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Human decidual macrophages suppress IFN-γ production by T cells through costimulatory B7-H1:PD-1 signaling in early pregnancy

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ABSTRACT

In human pregnancy, $CD14^+$ decidual macrophages (DMs) are the dominant professional antigen-presenting cells in the decidua, comprising 20–30% of the local leukocyte population. Although the relevance of DMs to feto-maternal immune tolerance has been described, the molecular mechanisms underlying these functions have not been fully elucidated. B7-H1, a costimulatory ligand in the B7 family, negatively modulates T cell activity by binding to its corresponding receptor, PD-1. The present study aimed to investigate the functional significance of costimulatory interactions between DMs and T cells, with a particular focus on B7-H1:PD-1 signaling. An analysis of the expression profile of B7 ligands on human DMs revealed that B7-H1 was present on DMs isolated from early but not term pregnancies. B7-H1 was not expressed on the peripheral monocytes (PMs) of pregnant women. In response to IFN-γ, B7-H1 expression was induced on PMs and was enhanced on DMs, suggesting that this cytokine might be a key factor in the control of B7-H1 expression in the decidua. The majority of decidual T cells were noted to exhibit robust expression of PD-1, whereas the expression was limited to a small subpopulation of circulating T cells. Functional assays demonstrated that DMs are able to suppress T cell IFN-γ production via B7-H1:PD-1 interactions. This suppressive property was not observed for PMs, which lack B7-H1. B7-H1 on DMs may function as a key regulator of local IFN-γ production and thereby contribute to the development of appropriate maternal immune responses to the fetus in early pregnancy.
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1. Introduction

The uterine decidua is the interface at which maternal immunocompetent cells encounter paternally inherited fetal antigens. The evasion of potentially harmful alloresponses by the maternal immune system is required for the maintenance of pregnancy. Although the mechanisms involved in the prevention of excessive maternal immune activation are still incompletely understood, it is hypothesized that the development of feto-maternal immune tolerance is multi-faceted and redundant and involves humoral factors and cell-to-cell interactions (Trowsdale and Betz, 2006).

In human pregnancy, $CD14^+$ myelomonocytic cells called decidual macrophages (DMs) comprise 20–30% of the total leukocyte population in the decidua (Trundley et al., 2006). This percentage remains stable until it decreases at term, implying that these cells might play a role in the maintenance of local homeostasis. Macrophages are categorized as professional antigen-presenting cells (APCs) and are therefore important contributors to the initial immune response to external pathogens and alloantigens (Mizuno et al., 1994). The tissue-specific activities of local macrophages are determined by the

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characteristics of the surrounding cytokine milieu and via receptor-ligand-induced signaling after direct contact with other local cells (Miller and Hunt, 1996). Although recent studies using gene expression arrays revealed that DMs display unique phenotypic attributes, such as showing M2 polarity (Gustafsson et al., 2008; Houser et al., 2011), their functional relevance to local immune regulation has not been fully elucidated.

Typical antigen presentation to T cells is mediated by primary interactions between major histocompatibility complex (MHC) molecules on APCs and the T cell receptors (TCR). Secondary or costimulatory signaling modifies the effects of primary ligand receptor binding and involves the binding of a second ligand on APCs to a corresponding receptor on the surface of T cells (Mueller et al., 1989). Costimulatory interactions can positively or negatively modulate primary signaling and will ultimately determine the type and quality of T cell responses such as clonal proliferation, cytokine production, and functional differentiation. The B7 family is a major costimulatory ligand group. B7.1 and B7.2, the first members of this family to be described, bind to their common corresponding receptors, CD28 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (Freeman et al., 1991, 1993). Ligation with CD28 induces activation of T cells, whereas interactions with CTLA-4 generate inhibitory signaling. In the last decade, several new members have been added to the B7 costimulatory ligand group, including B7-H1 (Freeman et al., 2000), B7-DC (Youngnak et al., 2003), B7-H2 (Yoshinaga et al., 1999), B7-H3 (Sun et al., 2002), B7-H4 (Ishitani et al., 2003), and B7-H6 (Brandt et al., 2009). B7-H1 and B7-DC act as inhibitory costimulatory ligands by binding to their common receptor, programmed death-1 (PD-1), which is expressed on activated but not on resting T cells (Freeman et al., 2000). Involvement of the PD-1 pathway in peripheral tolerance is suggested in PD-1-deficient mice that develop a lupus-like autoimmune disease (Nishimura et al., 1999) and autoimmune dilated cardiomyopathy (Lucas et al., 2008).

