Significant roles played by interleukin-10 in outcome of pregnancy

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**Abstract**

Imbalanced immune responses against fetus alloantigens can lead to abnormality in pregnancy. Interleukin-10 (IL-10) plays key roles in regulation of immune responses against self and foreign antigens to induce tolerance to these antigens. Therefore, alteration in expression of IL-10 during pregnancy may result in several pathologic conditions such as preterm labor. IL-10 leads to a normal pregnancy via several molecular mechanisms including development of tolerogenic dendritic cells, T regulatory lymphocytes, and activation of the JAK1/STAT3 pathway in the target cells. This review has collected recent data regarding the status of IL-10 expression during term and preterm deliveries and also its molecular mechanisms that lead to a normal pregnancy.

**Introduction**

It has been documented that pregnancy is a unique immunological state with both immune response and tolerance against fetus antigens (1). Previous studies demonstrated that the imbalanced immune responses against fetus antigens can result in abnormality in pregnancy. Cytokines as important immune molecules, play crucial roles in regulation of immune responses against microbes and foreign antigens including graft and fetus antigens (2). Interleukin-10 (IL-10), as a main anti-inflammatory cytokine, significantly participates in regulation of immune responses against self and foreign antigens in the case of tolerance to these antigens (3-5). Therefore, alteration in expression of this cytokine during pregnancy may lead to several pathologic conditions such as preterm labor (PTL) (6, 7). PTL is the common disorder in the pregnancy and is defined as birth before the 37th week of gestation (8). Previous studies revealed that PTL can be associated with inflammation: hence, regarding the important roles played by IL-10 in the suppression of inflammation, it appears that this cytokine can play key roles in the pathogenesis of PTL. Therefore, the main aim of this review article is to present the status and function of IL-10 in the pathogenesis of PTL.

**Preterm labor**

PTL is a birth that occurs before the 37th week of gestation and as described in the previous section the complication is a common disorder in the pregnancy occurring in approximately 10% of deliveries (9). In the normal human fetus, several organ systems mature between 34 and 37 weeks, and the fetus reaches adequate maturity by the end of this period (9, 10). The preterm birth is associated with several complications leading to mortality and morbidity such as neurological, respiratory, gastrointestinal and metabolic problems, hematologic disorders, and infection (10). Based on the fact that the etiology and the main responsible mechanisms that lead to preterm birth are unknown, several hypotheses are in process worldwide.

**IL-10, structure and intracellular signaling**

IL-10 is categorized as an anti-inflammatory cytokine and is produced by several cells including activated macrophages, T regulatory and Th2 lymphocytes and so on (11). The main function of this cytokine is to suppress Th1, Th2 and B lymphocytes, NK cells, macrophages, and dendritic cells inflammatory functions (12, 13). Sp1 and Sp3

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(two transcription factors) regulate IL-10 expression. 1q31-1q32 is the location of the IL-10 gene (approximately 5.2 kb), which consists of five exons (14), and encodes a protein of 178 amino acids called pro-IL-10 (13). Pro-IL-10 activation is done by cleavage of a signal peptide of 18 amino acids (13). IL-10 performs its actions via its corresponding receptor (IL-10R) (15). It has been demonstrated that IL-10R consists of α and β chains and is categorized as a type II cytokine receptor (15). Several intracellular signaling pathways will be activated following IL-10/IL-10R α and β chain interaction by phosphorylation of JAK1 (Janus Kinase-1) and TYK2 (Tyrosine Kinase-2), respectively, as intracellular protein kinases (16). In a positive feedback, activated JAK1 and TYK2 phosphorylate Y446 and Y496 positions of IL-10R α chain (17). The phosphorylation is a place for binding and phosphorylation of signal transducer and activator of transcription 3 (STAT3) tyrosine residues (18). Homodimerized STAT3 is translocated into the nucleus and recognizes STAT-binding element (SBE) regions at the promoters of several genes including IL-10, anti-apoptotic, cell-cycle-progression, suppressor of cytokine signaling 3 (SOCS3) genes, and so on (19). Several other pathways such as phosphoinositide-3 kinase (PI3K) (20) and Mitogen-Activated Protein Kinase (p38/MAPK) (21) are also regulated by IL-10/IL-10R interaction.

