Accumulation of CRTH2-positive T-helper 2 and T-cytotoxic 2 cells at implantation sites of human decidua in a prostaglandin D2-mediated manner

Toshihiko Michimata¹, Hiroshi Tsuda¹, Masatoshi Sakai¹, Masaki Fujimura¹, Kinya Nagata², Masataka Nakamura³ and Shigeru Saito¹,4

¹Department of Obstetrics and Gynecology, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-0194, ²R&D Center, BML, Kawagoe, Saitama 350-1101 and ³Human Gene Sciences Center, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo 113-8510, Japan

4To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Toyama Medical and Pharmaceutical University, 2630 Sugitani Toyama-shi, Toyama 930-0194, Japan. E-mail: s30saito@ms.toyama-mpu.ac.jp

T-helper (Th) 2-type cytokines predominate in decidua, plausibly accounting for protection of a semiallograft, the embryo and placenta, from attack by the maternal immune system. However, localization of Th2 and T-cytotoxic (Tc) 2 cells in decidua has not been reported, presumably because of the difficulty in detecting intracellular cytokines in tissues. Here, by staining tissues for a novel surface marker of Th2/Tc2, the chemoattractant receptor-homologous molecule CRTH2, which is expressed on Th2 cells, we show that CRTH2⁺ Th2 cells and CRTH2⁺ Tc2 cells are significantly increased at the materno–fetal interface (implantation site) in decidua. We also show that trophoblast, uterine epithelium and endometrial glands all express haematopoietic-type prostaglandin (PG) D2 synthase (hPGDS). Since CRTH2 is a chemoattractant receptor for PGD2 and mediates PGD2-dependent migration of blood Th2 cells, our findings suggest that Th2 and Tc2 cells may be recruited to the materno–fetal interface, at least in part in a PGD2-mediated manner.

Key words: CRTH2/decidua/PGD2/pregnancy/Th2

Introduction

CD4⁺ helper T cells are classified as T-helper (Th) 1 cells or Th2 cells according to patterns of cytokine production (Mosmann and Coffman, 1989; Romagnani, 1994; Mosmann and Sad, 1996). Th1 cells produce interleukin (IL)-2, interferon (IFN)-γ and tumour necrosis factor (TNF)-β. These mediators induce activation of cytotoxic T (Tc) cells, presumably leading to spontaneous abortion (Chauvat et al., 1995; Hill et al., 1995; Kirishnan et al., 1996; Piccinni et al., 1998) and pre-eclampsia (Saito et al., 1999a,b). Th2 cells produce IL-4, IL-5, IL-6, IL-10, IL-13 and leukaemia inhibitory factor (LIF), which inhibit the Th1 cell switch from Th0 cells. CD8⁺ cytotoxic T cells have similarly been shown to be divided into Tc1 cells synthesizing IL-2, IFN-γ and TNF-β, and Tc2 cells synthesizing IL-4, IL-5, IL-6, IL-10 and IL-13 (Mosmann and Sad, 1996; Adkis et al., 1999). The physiological protection from fetal rejection is believed to be due to a Th2-type response at the maternal–fetal interface (Lin et al., 1993; Wegmann et al., 1993; Russell et al., 1997; Piccinni et al., 1998; Saito, 2000), although IL-4 and IL-10 double deficient mice show neither maternal nor feto–placental deficiency under very clean conditions (Svensson et al., 2001).

We have found no significant differences in the subpopulations of Th2/Tc2 cells and Th1/Tc1 cells in peripheral blood T cells between non-pregnant women and women in early pregnancy (Saito et al., 1999b,c). On the other hand, we have shown that the proportion of Th2/Tc2 cells in decidua is significantly higher than in peripheral blood, while the number of Th1/Tc1 cells in decidua is significantly lower than in peripheral blood (Saito et al., 1999c).

Recruitment of Th2 and Tc2 cells into the endometrium may occur during endometrial decidualization in early pregnancy. Chemokine receptors are differentially expressed on Th1 and Th2 cells, resulting in different distributions of these cells (Sallusto et al., 1997, 1998ab; Bonecchi et al., 1998; Loetscher et al., 1998; Zingoni et al., 1998; Anunziato et al., 1999; Imai et al., 1999).

