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Role of Cytokines during Pregnancy

Gebelik Surecinde Sitokinlerin Rolu

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Abstract

The maternal immune system plays an important role in the establishment of a successful pregnancy. Pregnancy is a unique immunological challenge during which maternal immune system has to tolerate the fetal alloantigen while preserving the ability to fight infections and enviromental pathogens. In mammalian pregnancy this balance is also regulated by the complex cooperation between cytokines. Cytokines are immunoregulatory molecules that are crucial for normal reproductive functions, including implantation, placentation and trophoblast invasion. It is widely proposed that, during pregnancy, Th2 immune response is neccessary for successful pregnancy, whereas a Th1 response is detrimental to fetus. In addition to this, it has been suggested that Th1/Th2 activity balance displays a strong shift towards Th2 activity during the physiological pregnancy. Studies concerning Th1/Th2 balance in physiological and pathological pregnancy have shown that Th1/Th2 cooperation is needed for a successful pregnancy. This review focuses on the potential roles of cytokines during pregnancy and will contribute to the understanding of the roles and mechanisms behind the cytokines that effect physiological and several pathological conditions of pregnancy.

Keywords: Pregnancy; Cytokines; Th1/Th2 Cytokines.

Öz

Maternal immun sistem başarılı bir gebeliğin kurulmasında önemli rol oynamaktadır. Gebelik, maternal immun sistemin fetal alloantijenlerini tolere ederken aynı zamanda infeksiyonlar ve çevresel patojenlerle de savaşma yeteneğini koruduğu eşsiz immünolojik bir başarı sürecidir. Memelilerde gebelik sırasında bu denge sitokinler arasındaki işbirliği ile sağlanır. Sitokinler, implantasyon, plasentasyon, trofoblast invazyonu gibi normal üreme fonksiyonlarının gerçekleşebilmesi için gerekli olan immun düzenleyici moleküllerdir. Genel bir kanı olarak Th2 immun cevabın başarılı bir gebelik için gerekli olduğu ancak Th1 cevabın fetüs için zararlı olduğu önerilmiştir. Buna ek olarak fizyolojik bir gebelikte Th1/Th2 aktivitesinde dengenin Th2 yönünde olduğu ortaya konulmuştur. Th1/Th2 ilgili yapılan çalışmalar başarılı bir gebelik için Th1/Th2 ortaklığının gerekli olduğunu göstermiştir. Bu derleme, sitokinlerin gebelik sırasındaki potansiyel rolleri üzerine odaklanmıştır ve hem fizyolojik hem de çeşitli gebelik patolojilerinde sitokinlerin rolü ve mekanizmalarının anlaşılmasına katkı sağlayacaktır.

Anahtar Kelimeler: Gebelik; Sitokin; Th1/Th2 Sitokinler.

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The maternal immune system plays important roles in pregnancy. Cytokines, which act as immune regulators during pregnancy, determine the immune response. Cytokines play a critical role in this process and are of great importance for a successful pregnancy (1).

Cytokines, which are also defined as immune system hormones, are pleiotropic molecules that play important roles in immune system regulation (2). These molecules are synthesized by immune and non-immune cells through a stimulus, and they generally mediate multiple mechanisms by bonding to specific target cell receptors (3).

Cytokines are low molecular weight proteins secreted by peripheral blood lymphocytes (PBL), macrophages, oviductal and endometrial cells, and embryos. They play roles in the protection of cyclic corpus luteum, fetal adhesion and invasion, implantation, fetal and placental growth and differentiation, the regulation of some immunomodulatory mechanisms, and intercellular communication (3). This review attempts to explain the roles of cytokines that are critical during pregnancy.

General Properties of Cytokines

A regulated environment is necessary to prevent a fetus from being rejected by the maternal immune system. This environment must first be generated within the maternal–fetal interface and uterine tissue. Classically, CD4 T cells are the primary producers of cytokines (4). Cytokine-producing CD4 lymphocytes play essential roles in the immune response against antigens, the regulation of antibody production by B cells, and the function of cytotoxic T cells (5, 6).

According to their primary roles, cytokines in this cell population can be categorized as pro- and anti-inflammatory or Th1, Th2, and Th17 that are associated with different helper T cells (Th) and regulatory (Treg) cells (4). Th1 cells primarily produce interleukins (IL), including IL-1, IL-2, IL-12, IL-15, and IL-18; interferon-gamma (IFN-γ); and tumor necrosis factor-α (TNF- α), and Th2 cells produce IL-4, IL-5, IL-6, and IL-13 along with granulocyte-macrophage colony-stimulating factor (GM-CSF) (7). Th17 cells produce IL-17A and IL-17E (1), and Treg cells secrete IL-10 and transforming growth factor β (TGF-β) (4).