**IL-10 and delivery**

Based on the aforementioned information, it appears that IL-10 may significantly participate in the outcome of pregnancy. Interestingly, previous investigations approved the hypothesis. For instance, it is documented that IL-10 suppresses the production and function of pro-inflammatory cytokines including IL-12, IFN-γ, IL-1, and so on (22), and numerous studies have reported its expression at the maternal-fetal interface (23-25). It was also demonstrated that, under effects of progesterone, IL-10 serum levels are elevated, which results in suppression and activation of Th1 and Th2-type cytokines, respectively (i.e., IL-10 and IL-4). Robertson et al also showed that IL-10 mRNA and protein is up-regulated in gestational tissues in normal pregnancy. Interestingly, they have concluded that up-regulation of IL-10 can be considered as a critical factor for resistance to preterm labor (26). It has been demonstrated that LPS could induce preterm labor in some cases (27). Experimental studies have shown that exogenous IL-10 inhibits LPS-induced preterm labor (28, 29). A study by Gotsch et al revealed that in 41–57 days (third phase) after gestation, the concentration of IL-10 was increased by high levels of 17β-estradiol (30). Up-regulation of IL-10 and 17β-estradiol leads to the suppression of dendritic cells (DCs) and consequently inhibits the stimulation of T lymphocytes by DCs (30), which is associated with a normal pregnancy. Additionally, another study demonstrated that decreased number of peripheral blood mononuclear leukocytes that produce IL-10, leads to recurrent preterm births during the second trimester (31). It has also been documented that preterm delivery during mid-trimester is associated with unchanged levels of IL-10 in amniotic fluid, where the concentration of IL-10 needs to be increased (32). Our previous study also revealed that serum levels of IL-10 were not differed in preterm in comparison to term neonates (33). The results have been confirmed by Gotsch et al who reported that IL-10 is expressed in high concentrations in the amniotic fluid of normal term women (30). The investigators also showed that spontaneous parturition in either term or preterm gestation is associated with elevated concentrations of IL-10 in amniotic fluid (30). Increased amniotic fluid concentrations of IL-10 during intra-amniotic infection/inflammation have also been reported by Gotsch and colleagues (30). Moreover, another research demonstrated that preterm neonates compared to term neonates, produce higher and lower inflammatory and anti-inflammatory cytokines in response to specific bacteria, respectively (34). Therefore, it may result in uncontrolled inflammatory response, which is associated with preterm labor (34). Researchers have evaluated the expression profiles of IL-10 and cyclo-oxygenase-2 (COX-2), as an enzyme for producing prostanooids (prostaglandins, prostacyclin, and thromboxane), which are the potential inducers of delivery (35). They have reported that IL-10 significantly regulates the expression of COX-2 and consequently prostaglandins, hence, the authors concluded that IL-10 plays important roles in countering inflammation that is produced in preterm labor (35). Although, the aforementioned studies have demonstrated that the IL-10 levels were lower in preterm vs. term delivery, some investigations reported that IL-10 levels were high in preterm delivery associated with infection. For example, it was shown that the cord blood levels of IL-10 were significantly increased in infected versus non-infected mothers (36). Another study demonstrated that the cord blood IL-10 levels are increased during intrauterine infection (37). Based on these results, it may be concluded that up-regulation of IL-10 in the infected preterm delivery is a normal response of the immune system to regulate the infection-dependent inflammation. Accordingly, Ferguson et al reported that IL-10 is significantly associated with preterm delivery. For example, it has been demonstrated that IL-10 levels are positively associated with elevated odds ratio of placental-mediated preterm birth (38). It may be related to the infections that have not been examined in the evaluated preterm neonates. According to the data
Figure 1. Roles of interleukin-10 (IL-10) in determination of pregnancy. As mentioned in the figure, SP-A, 17β-estradiol, IDO vitamin D3, and IL-10 genetic variations can alter expression of IL-10. IL-10 inhibits preterm delivery using several mechanisms including development of T regulatory lymphocytes and tolerogenic DCs, activation of the JAK1/STAT3 pathway, down-regulation of COX-2, and also inhibition of LPS-induced preterm delivery.

