	Ser 207 → Ala	Exon4	nt 759+27 (T → G)	Intron5
nt 695 (T → C)	Ile 203 → Thr	Exon5		

Eleven single-nucleotide polymorphisms (SNPs) were confirmed to be FcγRIIB-specific, of these SNPs, three and one SNPs resulted in amino-acid substitutions in exon4 (Thr203-Met, Tyr205-Phe and Ser207-Ala) and exon5 (Ile232-Thr). The other five SNPs were detected in intron4 and 5, leading to no amino-acid substitution.

and healthy individuals was IgG_1>IgG_4>IgG_2>IgG_3 for the anti-*P. gingivalis*-40-KDa OMP response [32]. Furthermore, the ability of *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* and *Fusobacterium nucleatum* to bind IgG Fc fragments has been demonstrated, on the other hand, the ability of *P. gingivalis* possessed IgG Fc-binding activity has not been observed [33, 34]. Periodontitis is a complex chronic subgingival plaque-induced inflammatory diseases influenced by multiple factors, including genetics, behavior and the environment. Many genetic association studies have been conducted in periodontology [35].

According to the above reports, FcγRIIb gene polymorphisms may play a primary role in periodontitis development, because there are large numbers of FcγRII-bearing B lymphocytes in periodontal lesions. Additionally, to date FcγRIIb is the only known inhibitory receptor in the FcgR family, which is pivotal in the regulation of B cell activation. Yasuda *et al.* observed a significant difference in the FcγRIIb-232I/T allele (exon5) distribution between the aggressive periodontitis and healthy control groups, with enrichment of 232T in the aggressive periodontitis group. The same report revealed that FcγRIIb-nt646-184A/G allele (intron4) distribution was significantly different between the chronic periodontitis and healthy control groups, with enrichment of nt646-184A in the chronic periodontitis group [5]. These results support the association of FcγRIIb gene polymorphism with periodontitis susceptibility. Additionally, the FcγRIIb-232T allele might be related to the reduced IgG antibody response to *P. gingivalis* in chronic periodontitis patients [20]. FcγRIIb-nt645+25AA carriers with chronic periodontitis displayed significantly higher mean clinical attachment (CAL) levels and a significantly lower IgG response to *P. gingivalis* sonicate and to the 40-KDa OMP (outer membrane protein) compared with patients with those of FcγRIIb-nt645+GG carriers [7]. These results suggest that the association of the FcγRIIb gene polymorphisms with periodontitis might be related to the lower levels of antibody response to periodontal bacteria. Human FcγRIIb suppresses B lymphocytes activation through cross-linking with the B cell receptor via immune complexes. This function of FcγRIIb is essential for the negative regulation of antibody complexes [20]. Higher FcγRIIb expression in subjects caused by FcγRIIb gene polymorphisms might induce a lower IgG level response to periodontal bacteria. The association of FcγRIIb gene polymorphisms with periodontitis susceptibility may be related to inflammation caused by a lower level of production of IgG against periodontal bacteria. The FcγRIIB genetic polymorphism in mouse strains was associated with down-regulation of its expression, possibly contributing to autoimmune diseases susceptibility caused by high-affinity IgG autoantibodies [36]. Unlike other genetic polymorphisms reported in periodontology, most Fcγ receptor polymorphisms reported not only have established biological functions but also associate with other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [35].

Adverse pregnancy outcomes and periodontitis

Adverse pregnancy outcomes are caused by miscarriage, threatened premature labor, preterm birth (with low birth weight), preeclampsia and pregnancy-induced hypertension (PIH), gestational diabetes mellitus, intrauterine growth retardation (IUGR), stillbirth. Associations between preterm birth (with low birth weight) and preeclampsia with periodontitis have been mainly and widely reported [37-42] (**Table 2**). Preterm birth is defined as delivery after week 22 but before week 37 of gestation, while low birth weight is defined as fetal weight <2500 g.

Table 2. Associations between adverse pregnancy outcomes and periodontitis in different population

Adverse pregnancy outcomes	Population	Periodontitis	References
Preterm birth (PTB)	UK	+	Siqueira et al., 2007
		+	Piscoya et al., 2012
		+	Lopez et al., 2002
		+	Guimaraes et al., 2010
		+	Lunardelli & Peres, 2005
	Italian	-	Vettore et al., 2008
	French	-	Nabet et al., 2010
	Canadian	-	Wood et al., 2006
	UK	-	Moore et al., 2004
	American	+	Rakoto-Alson et al., 2010
		+	Offenbancher et al., 2006
	Spain	+	Agueda et al., 2008
	Jordanian	+	Habashneh et al., 2012
	American	-	Srinivas et al., 2009
Low birth weight (LBW)	American	+	Offenbacher et al., 1996
	US	+	Gomes-Fillho et al., 2007
	Italian	+	Vettore et al., 2008
	Jordanian	+	Khader et al., 2009
	Spain	-	Agueda et al., 2008
	US	-	Davenport et al., 2002
	German	-	Noack et al., 2005
Preeclampsia (PE)	Turkish	+	Canakci et al., 2004
	Brazil	+	Cota et al., 2006
	French	+	Nabet et al., 2010
	Canadian	-	Taghzouti et al., 2011
	Jordan	-	Khader et al., 2006

Abbreviation: +, positive association reported; -, negative associationreported.