Cellular immunity primarily depends on the activity of Th1 cells, whereas the regulation of humoral response is mainly associated with the activity of Th2 cells. Macrophages and "natural killer" (NK) cells are the main components of the natural immunity. These cells produce suitable cytokines, thus playing a role in the movement of T CD4 lymphocytes to their target locations of function. IFN-γ and IL-12 are essential for the movement in the direction of Th1 activation, and the presence of IL-4 is necessary for Th2 activation (8).

In 2004, the important role of Treg lymphocytes in pregnancy was first demonstrated in mice. Reportedly, the earliest detection of Treg cells was in the lymph nodes, which drain uterus after copulation (9). Levels of IL-10 and TGF-β, which play important roles during pregnancy, increase during immune suppression (10).

Th17 cells, a subtype of helper T cells, produce pro-inflammatory IL-17A, and these play essential roles in inflammation and the initiation of acute transplant rejection. In recent studies comparing normal pregnant women and pregnant women with idiopathic recurrent miscarriages, an increase in the number of Th17 cells in the peripheral blood and decidua was observed (11).

Activation of Cytokines During Pregnancy

Human endometrium produces various cytokines during proliferative and secretory phases of the menstrual cycle. These cytokines play important roles, such as the regulation of uterine environment during pregnancy, the preparation of the uterus for the implantation of developing conceptus, and the formation of the functional placenta (4).

During pregnancy, the decidual epithelium and stroma, cyto- and syncytiotrophoblast, chorion, amnion and Haufbauer cells serve as the sources of Th1 and Th2 cytokines. These cytokines participate in the initiation of maternal tolerance against fetal allograft, the regulation of local immunity against infectious factors, and hormonal production and tissue regeneration during trophoblast invasion (7).

Th-related cytokines are also produced by trophoblast cells, stromal cells, epithelial cells, maternal T lymphocytes, macrophages, NK cells, and other maternal leukocytes, indicating that development and maintenance of fetal–placental unit depend on these cytokines (12). The presence of these cytokines in the maternal–fetal space regulates processes, such as implantation, placental development, cytotrophoblast proliferation, angiogenesis, extravillous trophoblast cell invasion, reconfiguration of spiral arteries, cell growth, and apoptosis, thus participating in the formation of a suitable environment (4).

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In vitro experiments have demonstrated that Th1 cytokines (IL-1 and TNFα) negatively affect endometrial decidualization. Low concentrations of serum leukemia inhibiting factor (LIF), IL-4, IL-6, and IL-10 have been observed in women who had experienced multiple implantation failures (13).

During implantation, the embryo is spontaneously activated via TGF-β and prostaglandin PGE_2, and its interaction with the decidua is primarily regulated via the decline of Th1 (IL-2 and TNF-α) secretion and the elevation of Th2 (GM-CSF) cytokine production. In addition, the embryo has been reported to secrete Th2 cytokines (IL-10 and TGF-β) via the autocrine pathway, suppress invasive properties of trophoblasts, and cease the production of proinflammatory Th1 cytokines (TNF-α and IFN-γ) from maternal tissues via the paracrine pathway (14, 15).

Increased levels of Th1 cytokines, including IL-2, IL-12, TNF-α, and IFN-γ, lead to the inhibition of trophoblast development, resulting in the fetal loss. Th1 differentiation from Th0 cells and NK cell expression are inhibited by excess Th2 cytokines in the maternal decidua. Predominantly, the presence of such Th2 shifts in the uterus of pregnant women is strongly associated with the continuation of pregnancy (6).

IL-10 and its receptors, produced by Treg cells, must be present in the endometrium and decidua during early pregnancy under normal circumstances. Together, these lead to the proliferation of decidual cells and the secretion of TNF-α (16). Reportedly, IL-10 levels markedly increase during early pregnancy and remain high immediately before the start of labor during the third trimester (17). Although IL-10 was originally considered to be one of the Th2 cytokines, it is not exclusively secreted by Th2 cells. It is also produced by IL-10-regulating T cells in the maternal–placental interface (18). IL-10 suppression leads to the subsequent suppression of Th1 and Th2 immunities through the activation of some inflammatory mediators. Therefore, it is more accurate to classify it as an anti-inflammatory cytokine (19). TGF-β, another anti-inflammatory cytokine, plays a role in the development of maternal immune tolerance during implantation and the regulation of molecules involved in implantation such as various vascular endothelial growth factors, matrix metallopeptidase-9 (MMP-9), insulin-like growth factor-binding protein-1 (IGFBP-1), and LIF (20, 21). In addition, early embryonic and postnatal deaths have been reported in TGF-β knockout mice (22). Reportedly, the immune suppression in the maternal tissues, which is necessary during pregnancy, simultaneously occurs with the suppression of IL-10, tumor growth factor-β, and pro-inflammatory TH1 cytokines, such as IFN-γ and TNF-α (23).