We have developed a novel method to detect Th2 cells by staining a chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). Compared with intracytoplasmic cytokine molecules, detection of CRTH2 is easier by immunohistochemistry. CRTH2 is selectively expressed on Th2 cells, Tc2 cells, eosinophils and basophils (Nagata et al.,...
1999a,b; Cosmi et al., 2000; Tsuda et al., 2001), and has been shown to be a second receptor for prostaglandin D2 (PGD2), additional to the PGD receptor (DP) (Hirai et al., 2001). In addition, CRTH2, but not DP receptor, mediates PGD2-dependent cell migration of Th2 cells (Hirai et al., 2001). Thus, PGD2-dependent migration of Th2 and Tc2 cells in early pregnancy decidua may be mediated by CRTH2. Two PGD2 synthases (PGDS) have been characterized: (i) lipocalin type, or brain type, PGDS (Boie et al., 1995) and (ii) haematopoietic PGDS (hPGDS), which is expressed in placenta, Fallopian tube, lung and fetal liver (Kanaoka et al., 1997).

In this report, we show the localization of Th2 and Tc2 cells in human decidua and the expression of hPGDS at the implantation site by immunohistochemistry.

### Materials and methods

#### Specimens

Human decidual tissues (6 and 10 weeks of gestation) were obtained from induced abortion cases ($n = 15$). Informed consent was obtained for all cases. All of the sampling and use of the tissues for this study were approved by the Toyama Medical and Pharmaceutical University Ethics Committee. Tissues were fixed in 10% neutral buffered formalin for 48 h and embedded in paraffin.

#### Monoclonal antibodies

CD45 (specific for leukocytes; 1:200 dilution; Dako, High Wycombe, Buckingham, UK), CD56-1B6 [a marker for natural killer (NK) cells; 1:200 dilution; Novocastra, Newcastle upon Tyne, UK], CD3-PS1 (CD3ε, a marker for T cells; 1:200 dilution; Novocastra), CD8 (a marker for cytotoxic/suppressor T cells; 1:20 dilution; Dako) and

### Table I. The numbers and ratios of lymphocyte subpopulations in decidua

<table>
<thead>
<tr>
<th>Decidua</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation site</td>
<td>Area remote from</td>
</tr>
<tr>
<td>CD45+ (cells)</td>
<td>P value</td>
</tr>
<tr>
<td>967.60 ± 277.79</td>
<td>834.13 ± 251.55a</td>
</tr>
<tr>
<td>CD56+ (cells)</td>
<td>663.17 ± 198.52</td>
</tr>
<tr>
<td>534.01 ± 183.13</td>
<td>0.0487</td>
</tr>
<tr>
<td>CD56+/CD45+ (%)</td>
<td>69.10 ± 11.03</td>
</tr>
<tr>
<td>63.76 ± 8.97</td>
<td>0.0943</td>
</tr>
<tr>
<td>CD3+ (cells)</td>
<td>114.92 ± 54.77</td>
</tr>
<tr>
<td>57.58 ± 38.24</td>
<td>0.0012</td>
</tr>
<tr>
<td>CD3+/CD45+ (%)</td>
<td>11.60 ± 2.61</td>
</tr>
<tr>
<td>6.42 ± 2.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD8+ (cells)</td>
<td>61.54 ± 34.04</td>
</tr>
<tr>
<td>30.47 ± 23.06</td>
<td>0.00034</td>
</tr>
<tr>
<td>CD8+/CD45+ (%)</td>
<td>6.08 ± 1.70</td>
</tr>
<tr>
<td>3.33 ± 1.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD3+/CD8+ (cells)</td>
<td>53.15 ± 22.46</td>
</tr>
<tr>
<td>27.33 ± 16.03</td>
<td>0.0006</td>
</tr>
<tr>
<td>CD3+/CD8+/CD45+ (%)</td>
<td>5.48 ± 1.35</td>
</tr>
<tr>
<td>3.11 ± 0.90</td>
<td>&lt;0.0001</td>
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*Per 5000 cells.
*CD3+CD8− = number of CD3+ cells minus number of CD8+ cells.