Preeclampsia is a pregnancy condition characterized by hypertension and proteinuria after 20 weeks of gestation and is one of the leading causes of maternal, fetal and neonatal mortality worldwide. Infections play a significant role in spontaneous preterm labor and birth as well as in related neonatal complications [43]. Furthermore, birth canal infections play an important role in the etiopathogenesis of preterm birth [44]. Systemic maternal infections are hypothesized to raise the risk of placental infection, premature rupture of membranes, premature labor and preterm birth as a result of inflammatory cytokines release and increased prostaglandin production [45].

Periodontitis is an infectious disease caused by the direct effect of periodontopathic bacteria and the accompanied host immune response [46-48], which is associated with an increase in systemic inflammatory cytokine levels. Periodontal organisms have been isolated from the amniotic fluid, suggesting hematogenous spread [49]. Therefore, it is possible that periodontal disease could potentially affect pregnancy outcomes through indirect mechanisms involving inflammatory cytokines or direct translocation of bacteria and its products to the fetoplacental unit. Moreover, periodontal disease is associated with adverse pregnancy outcomes, such as preterm delivery, preeclampsia abortion and stillbirth, low birth weight (LBW) infants and preterm LBW infants [2, 3, 37, 50-53].

Bacteria cause local immune response in periodontal pockets. Proinflammatory cytokines and IgG against periodontal bacteria released from immune-related host cells can enter the bloodstream and increase prostaglandin and cytokine levels, which may induce adverse pregnancy outcomes [54-57]. Previous studies showed that maternal subgingival *A. actinomycetemcomitans* DNA levels were associated with preterm birth and preeclampsia [6, 10]. A prospective cohort study of 13 circulation cytokines mid-pregnancy revealed significant associations between IL-1β, IL-2, IL-12, interferon-γ (IFNG), IL-4, IL-6 and transforming growth factor-β levels and preterm delivery at <35 weeks with histological chorioamnionitis [58]. This study showed that both periodontitis and preterm birth were caused by infection and aggravatedbyhost-inducedinflammation.Additionally, a lower level of serum IgG against periodontopathic bacteria was more closely associated with preterm birth compared with term birth [59].

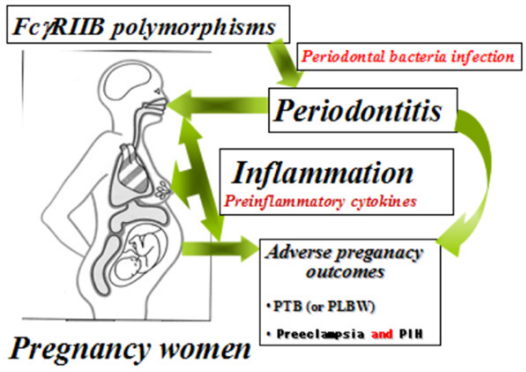

Figure 2. The mechanism of associations between FcγRIIB gene polymorphisms, periodontitis, and adverse pregnancy outcomes. The development of adverse pregnancy outcomes might be attributable to FcγRIIB gene polymorphisms-associated inflammation caused by periodontal infection through up-regulated proinflammatory cytokines.

A meta-analysis by Khader and Ta'ani indicated that periodontal diseases in pregnant women significantly increased the risk of subsequent preterm birth or low birth weight [55]. In contrast, Michalowicz *et al.* reported that treatment of periodontitis in pregnant women did not significantly alter rates of preterm birth and low birth weight [60]. Vettore *et al.* compared periodontal clinical measurements and the levels and proportions of 39 bacterial species in subgingival biofilm samples in women with preterm and non-preterm births and concluded that maternal periodontal microbiota and periodontal disease clinical characteristics were not associated with preterm birth [61]. In our previous studies, a significant association between clinical periodontal parameters and adverse pregnancy outcomes was not observed. It suggested that subgingival periodontal bacteria were associated with adverse pregnancy outcomes susceptibility [8, 10].