Presented here, it appears that IL-10 plays significant roles in the induction of an appropriate pregnancy because its expression is up-regulated in the normal pregnancy, while its production is disrupted during preterm labor. Several documents approve this hypothesis. For example, it has been established that surfactant protein A (SP-A) is produced in the fetus to provide signals for the onset of parturition (39). Interestingly, the study revealed that SP-A suppresses preterm delivery via TLR2-dependent IL-10 production (39). Indoleamine 2,3-dioxygenase (IDO) is an enzyme for catabolism of tryptophan, which is crucial for T lymphocyte activation and proliferation (40). IDO regulate maternal immune responses against fetus alloantigens via suppression of maternal T lymphocytes and also up-regulation of anti-inflammatory cytokines such as IL-10 (40). Additionally, it has been evidenced that tolerogenic DCs plays key roles in the induction of maternal immune tolerance to fetus alloantigens (41). Interestingly, IL-10 is a potential factor that stimulates the production of tolerogenic DCs (42), hence, it can induce a successful pregnancy. Previous investigations identified that regulatory T lymphocytes also significantly participate in induction of maternal immune tolerance to fetus alloantigens and subsequently a successful pregnancy (43). IL-10 is not only produced by regulatory T lymphocytes, but also leads to the development of these cells (43).

IL-10 binding to its corresponded receptor (IL-10R) leads to activation of the IL-10/JAK1/STAT3 cascade and subsequently phosphorylation of STAT3. The phosphorylation leads to the production of STAT3 homodimer (STAT3/STAT3) and its translocation to the nucleus...
can trigger the expression of the target gene (see the previous section), which participates in the induction of a successful pregnancy (44–46). The molecular mechanisms played by IL-10 in pregnancy are summarized in Figure 1.

Interestingly, genetic research revealed that the genetic variations in the IL-10 gene are also associated with preterm delivery. It has also been evidenced that the polymorphisms within IL-10 gene are associated with its expression during pregnancy (47, 48). For instance, it was shown that IL-10 (rs1800896) polymorphism is associated with gram-negative infections in preterm labor (49). The relation between the polymorphisms within the promoter region of IL-10 and cervical insufficiency have been reported by Warren and colleagues (50). Another study also revealed that IL-10 (-1082A) polymorphism is significantly associated with genitourinary infections and/or inflammation (51). Another study has shown that IL10 (-1082)G plays crucial roles in less than 29 weeks extreme preterm delivery (52). A study on Australian population revealed that IL-10 82A/-819T/-592A haplotype is associated with preterm delivery (53). Interestingly the study demonstrated that this haplotype is more prevalent in women with preterm premature rupture of membranes (53).

Contrastly, one study was unable to find a relation between IL-10 polymorphisms and preterm delivery (54). Another study was also unable to find an association between the polymorphisms within IL-10 gene (IL10 -1082 G>A, IL10 -819 C>T, and IL10 -592 C>A) and spontaneous preterm delivery (55). A study on Austrian population demonstrated that IL-10 -1082 G/A single nucleotide polymorphism was not associated with preterm delivery (56). No association between this polymorphism and preterm delivery was also demonstrated by Brazilian researchers (57).

It appears that further studies are essential to complete our knowledge regarding the roles of genetic variations in the induction of preterm delivery.

Conclusion

Due to the aforementioned results, it appears that IL-10 plays key roles in the induction of a normal delivery via development of tolerogenic DCs, T regulatory lymphocytes, and up-regulation of STAT3 target genes. Up-regulation of this anti-inflammatory cytokine leads to suppression of NK cells and T lymphocytes against their fetus alloantigens. The factors that alter the expression of IL-10, including infections and genetic variations within IL-10 gene, could determine the outcome of pregnancy. Additionally, it has also been demonstrated that preterm delivery is associated with several short and long-term health problems. It may be hypothesized that alteration in expression of IL-10 is also associated with the incidence of the complications. Moreover, IL-10 can decline the pathologic effects of inflammation that is prevalent in the preterm delivery. Therefore, it appears that regulation of IL-10 expression during normal pregnancy is cautiously regulated.

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