### Figure 1. Localization of CRTH2+CD3+ and CRTH2+CD8+ cells in early pregnancy decidua. CRTH2+ T cells were detected by double fluorescence staining of CRTH2 and CD3 or CD8. Immunofluorescence staining for CD3 (A green), CD8 (D green), and CRTH2 (B and E red) is shown. Yellow staining (arrows) in C and F represents the overlap of green and red, identifying CRTH2+CD3+ (C) and CRTH2+CD8+ (F) cells. Original magnification ×400.
Figure 2. Localization of CRTH2⁺CD3⁺ cells in early pregnancy decidua. CRTH2⁺CD3⁺ cells were detected around extravillous trophoblasts (A), decidual vessels and endometrial gland cells (B) and at distance from the implantation area (C) by immunofluorescence staining of CRTH2 and CD3. Immunofluorescence staining for CRTH2⁺CD3⁺ cells (green, arrows) and CRTH2⁺CD3⁺ cells (yellow, arrowheads) is shown. Non-specific immune serum staining was used for a control (D). ET = extravillous trophoblast; V = blood vessel; EG = endometrial gland cell. Original magnification ×400.

Figure 3. Localization of haematopoietic prostaglandin D₂ synthase (PGDS) in the early pregnancy placenta and decidua. Haematopoietic PGDS was detected in uterine epithelial cells (A), syncytiotrophoblasts and cytotrophoblasts (B arrow head) and extravillous trophoblasts (B arrow), and endometrial gland cell (C) by immunofluorescence staining. Non-immune serum was used for a control (D). Original magnification ×100.
Table II. Numbers of CRTH2^+CD8^+ and CRTH2^+CD4^+ T cells

<table>
<thead>
<tr>
<th>Decidua</th>
<th>Area remote from implantation site</th>
</tr>
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<tbody>
<tr>
<td>CD3^+ (cells/HPF)</td>
<td>20.28 ± 7.51</td>
</tr>
<tr>
<td>CRTH2^+CD3^+ (cells/HPF)</td>
<td>4.11 ± 1.69</td>
</tr>
<tr>
<td>CRTH2^+CD3^+ /CD3^+ (%)</td>
<td>22.05 ± 9.84</td>
</tr>
<tr>
<td>CD8^+ (cells/HPF)</td>
<td>11.95 ± 4.50</td>
</tr>
<tr>
<td>CRTH2^+CD8^+ (cells/HPF)</td>
<td>2.23 ± 0.79</td>
</tr>
<tr>
<td>CRTH2^+CD8^+ /CD8^+ (%)</td>
<td>20.31 ± 7.76</td>
</tr>
<tr>
<td>CD4^+ (cells/HPF)^a</td>
<td>8.33 ± 3.98</td>
</tr>
<tr>
<td>CRTH2^+CD4^+ (cells/HPF)</td>
<td>1.85 ± 0.56</td>
</tr>
<tr>
<td>CRTH2^+CD4^+ /CD4^+ (%)</td>
<td>25.81 ± 18.18</td>
</tr>
</tbody>
</table>

^aCD4^+ = number of CD3^+ cells minus number of CD8^+ cells.

CRTH2^+ cells among human decidual T cells were localized by double immunofluorescence staining of CRTH2 and CD3 or CD8. The numbers of positive cells per five high-power field (HPF) at the implantation site and at a distance from the implantation site are shown (n = 15).

**Immuno histochemical staining**

Paraffin-embedded tissues sectioned at a 5 μm thickness were deparaffinized in xylene and rehydrated in a graded ethanol series to phosphate-buffered saline (PBS, pH 7.2). Antigen retrieval of the sections was performed by autoclaving in 10 mmol/l citrate buffer (pH 6.0) at 120 °C for 10 min. The embedded sections were stained immuno histochemically using anti-CD45, anti-CD3 and anti-CD8 antibodies in conjunction with a streptavidin-biotin-peroxidase kit (Nichirei, Tokyo, Japan).

Briefly, the sections were pretreated for 15 min in 3% hydrogen peroxide in methanol to quench endogenous peroxidase activity. Then, after a brief wash in a large amount of water, the sections were incubated for 10 min in 10% normal goat serum to block non-specific binding sites prior to the application of primary antibodies. Sections were then incubated overnight at 4 °C with the primary monoclonal antibodies (mAbs). Biotinylated rabbit anti-mouse immunoglobulins (Ig) and then streptavidin-biotinylated peroxidase reagent were applied according to the manufacturer’s instructions. After each incubation step, sections were washed briefly in PBS. Antibody staining was carried out with diaminobenzidine (DAB; Nichirei) for 10 min. Finally, sections were counterstained with Mayer’s haematoxylin and coverslipped using mounting medium. Serial sections were stained with anti-cytokeratin antibody to detect extravillous trophoblasts.

