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Elsevier Trophoblast Research Award Lecture: Unique Properties of Decidual T Cells and their Role in Immune Regulation during Human Pregnancy

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ABSTRACT

Maternal lymphocytes at the fetal–maternal interface play a key role in the immune acceptance of the allogeneic fetus. Most studies focus on decidual NK cells and their interaction with fetal trophoblasts, whereas limited data are available on the mechanisms of fetus specific immune recognition and immune regulation by decidual T cells at the fetal–maternal interface. The aim of this review is to describe the phenotypic characteristics of decidual T cell subsets present at the fetal–maternal interface, their interaction with HLA-C expressed by fetal trophoblasts and their role in immune recognition and regulation at the fetal–maternal interface during human pregnancy.

1. Introduction

During pregnancy the maternal immune system has to tolerate the persistence of 'non-self' (allogeneic) fetal cells. Although different mechanisms have been shown to contribute to the prevention of a destructive immune response mediated by maternal alloreactive lymphocytes, the immune acceptance of the allogeneic fetus in pregnancy remains an immunological paradox [1]. Fetus specific HLA antibodies and cytotoxic T lymphocytes (CTLs) specific for fetal HLA and minor histocompatibility antigens have been detected in maternal peripheral blood during pregnancy [2–4]. This indicates that maternal peripheral blood T cells are able to recognize and respond to fetal alloantigens during pregnancy, which leads to the hypothesis that local immune tolerance at the fetal–maternal interface must be established for the immune acceptance of the allogeneic fetus.

Fetal trophoblasts at the fetal–maternal interface play a crucial role in circumventing a destructive maternal immune response in different ways. Trophoblasts can inhibit allogeneic immune responses by expressing indoleamine 2,3-dioxygenase (IDO) (which inhibits proliferation of potentially alloreactive cells) [5], FAS ligand (which causes apoptosis of activated alloreactive cells that express FAS) [6] and complement inhibitory proteins to prevent complement activation [7]. These mechanisms can inhibit immune responses at the fetal–maternal interface in an antigen non-specific manner [8]. Trophoblasts do not express the classical HLA-A, HLA-B and HLA-DR, -DQ and -DP molecules that are the main targets for alloreactive T cells in transplantation. However, trophoblasts do express HLA-C, HLA-E and HLA-G molecules by which they can avoid NK cell mediated cytotoxicity [9]. HLA-G inhibits antigen-specific cytotoxicity by T cells and can modulate antigen-presenting cells in such a way that CD4+ regulatory T cells are induced [10]. In contrast, HLA-E and the highly polymorphic HLA-C can both induce NK cell tolerance or serve as targets for allogeneic T cells [11–13]. Prevention of the reactivity of cytotoxic T cells with specificity for HLA-C, HLA-E or minor histocompatibility antigens therefore seems essential for the immunologic acceptance of the allogeneic fetus.

2. Decidual T cells

In endometrial tissue before pregnancy, T cells constitute 50–60% of total lymphocytes [14] but limited data have been reported on which T cell types are present. Studies have shown that lymphocyte subsets in endometrial tissue change during the menstrual cycle [15]. However, whether or not the presence of T cells in endometrial tissue is menstrual cycle dependent is controversial [14,15]. In early pregnancy decidua, T cells constitute

Abbreviations: APC, antigen presenting cell; cPBL, control peripheral blood lymphocytes; mPBL, maternal peripheral blood lymphocytes; FOXP3, forkheadbox protein-3; HLA, human Leucocyte Antigen; RSA, recurrent spontaneous abortion; TCR, T cell receptor.

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5–20% of total CD45 + decidual lymphocytes and this increases with gestational age up to 40–80% (Fig. 1a, d). Decidual T cells comprise a heterogenic subset of cells with major differences compared to peripheral blood T cells. Furthermore in endometrial and decidual tissue an inverse CD4/CD8 ratio is found, which in decidua is due to the fact that CD8+ T cells are the most abundant T cell type [15,16]. Besides CD4+ and CD8+ T cells, atypical T cell types like TCRγδ+ T cells [17,18], CD4−CD8− TCRαβ+ T cells [16] and Vα24+Vβ11 + NKT cells [19] are found in decidual tissue, although their function is largely unknown [16,19]. CD4+CD25^{bright}FOXP3+ T regulatory cells are the most extensively studied T cell subset in pregnancy. This population of T cells is concentrated in decidual tissue (Fig. 1b, e) where it may play a role in both fetus specific and non-specific immune suppression [20,21]. Besides T cells with a merely regulatory function, decidual T cells include high percentages of CD4+CD25^{dim} and CD8+CD28− activated T cells (Fig. 1b, c, f, g) [22]. The function and phenotype of the most important decidual T cell subsets are summarized in Table 1.