Association of FcγRIIB gene polymorphisms and periodontitis with adverse pregnancy outcomes

As infection caused by periodontal bacteria in periodontal pockets can alter serum proinflammatory cytokine levels in pregnant women, infection may induce chorioamnionitis and result in adverse pregnancy outcomes. Significant associations between levels of proinflammatory cytokines, such as IL-1β, IL-2, IL-12, interferon-γ (IFNG), IL-4, IL-6 and transforming growth factor-β and preterm delivery at <35 weeks with histological chorioamnionitis were identified [58]. Low IgG production against the periodontal bacterium *P. gingivalis* in early pregnancy was associated with intrauterine growth retardation and some instances of preterm birth. Furthermore, lower serum IgG1 levels against anti-*P. gingivalis* OMP and higher C-reactive protein (CRP) levels were associated with preterm birth with chorioamnionitis [59]. Maternal IgG against bacterial antigens are transported into fetal blood using endosomes and Fc receptors.

In previous reports, FcγRIIb-232I/T and FcγRIIb-nt645+25A/G polymorphisms were associated with periodontitis. The association of the 232T allele and nt645+25AA genotype carriers with periodontitis might be related to the lower levels of IgG antibody response to *P. gingivalis [7, 20]*. Moreover, the FcγRIIb-nt645+25A/G polymorphism has been suggested to be a susceptibility factor for adverse pregnancy outcomes, such as preterm birth or preeclampsia [6, 8]. FcγRIIb protein expression on the cell surface in peripheral B lymphocytes was higher in healthy donors with the FcγRIIb-nt645+25AA genotype than that of FcγRIIb-nt645+25GG genotype carriers [7]. Therefore, we assume that adverse pregnancy outcomes might be attributed to FcγRIIb gene polymorphism-associated inflammation caused by periodontal infection through up-regulated proinflammatory cytokines levels (**Figure 2**). However, no significant association between clinical periodontal parameters and adverse pregnancy outcomes has been found. Rather only subgingival periodontal bacteria DNA levels were associated with adverse pregnancy outcomes in our previous studies (**Table 3**) [6, 8, 10].

Summary of previous studies

FcγRIIb gene polymorphisms were significantly associated with preterm birth, preeclampsia, pregnancy-induced hypertension, periodontitis and antibacterial IgG levels in previous reports. Among 22 immunnoregulatory polymorphisms, only IL-6 and FcαR polymorphisms were significantly associated with preterm birth after adjustment for confounders.

We did not identify significant associations between adverse pregnancy outcomes and periodontitis or any clinical periodontal parameters, inconsistent with the results from most

Table 3. Associations between gene polymorphisms, periodontitis and adverse pregnancy outcomes in our previous studies

	Preterm Birth	Preeclampsia
Periodontitis (+)	N	N
Mean Clinical Attachment Loss	N	N
Subgingival bacterial level (log per 10 μL)		
Actinobacillus actinomycetemcomitans	Y	Y
Porphyromonas gingivalis	N	N
Serum IgG antibody level		
A. actinomycetemcomitans	N	N
P. gingivalis	Y	N
FcγRIIA polymorphism	N	N
FcγRIIB polymorphism	Y	Y
FcγRIIIB polymorphism	N	Y
IL-6 gene polymorphism	Y	NT
FcαR polymorphism	Y	NT

N-no significant association; Y-Significant association; NT-Not tested.

previous case-control studies. These discrepancies may be explained by differing parities and periodontitis severity. Mean CAL (2.42 mm) in the preterm birth group in our study was lower than that in previous studies (3.00 mm) [62]. The periodontitis definition criterion in our study was 60% of sites with a clinical attachment level of ≥3 mm. In contrast, in most other studies, they adopted one or more sites of pocket depth ≥4 mm and attachment loss ≥3 mm in the same site, or one or more sites of attachment loss ≥4 mm [63, 64].

However, subgingival *A. actinomycetemcomitans* DNA level was associated with preterm birth and preeclampsia [6, 10]. Moreover, significantly lower serum anti-*P. gingivalis* OMP IgG1 and higher CRP were observed in sera obtained during the first trimester from women who delivered preterm with chorioamnionitis [58].

Previously, we demonstrated the association of FcγRIIb gene polymorphisms with periodontitis susceptibility in patients with chronic periodontitis [7, 20]. However, periodontal conditions and subject age differed between the previous studies with chronic periodontitis patients and the present studies with pregnant women.

Adverse pregnancy outcomes associated with periodontitis may be caused by translocation of periodontal bacteria and/or its products to the fetoplacental unit which induced proinflammatory cytokines up-regulation [49]. The association of FcγRIIb gene polymorphisms with preterm birth with low birth weight and preeclampsia might result from lower immune protection against bacterial infection and subsequent up-regulation of proinflammatory cytokines and CRP. Further studies should be undertaken to confirm this hypothesis.

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Disclosure of conflict of interest

None.

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