Decidual T cells were also stained for CRTH2 along with CD3 or CD8. Briefly, after deparaffinization, antigen retrieval was performed by autoclaving at 120 °C for 10 min. Sections were washed in PBS and incubated for 10 min in 10% normal goat serum prior to application of primary antibodies. For double staining, sections were incubated overnight at 4 °C with a combination of rat monoclonal anti-human CRTH2 antibody (5 μg/ml) and mouse monoclonal anti-human CD3 antibody (diluted 1:200), or anti-human CRTH2 antibody (5 μg/ml) and mouse monoclonal anti-human CD8 antibody (diluted 1:20). Sections were washed in PBS and incubated for 30 min with Alexa Fluar 594-labelled goat anti-rat IgG (diluted 1:100; Molecular Probes, OR, USA) and Alexa Fluar 488-labelled goat anti-mouse IgG (diluted 1:100; Molecular Probes). Sections were mounted with SlowFade antifade kits (Molecular Probes) and examined under a confocal laser scanning microscope (LSM510; Carl Zeiss, Tokyo, Japan). All images were processed with LSM510 version 2.02 software for image analysis.

Haematopoietic PGDS was detected by immunofluorescence staining using the method described above with mouse monoclonal antibody against hPGDS (as a first antibody 5 μg/ml) and Alexa Fluor 488-conjugated goat anti-mouse IgG (diluted 1:100) as a second antibody.

**Quantification and data analysis**

The implantation sites were identified by cytokeratin staining to detect trophoblasts and epithelial cells in decidua and the areas examined were classified as representing implantation site decidua (near the extravillous trophoblastic area), or non-implantation site decidua (distant from the extravillous trophoblast area). CD45^+ , CD56^− , CD3^− and CD8^+ -positive cells per 5000 cells were counted in these areas, and the ratios were calculated. CRTH2^+CD3^+ and CRTH2^+CD8^+ cells per five different fields were separately counted under a confocal laser scanning microscope, and ratios were calculated.

**Statistical analysis**

Data are expressed as the mean ± SD. Statistical differences were evaluated by analysis with Student’s t-test. Values of P < 0.05 were accepted as indicating significance.

**Results**

**Cell numbers of the lymphocyte subpopulation in decidua**

To clarify the distribution of lymphocyte subsets at the materno–fetal interface (implantation site), tissue specimens were stained and the numbers of cells positive for CD56 (a marker for NK cells), CD3 (a marker for all T cells), CD8 [a marker for cytotoxic T (Tc) cells] and CD45 (a marker for all leukocytes) were counted. The numbers of CD45^+ cells were slightly increased at the materno–fetal interface compared with those in the area remote from the implantation site (Table I). There was a particularly dense infiltration of CD56^+ cells in the decidua. The numbers of CD56^+ cells at the materno–fetal interface (implantation site) were significantly higher than at the distant site, but no significant difference was noted in the CD56^+ /CD45^+ ratio.
between these locations. On the other hand, CD3^+ and CD8^+ cells in decidua at the materno–fetal interface (implantation site) were significantly more numerous compared with those in decidua remote from the materno–fetal interface. The CD3^+ /CD45^+ and CD8^+ /CD45^+ ratios at the materno–fetal interface were significantly higher than those far from the implantation site (Table I). Unfortunately, the marker for Th cells, the commercially available CD4 monoclonal antibody (Dako and Novocastra) was not effective in staining paraffin-embedded tissue samples (by any antigen-retrieval treatment such as autoclaving, microwaving or trypsin digestion); thus, the numbers of Th cells (CD4^+ cells) were calculated by subtracting the CD8^− cell count from the CD3^+ cell count. The numbers of CD3^+CD8^− cells and the ratio of CD3^+CD8^− to CD45^+ cells at the materno–fetal interface (implantation site) were also significantly higher than those in decidua remote from the implantation site similar to CD8^+ cells (Table I). These results clearly indicate that both the numbers and ratios of Th and Tc cells increase at the materno–fetal interface.