In a study conducted by Jenkins et al. (2000) the serum IL-10 levels of women who presented with a history of recurrent miscarriages but experienced a subsequent successful pregnancy were found to be significantly higher than those of women who experienced subsequent miscarriages (24). The examination of endometrial T helper cells of non-pregnant women who presented with a history of recurrent miscarriage and healthy women revealed that Th1 cytokines were primarily produced in women with a history of recurrent miscarriage, while and Th2 cells were more abundant in healthy women (25, 26). Th2 cytokines (IL-4, IL-6, and IL-13) and cytokines such as IL-10 and TGF-β enable the formation of a suitable environment for the further development of Th2. IL-1β limits the pro-inflammatory effects of TNF-α, IL-8, and prostaglandins. In addition, human cytotrophoblasts produce IL-4, which contributes to the differentiation of Th2 lymphocytes (4). Makrigiannakis et al. (2001), have noted that corticotropin-releasing hormone (CRH), which is produced by trophoblasts and the placental decidua, promotes the continuation of early pregnancy and implantation in humans by killing activated T cells.

IL-6 is an important mediator of the acute-phase responses to injuries and infections (4). IL-6 is present in human endometrium during the menstrual cycle and in the decidua during early pregnancy (28). In addition, extravillous trophoblast cells express IL-6, and it may affect trophoblast invasion by up-regulating the MMPs (29).

IL-8 (now known as CXCL8) is classified as a pro-inflammatory multifunctional CXC chemokine. NK cells present in the decidua during early pregnancy are the primary producers of CXCL8. In addition, CXCL8 has been shown to stimulate trophoblast invasion in *in vitro* models (30).

IL-1 and IL-18 are important factors the regulate invasion during embryonic–endometrial communication, neoangiogenesis, and implantation (31). Other cytokines, such as IL-1β, IL-6, and TNF-α, are essential for the regulation of ovarium cycle, and they play an important role in the growth and development of the ovarian follicle (32). Compared with IL-10, increased production of TNF-α and Th1 cytokines, such as IFN-γ, is associated with infertility and recurrent spontaneous miscarriages (33).

TNF-α cytokine, produced by Th1 cells, is predominantly secreted by monocytes/macrophages. TNF-α is a multifunctional pro-inflammatory cytokine that plays a role in lipid metabolism, coagulation,

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insulin resistance, and endothelium (34). TNF-α suppresses the growth of trophoblasts by inducing apoptotic changes in cells (35). Studies have revealed increased serum TNF-α level in cases that experienced recurrent spontaneous miscarriages or reproductive failures (34). In addition, with the administration of anti-TNF-α medication, a new treatment approach has been developed for patients with Th1 cytokine-dependent infertility (36).

IL-1, present in the maternal–fetal space, is produced by trophoblastic cells and decidualized stromal cells. IL-1 receptors are present both in endometrial epithelium cells and trophoblasts (37). IL-1 is one of the first signals that originate from blastocysts and affect endometrium. IL-1 increases the endometrial secretion of prostaglandin E_2 and the expression of LIF and integrin β_3 subunits (16).

The number of implanted embryos significantly decreases when IL-1 receptor antagonist is administered to mice before implantation, indicating the importance of IL-1 in embryo implantation. IL-1 stimulates the activation of MMP-9 in trophoblasts and the expression of endometrial stroma cells. Thus, it induces trophoblast invasion by stimulating the activation of IL-6, MMP-2 and, MMP-9 cytokines present in maternal–fetal interface and suppresses IL-10, MMP-9, and trophoblast invasion (37).

IFN-γ, a Th1 cytokine, inhibits the growth of trophoblasts in *in vitro* cultures (38). In a study conducted by Mahdi (2011), the comparison between infertile and fertile women has demonstrated increased IFN-γ levels in infertile women (35). In another study, following the removal of IFN-γ or IFN-γ receptors, mice maintained their normal reproductive functions and produced offspring, suggesting that IFN-γ is not vital for fetal life (39).

