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Immune regulatory network in successful pregnancy and reproductive failures

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ABSTRACT

Maternal immune system must tolerate semiallogenic fetus to establish and maintain a successful pregnancy. Despite the existence of several strategies of trophoblast to avoid recognition by maternal leukocytes, maternal immune system may react against paternal alloantigenes. Leukocytes are important components in decidua. Not only T helper (Th)1/Th2 balance, but also regulatory T (Treg) cells play an important role in pregnancy. Although the frequency of Tregs is elevated during normal pregnancies, their frequency and function are reduced in reproductive defects such as recurrent miscarriage and preeclampsia. Tregs are not the sole population of suppressive cells in the decidua. It has recently been shown that regulatory B10 (Breg) cells participate in pregnancy through secretion of IL-10 cytokine. Myeloid derived suppressor cells (MDSCs) are immature developing precursors of innate myeloid cells that are increased in pregnant women, implying their possible function in pregnancy. Natural killer T (NKT) cells are also detected in mouse and human decidua. They can also affect the fetomaternal tolerance. In this review, we will discuss on the role of different immune regulatory cells including Treg, γd T cell, Breg, MDSC, and NKT cells in pregnancy outcome.

Contents

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1. Introduction

Since the fetus is a semiallograft, a successful pregnancy needs mechanisms to prevent allograft rejection [1]. Polymorphic genes inherited from the father generate alloantigenes which provoke the maternal immune responses leading to fetal rejection. Adaptation of immune system is crucial to prevent rejection of the semi-allogeneic conceptus in pregnancy [2]. Dysregulation of immune responses may lead to reproductive failures such as recurrent pregnancy loss (RPL), implantation failure, preterm birth, intrauterine fetal growth restriction and preeclampsia [3]. The most common pregnancy problems are miscarriage and pre-eclampsia [4,5]. Miscarriage occurs in about 15% of the cases, and recurrent miscarriages in 2–5% [4]. Although the exact cause of about 50% of recurrent miscarriages remains elusive, however immunological rejection may account for most of these unexplained cases of pregnancy loss [6–8]. Several immunological mechanisms have been proposed for tolerance to the semi-allogeneic fetus. It is suggested that miscarriage occurs in mice and humans when these mechanisms become dysregulated [9]. Since maternal alloreactive lymphocytes are not systemically depleted, the local mechanisms may act to avoid maternal immune attack [10]. Fetal trophoblast with its special features including low tryptophan levels, the expression of HLA-G/C and so lack of activation of natural killer (NK) cells, absence of classical HLA Class I and Class II trophoblast expression, high progesterone levels and antiidiotype network modulation plays an important role in immune tolerance to the fetus [11–15]. In addition, it has been demonstrated that maternal T cell recognition of fetal antigens occurs in an indirect manner that means fetal allograft is ignored by directly alloreactive T cells that cause acute transplant rejection [16]. Despite the presence of various mechanisms in immune evasion, maternal adaptive immune system can recognize paternal alloantigens [2], as a study published in 2003 has reported that pregnancy induces cytotoxic T cells specific for minor histocompatibility antigens [17]. Fetal specific adaptive immune responses develop as a consequence of normal human pregnancy and unlike the murine models, T cells specific for fetal alloantigens are not deleted during human pregnancy [6]. So, immunoregulatory mechanisms are requested to suppress activated fetal-specific T lymphocytes. Maternal recognition of embryo-derived paternal antigens has been demonstrated to occur in several ways. Trophoblast tissue is the main contact region between mother and fetus, but there is a wide micro-chimerism between them [18,19]. It has been found that fetal cells are present in mother's blood throughout the pregnancy and for a long time further. Moreover, maternal cells have been detected in the progeny long after delivery and remain at adulthood. Trophoblast is clearly penetrable, not impenetrable physical barrier through which the exchange of cells between mother and fetus takes place [2]. Interestingly, microvesicles containing fetal antigens are shed from human placenta [20]. It has been demonstrated that leukocytes which are important constituents of decidua and myometrium affect multiple events during pregnancy, including implantation, maternal tolerance to the semiallogeneic fetus, defense against infections, and the induction of labor [21]. Leukocytes comprise around 30–40% of the total endometrial cells in early to midpregnancy uteri [22]. Leukocytes have been found even in the proliferative and early secretory phases of menstrual cycle in nonpregnant endometria [23]. To elucidate the maternal awareness of paternal-derived alloantigens, it has been proposed that antiallogenic T cells are anergized during pregnancy [24]. But the maternal immune system maintains the ability to respond to paternal alloantigens during pregnancy [2]. Fetal-specific cells demonstrated an effector memory phenotype and were broadly functional in a study conducted by Lissauer and coworkers. Fetal specific cells show proliferation, IFNγ secretion and ability to lyse target cells following recognition of processed male antigens [6]. Involvement of suppressor cells in the prevention of rejection of the fetus was initially suggested based on mixed lymphocyte reactions using splenocytes from either pregnant or virgin females [25]. The predominance of Th2 type immunity in Th1/Th2 balance has been proposed as a possible strategy for survival of the fetus in the uterus [26]. Increased Th2 polarization in maternal peripheral blood mononuclear cells (PBMCs) and decreased IFNγ secretion are associated with the normal pregnancy [27]. Women with RPL show increased Th1 to Th2 cell ratio and increased IFNγ production compared with normal healthy group [28]. In addition, Th17 cells are positively associated with idiopathic RPL [29]. The necessity of Th2 cytokines in a normal pregnancy is unknown, since studies on genetically-deficient mice which lack the ability to secret Th2 cytokines did not always lead to miscarriage [15,30]. Therefore, other mechanisms such as the function of regulatory cells regulate alloreactive Th1 cells [15]. Increased number of Treg in normal pregnancy and impaired function and frequency of these cells during pregnancy failures demonstrate importance of regulatory cells in pregnancy [15]. Recently the other immune cell populations with regulatory effects have been reported to exist in fetomaternal interface and play critical roles in pregnancy maintenance.