**Localization of the CRTH2-positive T cell subpopulation**

CD3^+ populations in decidua were further characterized by staining with the antibody specific to CRTH2. CRTH2− (red, Figure 1B,E), CD3- or CD8-positive cells (green, Figure 1A,D), and cells expressing both antigens (yellow, Figure 1C,F, arrow) were separately counted. At the materno–fetal interface (implantation site), many CD3^+ cells were surrounded by extravillous trophoblasts (Figure 2A), endometrial gland cells (Figure 2B) and decidual vessels (Figure 2B). On the other hand, few CD3^− cells, limited to a perivascular distribution, were found in sites remote from the materno–fetal interface (Figure 2C). No staining was observed when non-immune mouse IgG was used in lieu of the first antibody (Figure 2D). The numbers of CRTH2^+ CD3^+ and CRTH2^+ CD8^+ cells were greater at the materno–fetal interface than at the distant site (Table II). The proportion of CRTH2^+ cells among CD3^+ cells at the materno–fetal interface was significantly higher than that at the remote site (Table II). A similar increase in ratio of CRTH2^+ cells among CD8^+ cells was observed. The calculated numbers of CRTH2^+ CD3^+CD8^− and the ratio of CRTH2^+ CD3^+CD8^− cells to CD3^+CD8^+ cells at the materno–fetal interface were also significantly higher than those at the remote site (Table II). Our results indicate that Tc cells, in addition to Th2 cells, predominate at the materno–fetal interface.

**Localization of hPGDS**

To gain insight into a mechanism which may induce the predomination of Th2 and Tc2 cells at the implantation site, the localization of cells producing hPGDS, an enzyme synthesizing PGD_2, was determined by immunofluorescence. Uterine epithelial cells (Figure 3A), villous trophoblasts (Figure 3B, arrow head) and extravillous trophoblasts (Figure 3B, arrow) were shown to express hPGDS, as did the cells of the endometrial glands (Figure 3C). Decidual stromal cells and stromal cells in the chorion did not express hPGDS (Figure 3A,B,C). No staining was recognized when non-immune mouse IgG was used as the first antibody (Figure 3D). These results suggest that PGD_2 is produced by uterine epithelial cells, endometrial gland cells and trophoblast.

**Discussion**

Because T cells are scattered throughout the decidua basalis and decidua parietalis (Kabawat *et al*., 1985; Bulmer 1992; Vassiliadou and Bulmer, 1996, 1998; King *et al*., 1998a; King 2000), few reports have compared the distribution of T cell subsets at the materno–fetal interface, i.e. the implantation site, with that in parietal decidua. In the present study, we show that CD8^+ T cells and CD3^+CD8^− T cells (i.e. CD4^− cells) are more numerous at the implantation site than remote from it. Not only T cells, but also CD56^+ NK cells, increased at the materno–fetal interface in terms of total lymphocyte numbers. However, only the T cell ratio against the total number of lymphocytes increased at the materno–fetal interface, suggesting that T cells are selectively recruited to the site of implantation.

Decidual CD16^+CD56^bright NK cells express weak surface CD8 and intracytoplasmic CD3ε, γ, and δ (Nishikawa *et al*., 1991; King *et al*., 1998a,b). Thus, cells positive for CD8 and CD3 include CD8^+ T cells and CD16^+CD56^bright CD8^dim^ NK cells, and CD3^+ T cells and CD16^+CD56^bright NK cells respectively. In this study, when CD8^bright and CD3^bright cells were considered as CD3^+ cells, the percentage of CD8^+ cells and CD3^+ cells in CD45^+ cells was 3–6% and 6–11% respectively. In contrast, the CD56^+ /CD45^+ ratio was ~70%, indicating that CD8^bright cells and CD3^bright cells were probably T cells, not CD16^+CD56^bright NK cells.