Reportedly, the concentration of IFN-γ, secreted by NK cells in the uterus, in the implantation area is essential for the maintenance of decidual cell vitality, changes in the maternal artery wall, and the inhibition of excessively increased trophoblast growth and invasion (35). Mahdi (2011) has compared his studies to other studies and noted that discrepancies regarding IFN-γ may be the differences in patient selection, body mass index, or ethnic origin and low cohort size (35).

Compared with Th1 cytokines (IL-2, IL-12, and IFN-γ), increased mRNA expressions of Th2 cytokines (IL-4 and IL-6) were observed in endometrial cells during the luteal phase of the menstrual cycle (40). IL-4 is secreted by lymphocytes infiltrated from the endometrium, which stimulates LIF production from endometrial tissues (41). IL-4 is an important cytokine for the peri-implantation process. IL-4 together with TGF-β facilitates trophoblast invasion process (41) and endometrial decidualization (42) and regulates the interaction between decidual lymphocytes and trophoblasts. Moreover, IL-4 together with IL-6 controls the angiogenesis inside trophoblastic villi (43).

In addition, IFN-γ has been reported to suppress the growth of trophoblast cells in *in vitro* cultures, while the activation of T cells by IL-2has been reported to induce apoptosis in trophoblasts and fetal losses (39).

Platelet-activating factor (PAF) is considered another important factor for the maintenance of pregnancy in humans. Preimplantation embryos and decidual cells secrete substantial amounts of PAF. Nasu et al. (1999) have estimated cytokine concentration in normal cultured endometrial stromal cells and have suggested that PAF secretion from decidual tissues and embryo development stimulated cytokine synthesis by endometrial stromal cells. This increased local cytokine concentration was considered to have vital importance for the continuation of pregnancy during the early stages (44).

Presumably, the detection of pregnancy by the mother in humans is achieved through the signals transmitted by the fertilized ovum, leading to dominant intrauterine Th2 cells (45). In addition, Th1/Th2 balance was observed to shift toward a Th2-dominant state, but Th1/Th2 ratio in the peripheral blood did not change during early pregnancy (46). Both Th1 and Th2 cytokines are produced in the maternal–fetal space and in the maternal decidua. However, Th2 is dominant in the decidua, particularly in the implantation area, during early pregnancy (47). The dominant Th1 cytokine state negatively affects embryo development and placental growth (48). In conclusion, the balance between Th1 and Th2 is crucial for successful normal reproductive functions, including implantation and pregnancy (23). Low-index Th1/Th2 immune response helps the realization of physiological pregnancy (49).

Following the discovery of the dual contradiction of Th1/Th2, Wegmann et al. (1993) have claimed that Th2 response is necessary during pregnancy, whereas Th1 response is harmful for pregnancy (50). The presence of Th1-related autoimmune diseases during pregnancy, such as multiple sclerosis and rheumatoid arthritis, supports this claim (4). However, when Th1 cytokines were shown to be essential for the continuation of pregnancy, this claim regarding Th1 was proven to be very simplistic. Reportedly, IFN-γ is required for a successful pregnancy, a successful completion of such pregnancy, and the reconfiguration of spiral arteries (51). In addition, normal reproduction results were demonstrated in Th2 knockout (IL-4, IL-5, IL-9, and IL-13) mice (52).

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Nonetheless, some studies do not support Th1/Th2 paradigm but suggest that etiological factors also play a role in recurrent miscarriages. Bates et al. (2002) have reported that women who experienced recurrent miscarriage exhibited low IFN-γ production and high IL-10 and IL-4 production. In addition, there was no significant difference between women who presented with a history of recurrent miscarriages and experienced a subsequent miscarriage and women who experienced successful pregnancies, but women that have recurrent miscarriage showed markedly decreased TNF-α levels (53).

CONCLUSION

In conclusion, mammal pregnancy is a unique immunological process that requires a balance between immune tolerance and suppression. The continuation of pregnancy in the early period depends upon the interaction between the fetal tissues and the maternal decidua. To mediate a successful interaction, a specific leukocyte population and suitable cytokine expression are imperative. This review explains that a certain balance between Th2 and Th1 activity is crucial during pregnancy and that this is the only mechanism through which suitable immunological reactions and successful pregnancy can be expected. This review also attempts to elucidate the cytokines that play critical roles in disorders of pregnancy, such as pre-eclampsia or recurrent loss of pregnancy and miscarriage.

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