Accumulating evidence implicates B7-mediated signaling in feto-maternal immune regulation. We have previously shown that decidual stromal cells constitutively express B7-H1 and B7-DC, and that interactions between B7-H1 and B7-DC with their ligands are likely involved in the suppression of excessive T cell activation in the decidua (Nagamatsu et al., 2009). Enhanced expression of inducible costimulator (ICOS), a receptor for B7-H2 (Nagamatsu et al., 2011) and PD-1 (Taglauer et al., 2008) has been confirmed by us and others on a majority of the T cells residing in the decidua. Taken together, these findings imply that B7 costimulatory pathways may be critical in the fine tuning of T cell activity at the feto-maternal interface.

The primary aim of this study was to clarify the association of B7-mediated costimulatory signaling system in immune regulatory interactions between DMs and T cells at the feto-maternal interface. We examined the expression profiles of B7 ligands on DMs and of their corresponding receptors on T cells in the human decidua.

The types and expression level of costimulatory ligands on local macrophages are controlled by locally produced inflammatory cytokines and determine specific immunological characteristics of these antigen-presenting cells (Nagamatsu and Schust, 2010). IFN-γ is known as a key inflammatory cytokine that modulates a wide variety of immunological processes, including costimulatory signaling. The production of this cytokine in the early decidua has been described (Ashkar et al., 2000). In this study, we confirmed specific B7-H1 expression on DMs in the early stages of pregnancy and the expression is controlled by IFN-γ. Additionally, we defined the possible impact of DM-derived costimulatory signaling via B7-H1 ligation with T cell-expressed PD-1 on IFN-γ production by T cells.

2. Materials and methods

2.1. Monoclonal antibodies

Purified mouse anti-human CD3 monoclonal antibody (mAb) (clone name: OKT3), FITC-conjugated mouse anti-human CD14 (HCD14) mAb, PE-conjugated mouse anti-human B7-H1 (MIH1), B7-DC (MIH18), B7-H2 (MIH12), B7.1 (2D10), B7.2 (IT2.2), PD-1(CD279) mAbs, and allophycocyanin-conjugated mouse anti-human HLA-DR (L243) mAb were purchased from Biolegend (San Diego, CA, USA). FITC-conjugated anti-human CD4 and APC-conjugated anti-human CD8 antibodies were purchased from e-Bioscience (San Diego, CA, USA).

2.2. Sample collection

Human first-trimester decidual samples were collected from elective pregnancy termination cases performed at 7 to 11 weeks' gestation ($n = 10$). Human term decidual samples were collected from elective cesarean section cases without maternal or fetal complications ($n = 10$). Peripheral blood was collected from each subject prior to initiation of the termination procedure or cesarean section. Informed consent was obtained and the use of human tissues was conducted under the IRB approval of the University of Tokyo.

2.3. Isolation of decidual macrophages, peripheral monocytes, and T cells

Decidual tissues from early pregnancy were isolated by removing macroscopic blood clots and trophoblast villi. Term decidual samples were prepared by carefully separating the decidual layer from the fetal membranes (decidua parietalis) and the maternal surface of the placentas (decidua basalis). Decidual samples were minced and enzymatically digested in 1 mg/ml type I collagenase and 300 U/ml DNAse I (Sigma Aldrich, St. Louis, MO, USA) for 20 min at 37 °C. Cell suspensions were filtered through a 40-μm cell strainer (BD Bioscience, San Jose, CA, USA) and centrifuged at 300 × g for 10 min. The resultant cell pellet was re-suspended in phosphate-buffered saline (PBS) and layered on Percoll Plus™ (GE Healthcare) diluted to a concentration of 35% with PBS. Ficoll-Paque Plus™ (GE Healthcare Japan, Asahigaoka, Tokyo) was then layered beneath the Percoll layer. The prepared tube containing three liquid layers was centrifuged at

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