Here, we have demonstrated increases in numbers of CRTH2^+CD3^+CD8^− and CRTH2^+CD3^+ cells as well as increases in the ratios of CRTH2^+CD8^− and CRTH2^+CD3^+CD8^− cells against total T cells at the materno–fetal interface compared with those far from the implantation site. These results imply that Th2 and Tc2 cells selectively accumulate at the site of implantation. This assumption may be supported by the observation that CRTH2^+ T cells were seen around decidual blood vessels, endometrial gland cells and extravillous trophoblasts, while few cells positive for CRTH2 were present around blood vessels in decidua away from the implantation site. Thus, it is likely that Th2 and Tc2 cells migrate into the materno–fetal interface by attraction of chemotactic factor(s) specific for Th2 and Tc2 cells. Such factors may be produced by trophoblast and endometrial gland cells at the implantation site. Drake *et al*. have reported that cytotoxic lymphocytes can attract monocytes and CD56^bright^ NK cells by producing monocyte inflammatory protein (MIP) 1α (Drake *et al*., 2001). They have also reported that cytotoxic lymphocyte-conditioned medium contains a chemotactic factor for T cells, though they did not identify this substance. Dang and Heyborne have reported that uterine NKT cells recognize a class I/II-like molecule other than CD1 and the fetal class I molecule could expand the number of uterine NKT cells (Dang and Heyborne, 2001). These data suggest that the fetus or fetal trophoblasts can regulate the maternal immune system.

Our data demonstrate that hPGDS is expressed not only in maternal endometrial gland cells and endometrial epithelial
cells, but also in fetal trophoblast, presumably resulting in the secretion, at the implantation site, of PGD$_2$ that functions as a chemoattractant for CRTH2$^+$ T cells. Indeed, decidual endometrial gland cells and chorionic tissues have been shown to secrete enough PGD$_2$ (Mitchell et al., 1982; Norwitz and Wilson, 2000) and we observed an overlap in the localizations of hPGDS-expressing cells and CRTH2$^+$ T cells. Collectively, Th2 and Tc2 cells may be recruited from peripheral blood into the implantation site, at least in part in a PGD$_2$-mediated manner.

Expression of hPGDS has been found to be high in the Fallopian tube, suggesting that PGD$_2$ may foster physiological or maturation functions in the embryo (Kanaoka et al., 1997). Luteotrophic effects of PGD$_2$ have been reported in humans (Bennegard et al., 1997). Progesterone has been reported to induce the conversion of Th0 cells into Th2 cells (Piccinni et al., 1995; Lim et al., 1998). Thus, progesterone and PGD$_2$ may interact with each other within decidual tissues, resulting in Th2- and Tc2-predominant immune conditions. Furthermore, endometrial PGD$_2$ release increases during the mid-luteal phase, when blastocyst implantation occurs (Rees and Kelly, 1986). PGD$_2$ secretion by monocytes and separated glandular cells of human decidua has also been reported (Norwitz et al., 1992; Norwitz and Wilson, 2000). The degradation product of PGD$_2$, 15-deoxy-$\Delta^{12}$, 14-PGJ$_2$, stimulates peroxisome proliferator-activated receptor-$\gamma$ (PPAR$\gamma$) activity in the trophoblast, and activated PPAR$\gamma$ enhances trophoblast differentiation (Schaff et al., 2000). PGD$_2$ is therefore thought to have essential functions in reproduction.

Interestingly, PGD$_2$, but not other major eicosanoids, produced by parasites, specifically impedes the TNF$\alpha$-triggered migration of epidermal Langerhans cells through the adenylate cyclase-coupled PGD2 receptor (DP receptor) (Angeli et al., 2001). In response to stimulation occurring during infection, Langerhans cell are activated, and a proportion of them migrate via afferent lymphatics to regional lymph nodes where they accumulate as immunostimulatory dendritic cells. Upon arrival in the lymph nodes, mature dendritic cells translate the tissue-derived information into the language of T cells, providing them with an antigen-specific signal. So, the inhibition of Langerhans cells migration could represent a stratagem for the parasites to escape the host immune system. Human decidua contains potent immunostimulatory dendritic cells (Kammerer et al., 2000). PGD$_2$ in the decidua may inhibit the dendritic cell migration towards draining lymph nodes, and as a result maternal T cells would not attack fetal cells. Thus, PGD$_2$ may contribute to the maintenance of pregnancy by suppressing antigen presentation by dendritic cells and by controlling the Th1/Th2 balance through its dual receptor systems, and, as suggested by this study, CRTH2.

References