2.1. CD4+CD25^{bright} regulatory T cells

Regulatory T cells were originally found to control immunologic self-tolerance and prevent autoimmune disease. Later, regulatory T cells were also shown to play a role in suppression of immunity

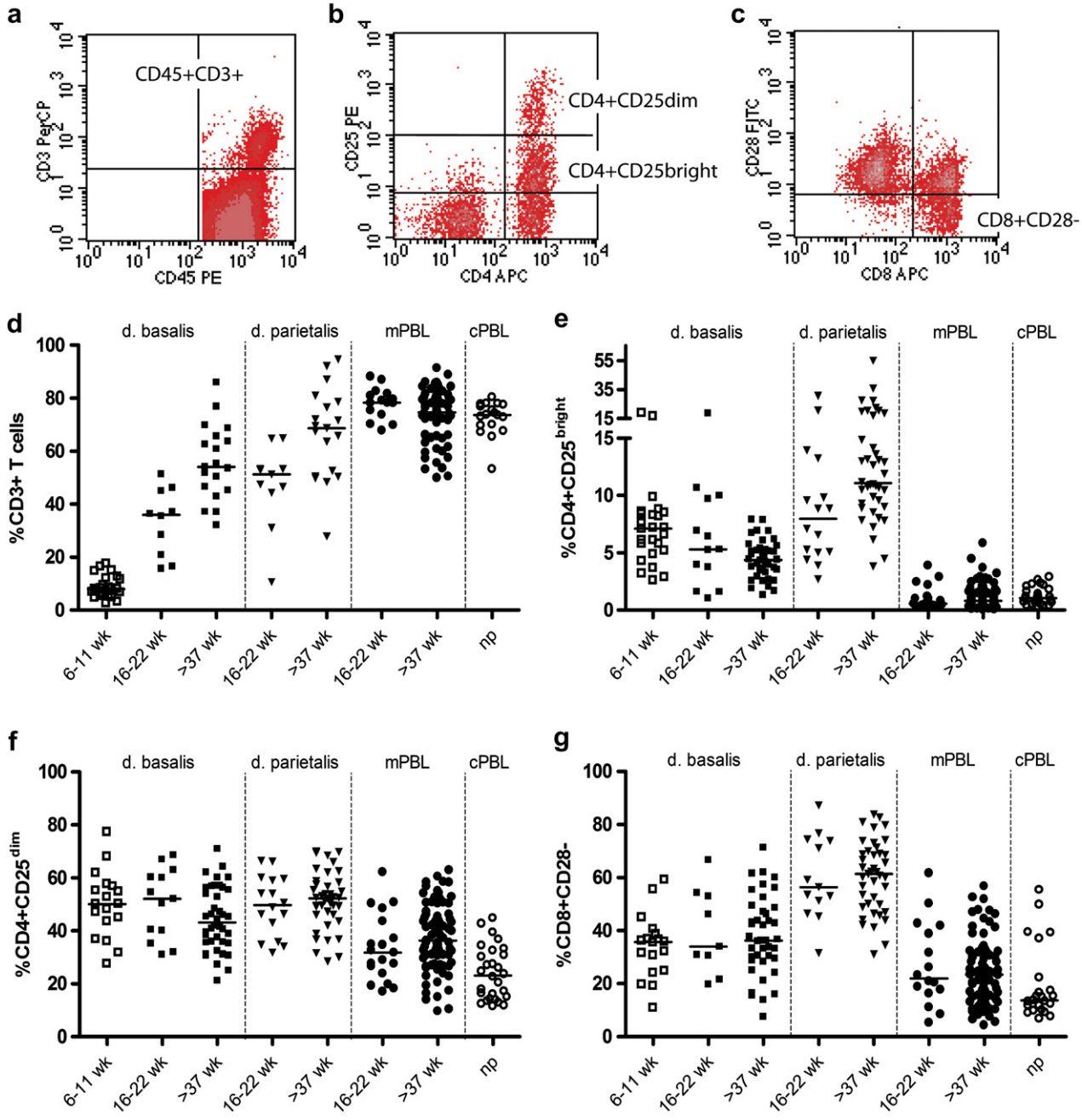

Fig. 1. Decidual T cell subsets. Representative dot plots of a 1st trimester decidual sample (a) CD45+CD3+ T cells, (b) CD4+CD25^{bright} and CD4+CD25^{dim} T cells (c) CD8+CD28− T cells. (d) shows percentage of CD3+ T cells within CD45+ cells, (e) CD4+CD25^{bright} and (f) CD4+CD25^{dim} cells within CD4+ cells and (g) CD8+CD28− T cells within CD8+ cells in 1st trimester (6–11 wk), 2nd trimester (16–22 wk) and term pregnancy (>37 wk) decidua, maternal peripheral blood (mPBL) and non-pregnant control peripheral blood (cPBL) samples (lines indicate median percentages). Data depicted is partly published previously [20,36] and all samples are processed and analyzed as described previously [18].