2. Suppressor and regulatory T cells in pregnancy

Based on phenotype, cytokine secretion and tissue origin, three subsets of CD4+ regulatory T (Treg) cells with different suppressive functions have been distinguished [30]. These are type 1 regulatory T cells (Tr1), Th3 cells, and CD4+CD25+ regulatory T-cells (Treg cells) [31]. CD8**+**/Foxp3**+** T cells with regulatory features have also been described, however their function, ontogeny and regulation are still unknown [32]. Tr1 cells are CD4**+**CD25+Foxp3⁻ T cells induced by IL-10 which also exert their suppressive activity by secretion of IL-10 [33]. They were at first characterized as suppressors of antigen-specific immune responses in mouse models of inflammatory bowel disease [34]. Th3 cells were initially discovered in mice as inducers of oral tolerance that inhibit immunity by synthesis of transforming growth factor-β (TGF-β), IL-10 and IL-4 [35]. Among these three cell subsets, CD4+CD25+Foxp3+ Treg cells obviously have essential role in a reproduction. Tregs are described as a distinct cell subset on the basis of surface phenotype and functional properties [36]. They constitute 5–10% of CD4+ T-cells in rodents and 1–3% of CD4+ T-cells in humans [37]. Although Tr1 and Th3 cells are present in the uterus [38], the precise role of these cells in pregnancy is unknown as White *et al.* showed that allogenic pregnancy is not compromised in IL-10 null mutant mice [39]. On the other hand, Robertson *et al.* has reported that IL-10 null mutant mice are susceptible to inflammation-induced fetal loss [40]. It has been demonstrated that HLA-G expressed on EVT cell which modulates alloreactive T cells induces generation of IL-10-producing Tr1 cells, in an IL10-dependent pathway [41,42]. Membrane-bound HLA-G and its inhibitory receptor Ig-like transcript (ILT)-4 are upregulated in chronic antigen stimulation in the presence of IL-10, suggesting a positive feedback loop in maintaining maternal tolerance by Tr1 and HLA-G [42]. Recently, DC-10 cells as a subset of human DCs which produce IL-10 has been characterized in the peripheral blood. DC-10 cells express surface HLA-G, ILT2, ILT3, ILT4 and secrete IL10 at high levels. *In vitro* experiments have shown that DC-10 cells induce IL10-producing Tr1 cells through IL10-dependant ILT4/HLA-G pathway [43]. It has been shown that a higher frequency of DC-10 is present in human decidua than in peripheral blood of pregnant women, suggesting the possible role of DC-10 in conjunction with inducing IL10-producing Tr1 cells in