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Mini-review

Immune interactions at the maternal–fetal interface

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Abstract

Models of murine allogeneic pregnancy have established that maternal T cells recognize fetal alloantigens and are normally suppressed or deleted. While the precise cellular interactions and mechanisms involved in maternal lymphocyte tolerance are not yet clear, the identity of some of the critical factors are beginning to be uncovered. Signals that have been shown in mice to have an obligatory role in immunological survival of the semiallogeneic fetus include, but are probably not limited to, indoleamine-2,3-dioxygenase and the newly discovered B7 family protein, B7-H1. Whether these proteins have intersecting functions is unknown, but it is possible that both are involved in the control of maternal T regulatory cells, which are also strictly required for successful allogeneic pregnancy in mice. Additional factors that are involved include trophoblast and/or maternally derived FasL, and in humans, class Ib HLA molecules. The potency of these mechanisms in protecting the fetal allograft is underscored by the scarcity of knockout and transgenic models in which pregnancy is immunologically compromised. Here, the current understanding of mechanisms of specific suppression of maternal lymphocytes is reviewed.

Keywords: Placenta; Lymphocytes; Indoleamine-2,3-dioxygenase; B7-H1; FasL; HLA; T regulatory cells; Tolerance

1. Introduction

A key feature of the immune system was originally considered to be the ability of lymphocytes and other immune cells to discriminate between self and non-self. Upon realization

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that there are transplantation antigens that can confer antigenicity of transplanted tissues, Medawar (1954) raised the question of how immunological attack of the semiallogeneic fetus by the maternal immune system is avoided. With the aid of primarily human and murine model systems, rapidly evolving molecular technology, and refinement of the 'self-non-self' theory of immunology (Matzinger, 2002), some of the salient features of the complex relationship between the maternal immune system and the fetus have begun to be understood.

Lymphocytes acquire the ability to discriminate between self and non-self both centrally in the neonatal thymus and peripherally. Peripheral tolerance accounts for the ability of lymphocytes to maintain tolerance to tissues that express unique antigens. Many peripheral tissues express surface molecules that signal 'self' to lymphocytes, thereby warding off potentially dangerous self-reactive lymphocytes that have escaped deletion in the thymus. Tissues of the reproductive tract are of special interest in this regard since many do not mature or develop until or beyond puberty. The placenta, with its unique expression of allogeneic antigens, presumably has an even greater requirement to induce tolerance. While the scarcity of T cells in the gravid uterus may attest to a lack of a role for these cells in promoting placental and fetal growth, there is clear evidence that control or tolerization of anti-fetal T cells is critical, and that trophoblast and maternal factors induce this tolerance.

2. B7 family proteins

B7 family members are type I transmembrane proteins that interact with receptors belonging to the CD28 family. B7-1 and B7-2 were the first B7s to be identified. These proteins ligate CD28 to deliver a co-stimulatory signal, which, in combination with the antigen-MHC/T cell receptor (TCR) signal, is required for initiation of a primary T cell response. This 'two-signal model' of lymphocyte activation also explains that the absence of co-stimulation leads to tolerance, thus illustrating the importance of tightly regulated expression of co-stimulatory molecules to cells of primarily lymphoid and myeloid origin (Greenfield et al., 1998).

Recently, a host of new members of the B7 and CD28 families have been identified (Greenwald et al., 2004). The inhibitory or stimulatory outcome of ligand binding is determined by the CD28 receptor on the lymphocyte that is bound. We have shown recently that at least five of the seven known B7 family proteins are expressed in the human placenta, including on trophoblast cells, where they are positioned to interact with maternal lymphocytes (Petroff et al., 2003, 2005). For example, B7-H2 and B7-H3, which can stimulate Th2-type immune responses and inhibit Th1-type immune responses, respectively, are highly expressed by extravillous trophoblast cells such that they could interact with decidual leukocytes and skew their cytokine profile towards a beneficial Th2 response.

PD-1 is a CD28 family inhibitory receptor that was initially identified on T cells undergoing apoptosis (Ishida et al., 1992). PD-1 binds two ligands, B7-DC and B7-H1; binding of either ligand to PD-1 inhibits antigen-stimulated T cell activation and cytokine production in vitro (Latchman et al., 2001). In vivo, PD-1 is expressed on activated T cells and is critically important in maintaining immunological self-tolerance. Null mutagenesis of PD-1 in mice results in fatal autoimmune disease, and in humans, polymorphisms in the PD-1 gene are associated with several autoimmune diseases (Nishimura and Honjo, 2001;